COMPOUNDS AND METHODS FOR MODULATING UBE3A-ATS

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 BIOL0349WOSEQ_ST25.tst, created on March 16, 2020, which is 1.87 MB in size. The information in the electronic format of the sequence listing is incorporated herein by reference in its entirety.

Field

Provided are compounds, methods, and pharmaceutical compositions for reducing the amount or activity of UBE3A-ATS, the endogenous antisense transcript of ubiquitin protein ligase E3A (UBE3A) in a cell or subject, and in certain instances increasing the expression of paternal UBE3A and the amount of UBE3A protein in a cell or subject. Such compounds, methods, and pharmaceutical compositions are useful to ameliorate at least one symptom or hallmark of a neurogenetic disorder. Such symptoms and hallmarks include developmental delays, ataxia, speech impairment, sleep problems, seizures, and EEG abnormalities. Such neurogenetic disorders include Angelman Syndrome.

Background

Angelman Syndrome (AS) is a developmental disorder that affects ~1/15,000 live births and is caused by a deficiency of ubiquitin protein ligase E3A (UBE3A). Of the two copies of the UBE3A gene in neurons, the maternal gene is typically expressed, while the paternal gene is subject to genetic imprinting and silencing. Angelman Syndrome is caused when a functional copy of the UBE3A gene is not inherited from the mother, either because of a mutation, a deletion, paternal uniparental disomy of chromosome 15, or an imprinting defect. See, Buiting, et al., "Angelman Syndrome – insights into a rare neurogenetic disorder", *Nature Rev. Neuro.,* 2016, 12:584-593.

Angelman Syndrome patients experience developmental delays and speech impairment, and commonly experience sleep problems, seizures, and EEG abnormalities. The disorder is usually diagnosed in the first few years of life and the diagnosis can be confirmed by genetic testing. However, therapies for Angelman Syndrome remain limited and focus mainly on symptomatic management. See, Williams, C.A. et al., Genet. Med., 12: 385–395, 2010.

Recently, topoisomerase inhibitors currently used in cancer treatment were found to "unsilence" paternal UBE3A expression in both a neuronal culture system and mice. See, Huang, H.S. et al., Nature, 481: 185–189, 2012. However, the exact mechanism of unsilencing paternal UBE3A expression remains unknown and topoisomerase inhibitors are fraught with safety concerns because they are known to be non-specific and capable of inducing DNA damage, such as single and double-strand breaks.

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

Summary of the Invention

Provided herein are compounds, methods and pharmaceutical compositions for reducing the amount or activity of UBE3A-ATS RNA, and in certain embodiments increasing the expression of paternal UBE3A RNA or protein in a cell or subject. In certain embodiments, the subject has a neurogenetic disorder. In certain embodiments, the subject has Angelman Syndrome (AS). In certain embodiments, compounds useful for reducing expression of UBE3A-ATS RNA, or a portion thereof, are oligomeric compounds. In certain embodiments, compounds useful for reducing expression of

UBE3A-ATS RNA, or a portion thereof, are modified oligonucleotides. In certain embodiments, compounds useful for increasing expression of paternal UBE3A RNA or protein are oligomeric compounds. In certain embodiments, compounds useful for increasing expression of paternal UBE3A RNA or protein are modified oligonucleotides.

Also provided are methods useful for ameliorating at least one symptom or hallmark of a neurogenetic disorder. In certain embodiments, the neurogenetic disorder is Angelman Syndrome. In certain embodiments, the symptom or hallmark includes developmental delays, ataxia, speech impairment, sleep problems, seizures, and/or EEG abnormalities.

Detailed Description of the Invention

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

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

Definitions

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

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

DEFINITIONS

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

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

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

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

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

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

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

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

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

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

As used herein, "ameliorate" in reference to a treatment means improvement in at least one symptom 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. In certain embodiments, the symptom or hallmark is developmental delays, ataxia, speech impairment, sleep problems, seizures, and EEG abnormalities.

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 thereby forming a bicyclic structure. In certain embodiments, the first ring of the bicyclic sugar moiety is a furanosyl moiety. In certain embodiments, the bicyclic sugar moiety does not comprise a furanosyl moiety.

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

As used herein, "complementary" in reference to an oligonucleotide means that at least 70% of the nucleobases of the oligonucleotide or one or more portions thereof and the nucleobases of a target nucleic acid or one or more portions thereof are capable of hydrogen bonding with one another when the nucleobase sequence of the oligonucleotide and the other nucleic acid are aligned in opposing directions. As used herein, complementary nucleobases means nucleobases that are capable of forming hydrogen bonds with one another. Complementary nucleobase pairs include adenine (A) and thymine (T), adenine (A) and uracil (U), cytosine (C) and guanine (G), 5-methyl cytosine (mC) and guanine (G). Complementary oligonucleotides and/or target nucleic acids need not have nucleobase complementarity at each nucleoside. Rather, some mismatches are tolerated. As used herein, "fully complementary" or "100% complementary" in reference to an oligonucleotide, or portion thereof, means that the oligonucleotide, or portion thereof, is complementary to another oligonucleotide or target nucleic acid at each nucleobase of the shorter of the two oligonucleotides, or at each nucleoside if the oligonucleotides are the same length.

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

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

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

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

As used herein, “constrained ethyl” or “cEt” or “cEt modified sugar moiety” means a β-D ribosyl bicyclic sugar moiety wherein the second ring of the bicyclic sugar is formed via a bridge connecting the 4’-carbon and the 2’-carbon of the β-D ribosyl sugar moiety, wherein the bridge has the formula 4'-CH(CH_3)-O-2', and wherein the methyl group of the bridge is in the *S* configuration.

As used herein, “cEt nucleoside” means a nucleoside comprising a cEt modified sugar moiety.

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

As used herein, “gapmer” means a modified oligonucleotide comprising an internal region having a plurality of nucleosides that support RNase H cleavage positioned between external regions having one or more nucleosides, wherein the nucleosides comprising the internal region are chemically distinct from the nucleoside or nucleosides comprising the external regions. The internal region may be referred to as the “gap” and the external regions may be referred to as the “wings.” Unless otherwise indicated, “gapmer” refers to a sugar motif. Unless otherwise indicated, the sugar moiety of each nucleoside of the gap is a 2’-β-D-deoxyribosyl sugar moiety. Thus, the term “MOE gapmer” indicates a gapmer having a gap comprising 2’-β-D-deoxynucleosides and wings comprising 2’-MOE nucleosides. Unless otherwise indicated, a MOE gapmer may comprise one or more modified internucleoside linkages and/or modified nucleobases and such modifications do not necessarily follow the gapmer pattern of the sugar modifications.

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

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

As used herein, “internucleoside linkage” means the covalent linkage between contiguous nucleosides in an oligonucleotide. As used herein, “modified internucleoside linkage” means any internucleoside linkage other than a

phosphodiester internucleoside linkage. “Phosphorothioate internucleoside linkage” is a modified internucleoside linkage in which one of the non-bridging oxygen atoms of a phosphodiester internucleoside linkage is replaced with a sulfur atom.

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

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

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

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

As used herein, “neurogenetic disorder” means a condition of the nervous system caused by a heritable genetic factor, including, but not limited to, a mutation, a deletion, uniparental disomy, or an imprinting defect.

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

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

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

As used herein, "oligonucleotide" means a strand of linked nucleosides connected via internucleoside linkages, wherein each nucleoside and internucleoside linkage may be modified or unmodified. Unless otherwise indicated, oligonucleotides consist of 8-50 linked nucleosides. As used herein, “modified oligonucleotide” means an oligonucleotide, wherein at least one nucleoside or internucleoside linkage is modified. As used herein, “unmodified

oligonucleotide" means an oligonucleotide that does not comprise any nucleoside modifications or internucleoside modifications.

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

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

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

As used herein, "prodrug" means a therapeutic agent in a form outside the body that is converted to a different form within a subject or cells thereof. Typically, conversion of a prodrug within the subject is facilitated by the action of an enzymes (e.g., endogenous or viral enzyme) or chemicals present in cells or tissues and/or by physiologic conditions.

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

As used herein, "RNA" means any RNA transcript, including endogenous antisense transcripts that do not encode a protein (e.g., UBE3A-ATS), and also includes pre-mRNA and mature mRNA unless otherwise specified.

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

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

As used herein, "standard cell assay" means the assay described in Example 1 and reasonable variations thereof.

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

As used herein, "subject" means a human or non-human animal.

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

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

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

As used herein, “target nucleic acid” and “target RNA” mean a nucleic acid that an antisense compound is designed to affect.

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

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

As used herein, “therapeutically effective amount” means an amount of a pharmaceutical agent that provides a therapeutic benefit to a subject. For example, a therapeutically effective amount improves a symptom or hallmark of a disease.

CERTAIN EMBODIMENTS

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

Embodiment 1. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides wherein the nucleobase sequence of the modified oligonucleotide is at least 90% complementary to an equal length portion of a UBE3A-ATS RNA, and wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage.

Embodiment 2. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 12, 13, 14, 15, 16, 17, 18, 19, or 20 contiguous nucleobases of any of SEQ ID NOs: 17-2762, 2786-2863, 2872-2904.

Embodiment 3. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 12, 13, 14, 15, 16, 17, or 18 contiguous nucleobases of any of SEQ ID NOs: 2763-2785 or 2864-2871.

Embodiment 4. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least

13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or at least 20 contiguous nucleobases complementary to:

an equal length portion of nucleobases 461,413-461,487 of SEQ ID NO: 1;

an equal length portion of nucleobases 468,968-469,013 of SEQ ID NO: 1; or

an equal length portion of nucleobases 483,965-484,003 of SEQ ID NO: 1

Embodiment 5. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, or at least 18 contiguous nucleobases of a sequence selected from:

SEQ ID Nos:1053, 1329, 1501, 1576, 1873, 1949, 2025, 2096, 2245, 2512,2591,2680-2682, and 2844;

SEQ ID Nos: 376, 377, 2751-2756, 2773-2776, 2872, 2873, 2876-2878; or

SEQ ID Nos: 172, 764-770, 995, 1445, 1668, 1743, 2255, 2595, 2762-2767.

Embodiment 6. The oligomeric compound of any of embodiments 1-5, wherein the modified oligonucleotide has a nucleobase sequence that is at least 80%, 85%, 90%, 95%, or 100% complementary to the nucleobase sequence of SEQ ID NO: 1, SEQ ID NO: 2915, or SEQ ID NO: 2916 when measured across the entire nucleobase sequence of the modified oligonucleotide.

Embodiment 7. The oligomeric compound of any of embodiments 1-6, wherein the modified oligonucleotide comprises at least one modified nucleoside.

Embodiment 8. The oligomeric compound of embodiment 7, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a modified sugar moiety.

Embodiment 9. The oligomeric compound of embodiment 8, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a bicyclic sugar moiety.

Embodiment 10. The oligomeric compound of embodiment 9, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a bicyclic sugar moiety having a 2'-4' bridge, wherein the 2'-4' bridge is selected from –O-CH_2-; and –O-$CH(CH_3)$-.

Embodiment 11. The oligomeric compound of any of embodiments 7-10, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a non-bicyclic modified sugar moiety.

Embodiment 12. The oligomeric compound of embodiment 11, wherein the non-bicyclic modified sugar moiety is a 2'-MOE modified sugar moiety or 2'-OMe modified sugar moiety.

Embodiment 13. The oligomeric compound of any of embodiments 7-8, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a sugar surrogate.

Embodiment 14. The oligomeric compound of embodiment 13, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a sugar surrogate selected from morpholino and PNA.

Embodiment 15. The oligomeric compound of any of embodiments 1-8 or 11-14, wherein the modified oligonucleotide does not comprise a bicyclic sugar moiety.

Embodiment 16. The oligomeric compound of any of embodiments 1-15, wherein the modified oligonucleotide is a gapmer.

Embodiment 17. The oligomeric compound of any of embodiments 1-16, wherein the modified oligonucleotide has a sugar motif comprising:

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

a central region consisting of 6-10 linked central region nucleosides; and
a 3'-region consisting of 1-6 linked 3'-region nucleosides; wherein
each of the 5'-region nucleosides and each of the 3'-region nucleosides comprises a modified sugar moiety and each of the central region nucleosides comprises a 2'-β-D-deoxyribosyl sugar moiety.

Embodiment 18. The oligomeric compound of embodiment 17, wherein the modified oligonucleotide has
a 5'-region consisting of 5 linked 5'-region nucleosides;
a central region consisting of 10 linked central region nucleosides; and
a 3'-region consisting of 5 linked 3'-region nucleosides; wherein
each of the 5'-region nucleosides and each of the 3'-region nucleosides comprises a 2'-MOE modified sugar moiety, and each of the central region nucleosides comprises a 2'-β-D-deoxyribosyl sugar moiety.

Embodiment 19. The oligomeric compound of embodiment 17, wherein the modified oligonucleotide has
a 5'-region consisting of 4 linked 5'-region nucleosides;
a central region consisting of 10 linked central region nucleosides; and
a 3'-region consisting of 6 linked 3'-region nucleosides; wherein
each of the 5'-region nucleosides and each of the 3'-region nucleosides a 2'-MOE modified sugar moiety, and each of the central region nucleosides comprises a 2'-β-D-deoxyribosyl sugar moiety.

Embodiment 20. The oligomeric compound of embodiment 17, wherein the modified oligonucleotide has
a 5'-region consisting of 6 linked 5'-region nucleosides;
a central region consisting of 10 linked central region nucleosides; and
a 3'-region consisting of 4 linked 3'-region nucleosides; wherein
each of the 5'-region nucleosides and each of the 3'-region nucleosides a 2'-MOE modified sugar moiety, and each of the central region nucleosides comprises a 2'-β-D-deoxyribosyl sugar moiety.

Embodiment 21. The oligomeric compound of embodiment 17, wherein the modified oligonucleotide has
a 5'-region consisting of 5 linked 5'-region nucleosides;
a central region consisting of 8 linked central region nucleosides; and
a 3'-region consisting of 5 linked 3'-region nucleosides; wherein
each of the 5'-region nucleosides and each of the 3'-region nucleosides a 2'-MOE modified sugar moiety, and each of the central region nucleosides comprises a 2'-β-D-deoxyribosyl sugar moiety.

Embodiment 22. The oligomeric compound of embodiment 17, wherein the modified oligonucleotide has
a 5'-region consisting of 4 linked 5'-region nucleosides;
a central region consisting of 8 linked central region nucleosides; and
a 3'-region consisting of 6 linked 3'-region nucleosides; wherein
each of the 5'-region nucleosides and each of the 3'-region nucleosides a 2'-MOE modified sugar moiety, and each of the central region nucleosides comprises a 2'-β-D-deoxyribosyl sugar moiety.

Embodiment 23. The oligomeric compound of embodiment 17, wherein the modified oligonucleotide has
a 5'-region consisting of 4 linked 5'-region nucleosides;
a central region consisting of 8 linked central region nucleosides; and
a 3'-region consisting of 6 linked 3'-region nucleosides; wherein

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

Embodiment 24. The oligomeric compound of any of embodiments 1-23, wherein the modified oligonucleotide comprises at least one modified internucleoside linkage.

Embodiment 25. The oligomeric compound of embodiment 24, wherein each internucleoside linkage of the modified oligonucleotide is a modified internucleoside linkage.

Embodiment 26. The oligomeric compound of embodiment 24 or 25 wherein the modified internucleoside linkage is a phosphorothioate internucleoside linkage.

Embodiment 27. The oligomeric compound of embodiment 24 or 26 wherein the modified oligonucleotide comprises at least one phosphodiester internucleoside linkage.

Embodiment 28. The oligomeric compound of any of embodiments 24, 26, or 27, wherein each internucleoside linkage is independently selected from a phosphodiester internucleoside linkage or a phosphorothioate internucleoside linkage.

Embodiment 29. The oligomeric compound of embodiments 1-24 or 27-28, wherein the modified oligonucleotide has an internucleoside linkage motif selected from among: soooosssssssssssooss, sooooossssssssssoss, soooossssssssoss, sooossssssssooss, sooossssssssssooss, or soossssssssoooss; wherein,

s = a phosphorothioate internucleoside linkage and o = a phosphodiester internucleoside linkage.

Embodiment 30. The oligomeric compound of any of embodiments 1-29, wherein the modified oligonucleotide comprises a modified nucleobase.

Embodiment 31. The oligomeric compound of embodiment 30, wherein the modified nucleobase is a 5-methyl cytosine.

Embodiment 32. The oligomeric compound of any of embodiments 1-31, wherein the modified oligonucleotide consists of 12-30, 12-22, 12-20,14-18, 14-20, 15-17, 15-25, 16-20, 18-22 or 18-20 linked nucleosides.

Embodiment 33. The oligomeric compound of any of embodiments 1-32, wherein the modified oligonucleotide consists of 18 linked nucleosides.

Embodiment 34. The oligomeric compound of any of embodiments 1-2, 4, or 6-32, wherein the modified oligonucleotide consists of 20 linked nucleosides.

Embodiment 35. The oligomeric compound of any of embodiments 1-34, consisting of the modified oligonucleotide.

Embodiment 36. The oligomeric compound of any of embodiments 1-34, comprising a conjugate group comprising a conjugate moiety and a conjugate linker.

Embodiment 37. The oligomeric compound of embodiment 36, wherein the conjugate linker consists of a single bond.

Embodiment 38. The oligomeric compound of embodiment 36, wherein the conjugate linker is cleavable.

Embodiment 39. The oligomeric compound of embodiment 36, wherein the conjugate linker comprises 1-3 linker-nucleosides.

Embodiment 40. The oligomeric compound of any of embodiments 36-39, wherein the conjugate group is attached to the modified oligonucleotide at the 5'-end of the modified oligonucleotide.

Embodiment 41. The oligomeric compound of any of embodiments 36-39, wherein the conjugate group is attached to the modified oligonucleotide at the 3'-end of the modified oligonucleotide.

Embodiment 42. The oligomeric compound of any of embodiments 1-34 or 36-41, comprising a terminal group.

Embodiment 43. The oligomeric compound of any of embodiments 1-42 wherein the oligomeric compound is a singled-stranded oligomeric compound.

Embodiment 44. The oligomeric compound of any of embodiments 1-38 or 40-43, wherein the oligomeric compound does not comprise linker-nucleosides.

Embodiment 45. An oligomeric duplex comprising an oligomeric compound of any of embodiments 1-42 or 44.

Embodiment 46. An antisense compound comprising or consisting of an oligomeric compound of any of embodiments 1-44 or an oligomeric duplex of embodiment 45.

Embodiment 47. A pharmaceutical composition comprising an oligomeric compound of any of embodiments 1-44 or an oligomeric duplex of embodiment 45 and a pharmaceutically acceptable carrier or diluent.

Embodiment 48. The pharmaceutical composition of embodiment 47, wherein the pharmaceutically acceptable diluent is artificial cerebral spinal fluid.

Embodiment 49. The pharmaceutical composition of embodiment 48, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide and phosphate buffered saline.

Embodiment 50. A method comprising administering to a subject a pharmaceutical composition of any of embodiments 47-50.

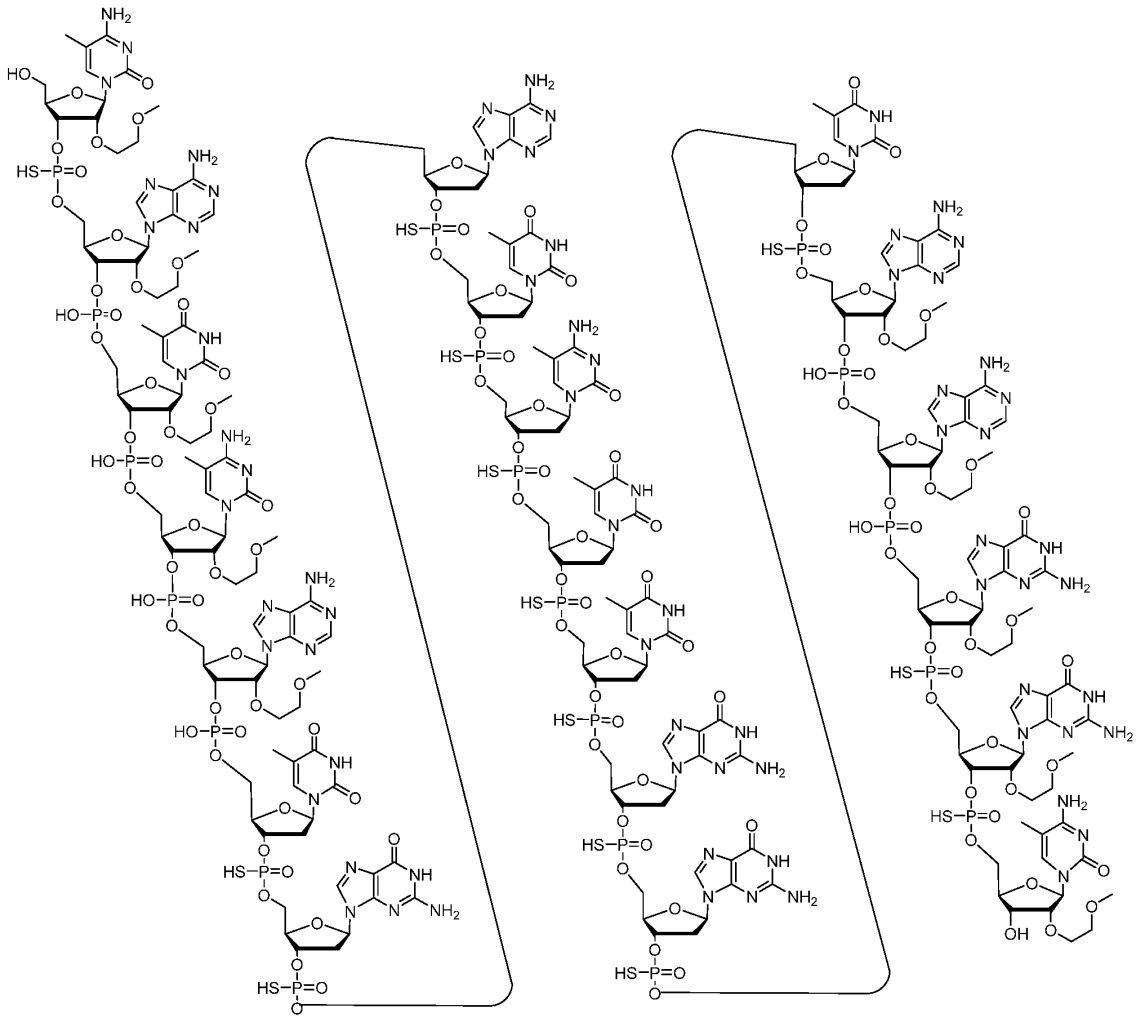
Embodiment 51. A method of treating a disease associated with UBE3A-ATS comprising administering to an individual having or at risk for developing a disease associated with UBE3A-ATS a therapeutically effective amount of a pharmaceutical composition according to any of embodiments 47-49; and thereby treating the disease associated with UBE3A-ATS.

Embodiment 52. The method of embodiment 51, wherein the UBE3A-ATS-associated disease is Angelman Syndrome.

Embodiment 53. The method of any of embodiments 50-52, wherein at least one symptom or hallmark of the UBE3A-ATS-associated disease is ameliorated.

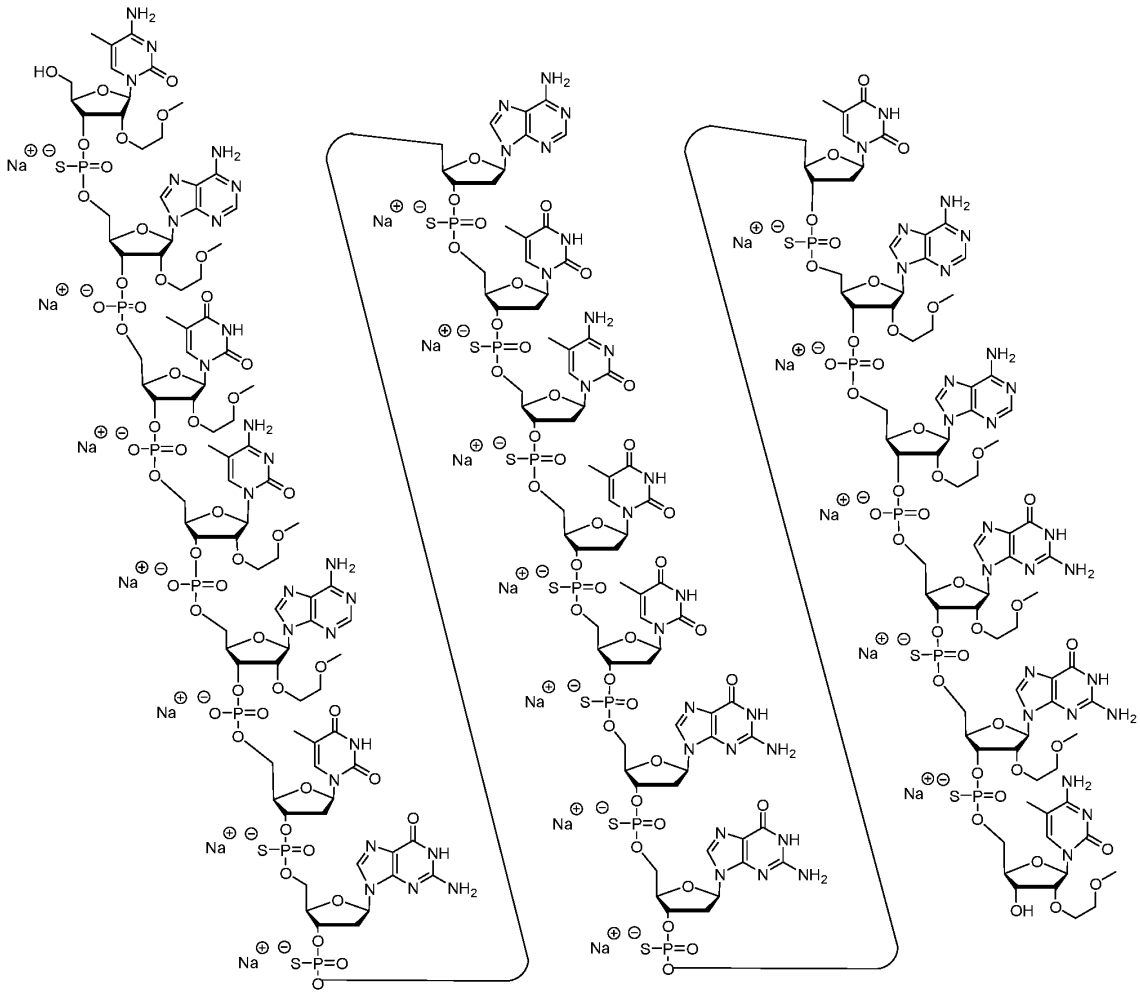
Embodiment 54. The method of embodiment 53, wherein the symptom or hallmark is developmental delays, ataxia, speech impairment, sleep problems, seizures, or EEG abnormalities.

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



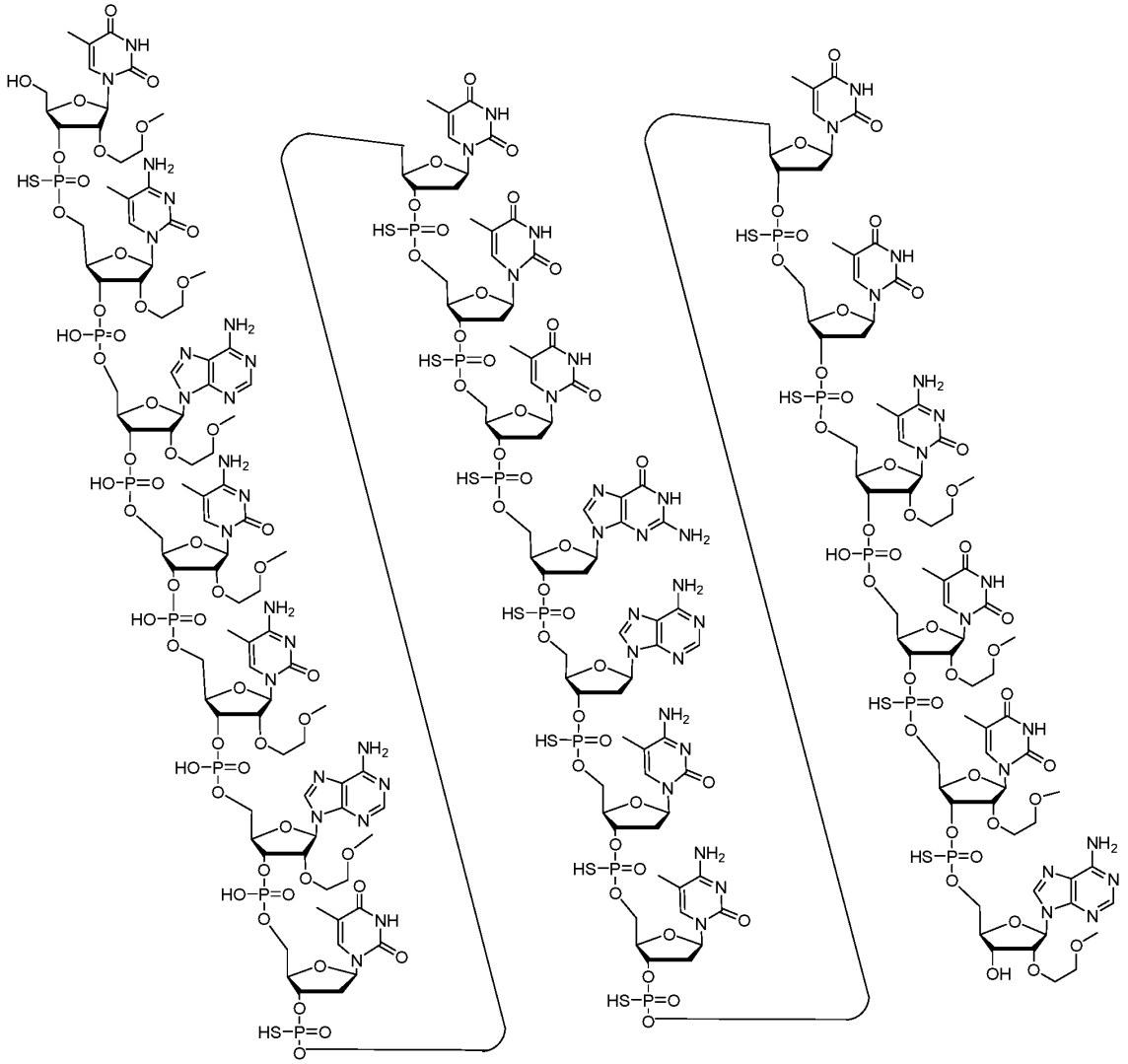
(SEQ ID NO: 1949), or a salt thereof.

Embodiment 56. A modified oligonucleotide according to the following chemical structure:



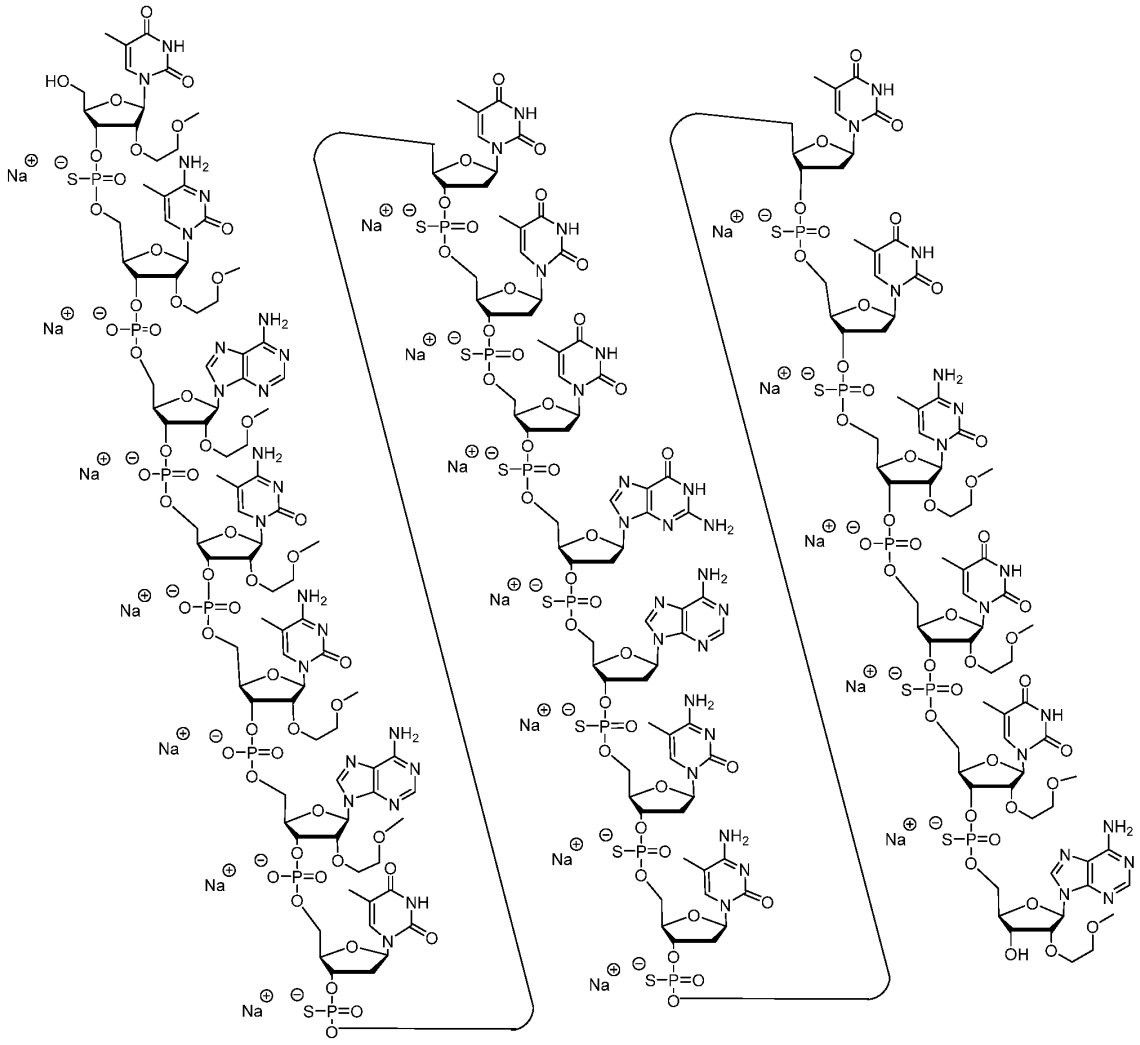
(SEQ ID NO: 1949).

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



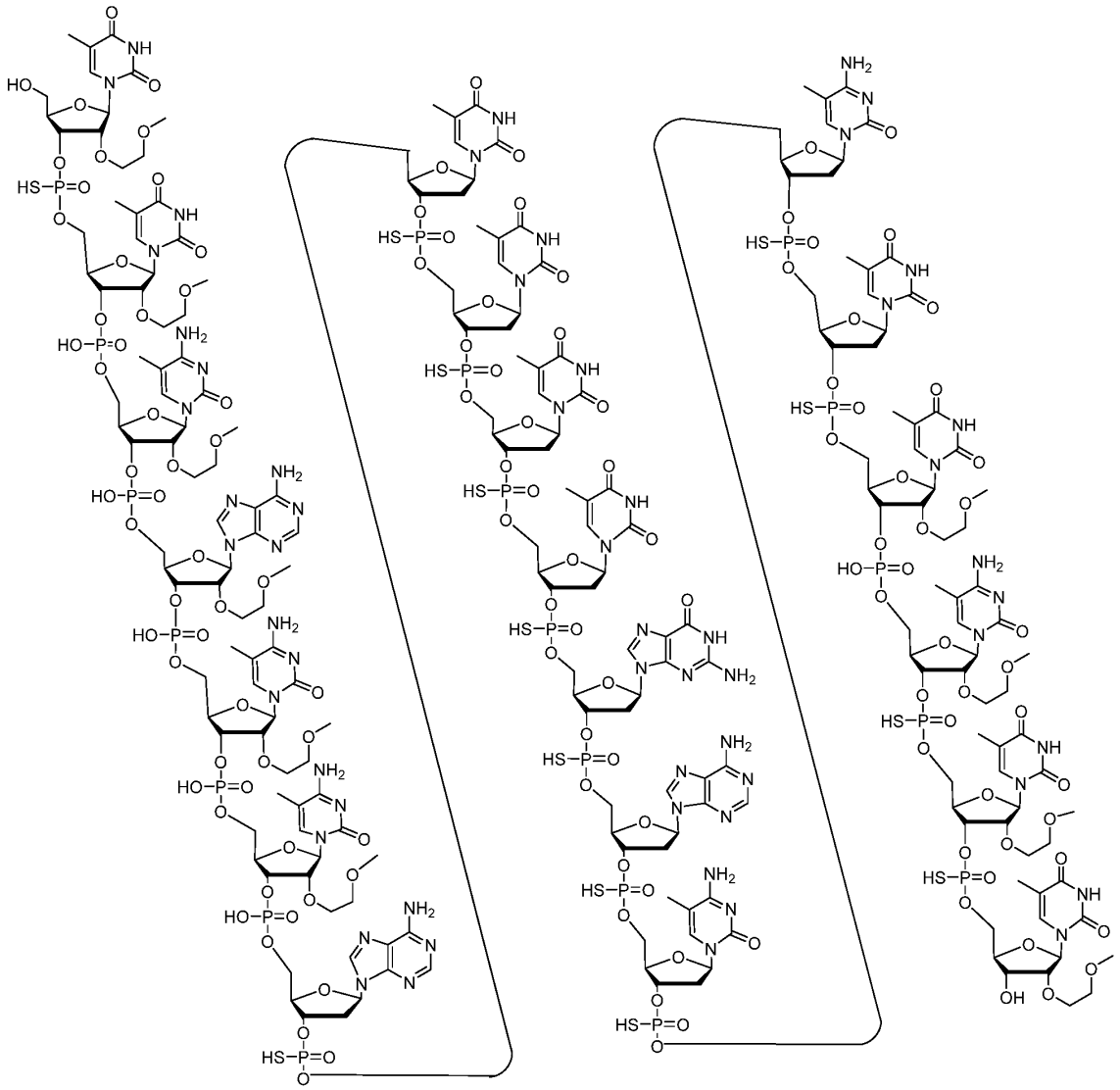
(SEQ ID NO: 2751), or a salt thereof.

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



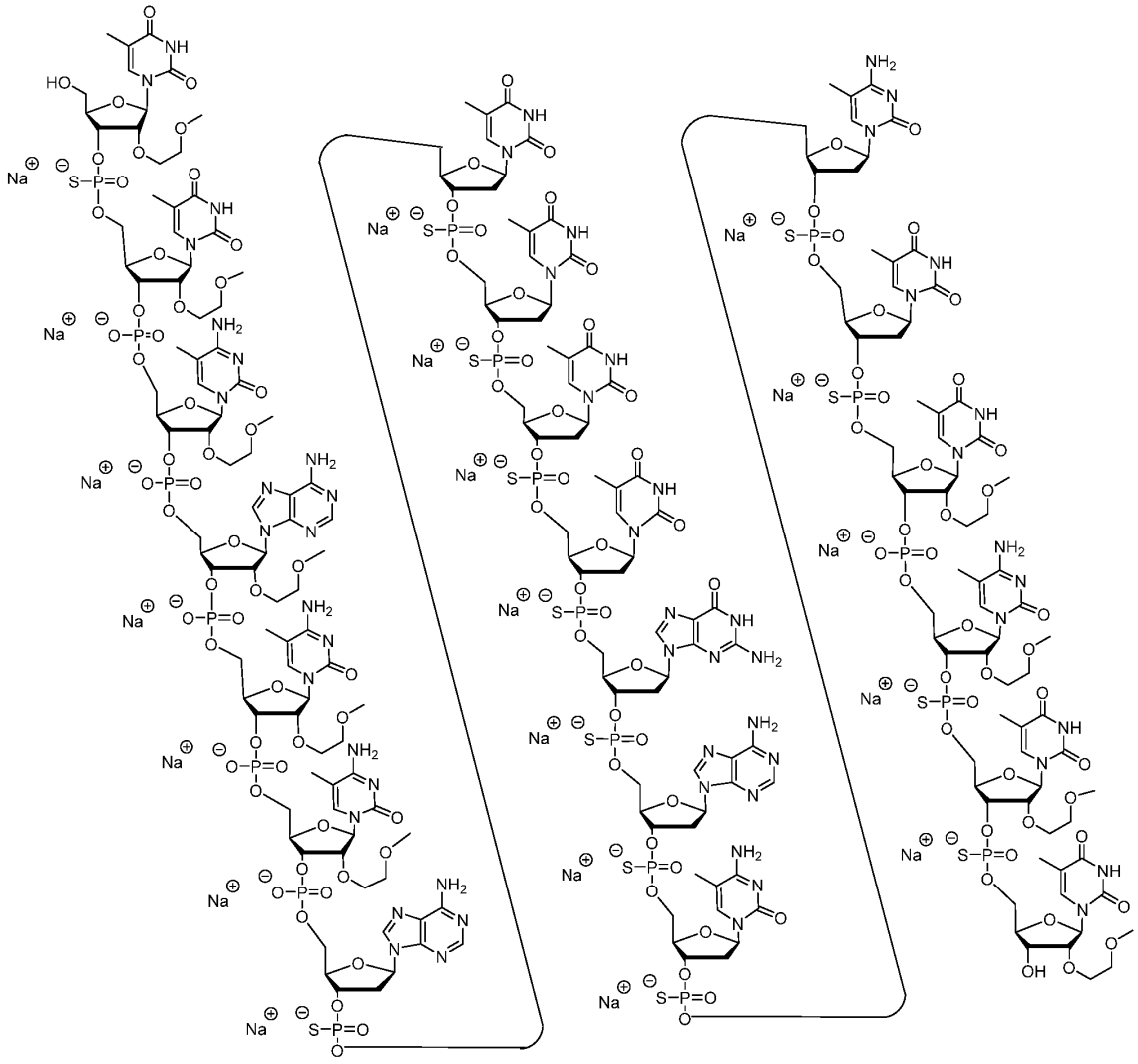
(SEQ ID NO: 2751).

Embodiment 59. A modified oligonucleotide according to the following chemical structure:



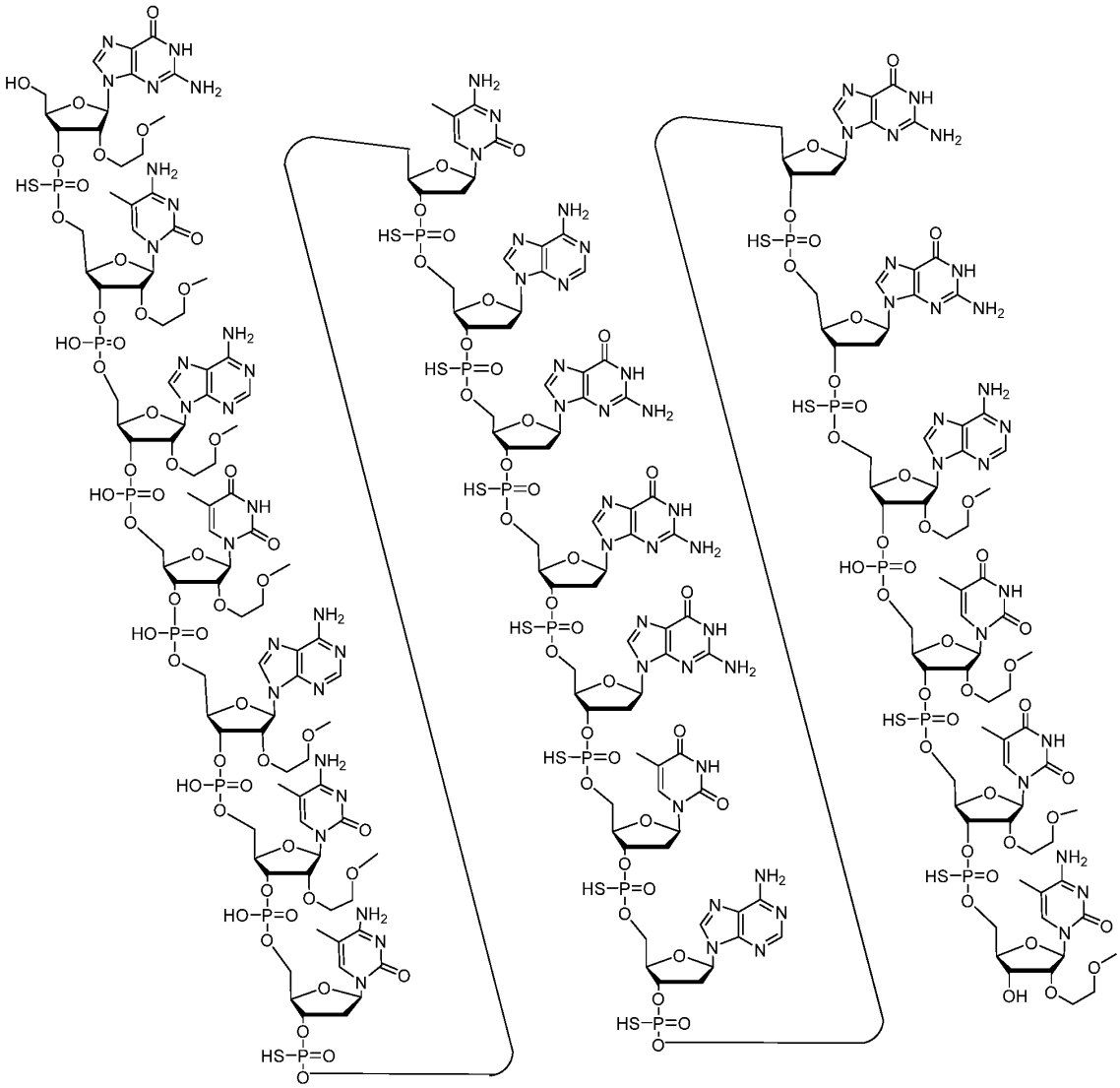
(SEQ ID NO: 2752), or a salt thereof.

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



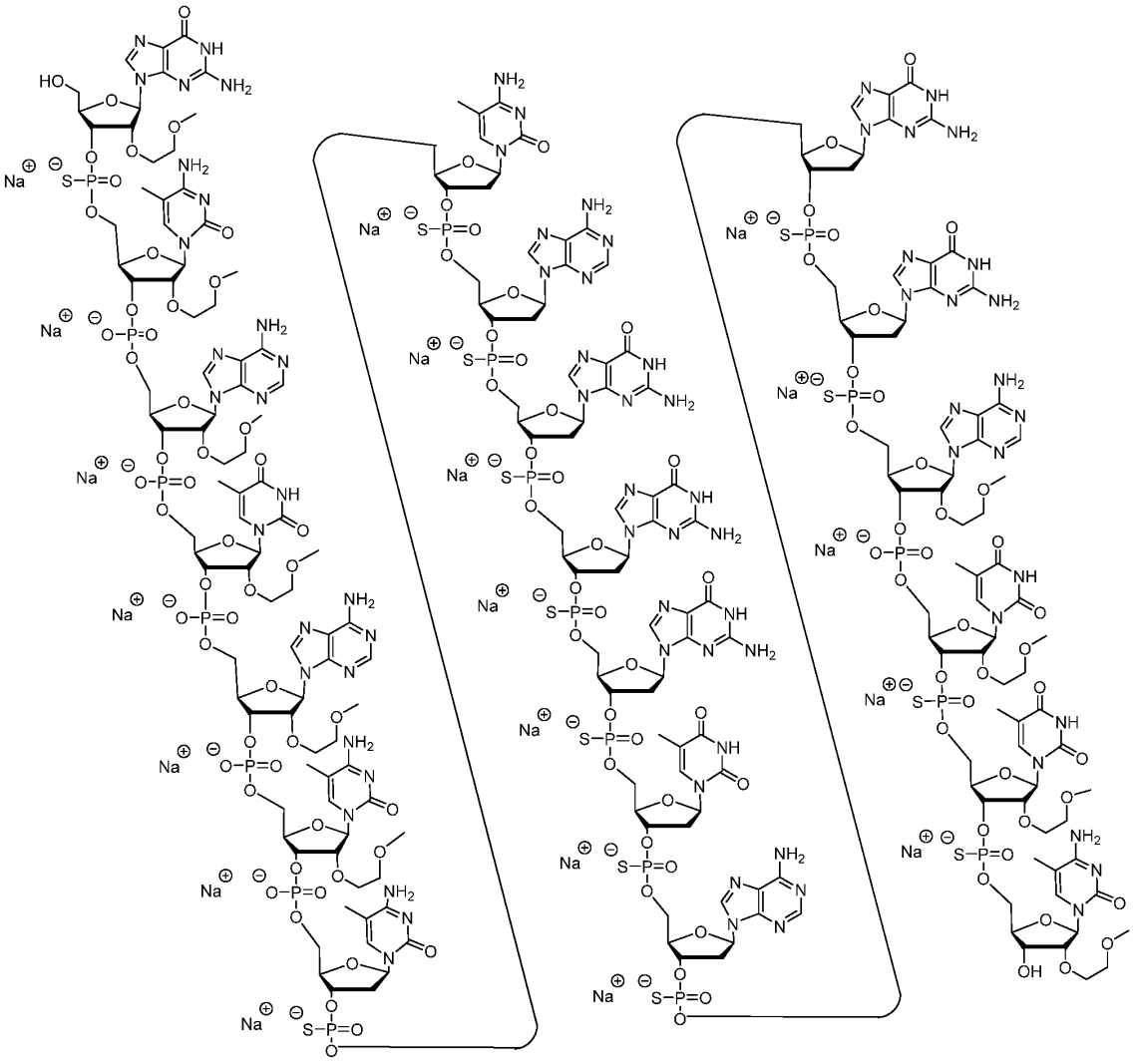
(SEQ ID NO: 2752).

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



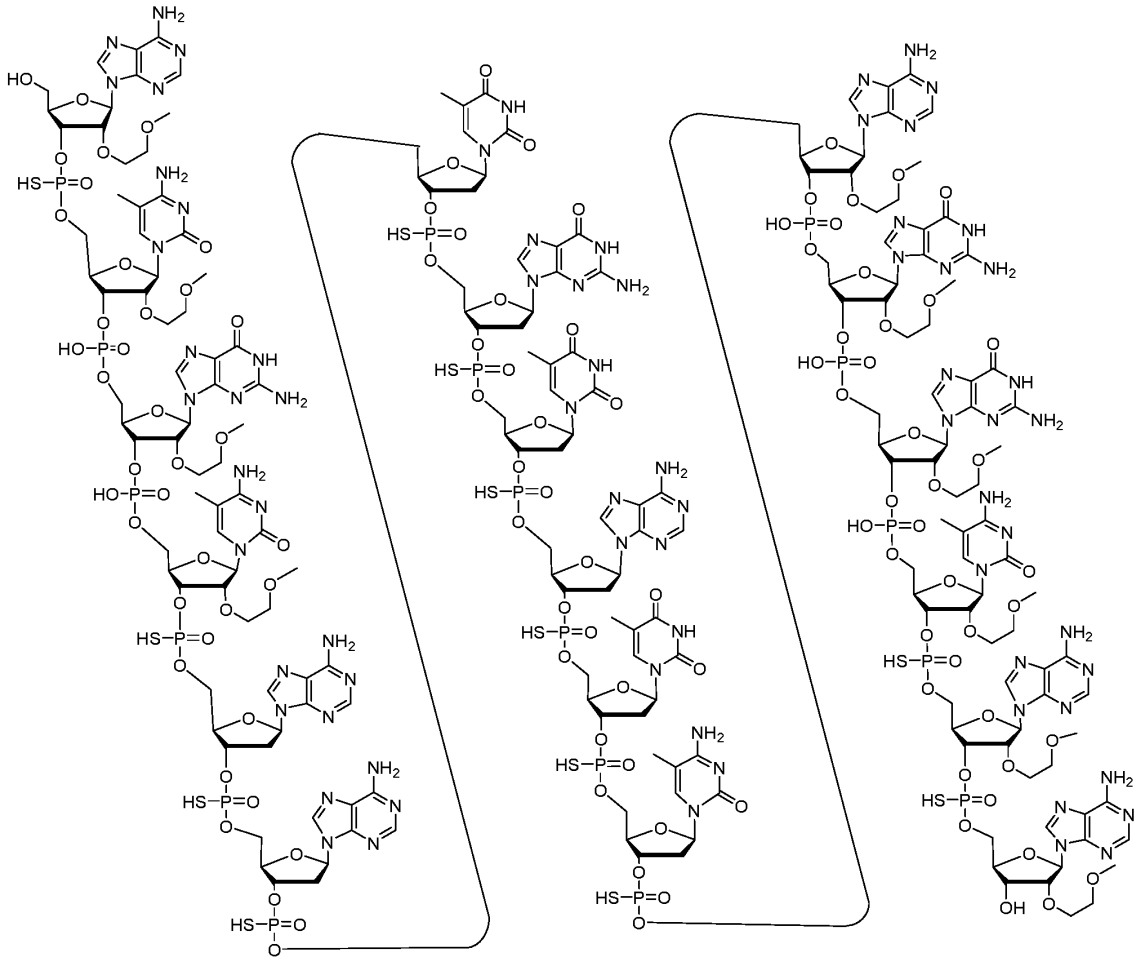
(SEQ ID NO: 765), or a salt thereof.

Embodiment 62. A modified oligonucleotide according to the following chemical structure:



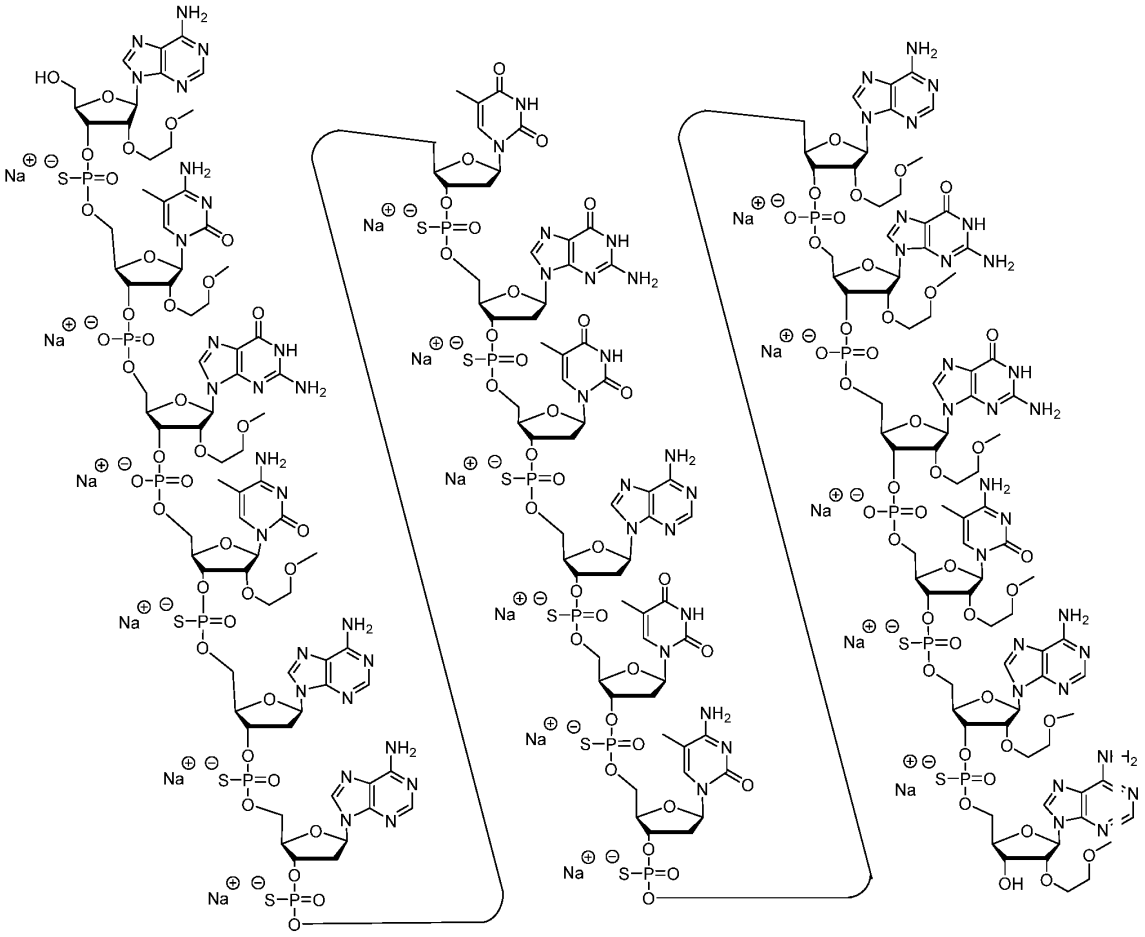
(SEQ ID NO: 765).

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



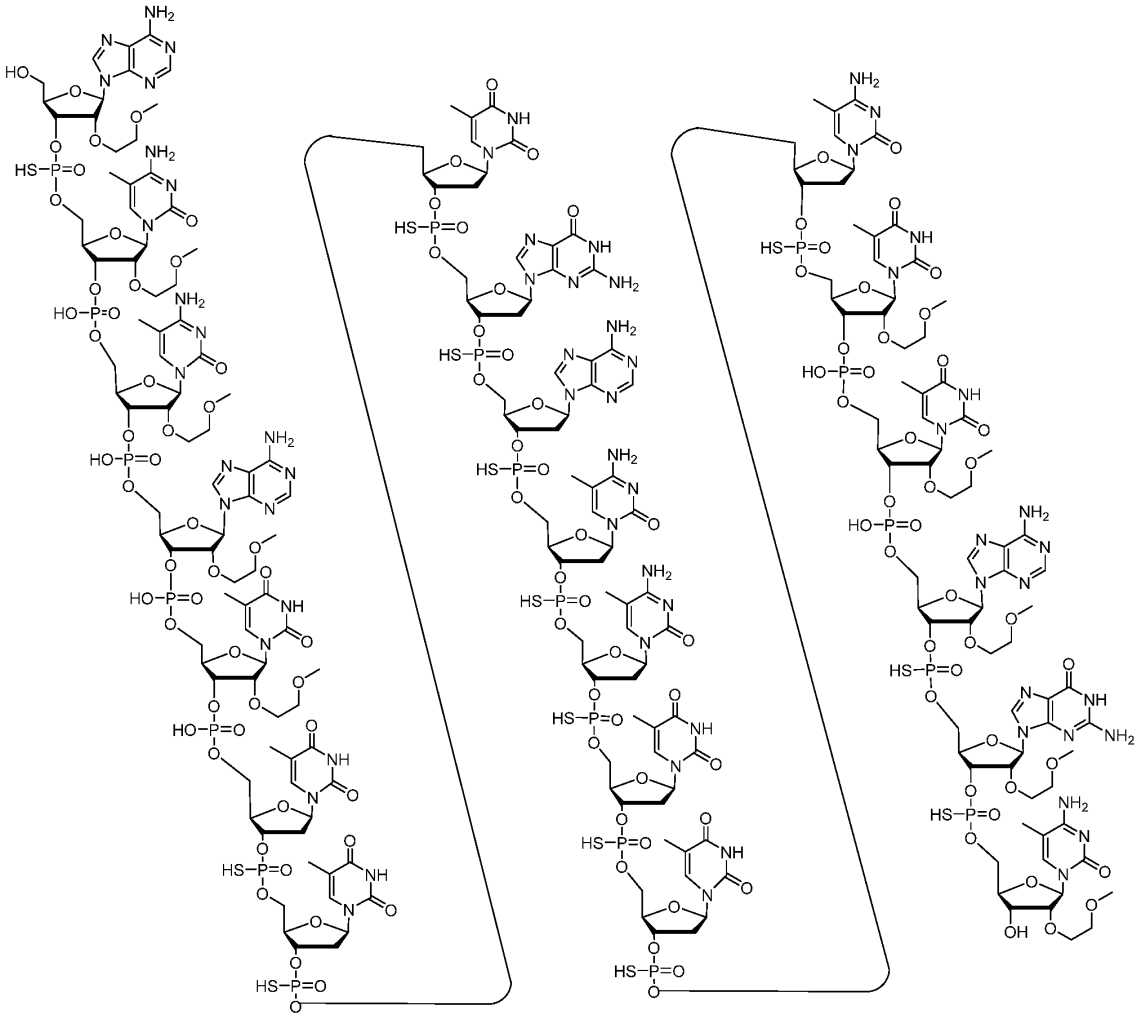
(SEQ ID NO: 2866), or a salt thereof.

Embodiment 64. A modified oligonucleotide according to the following chemical structure:



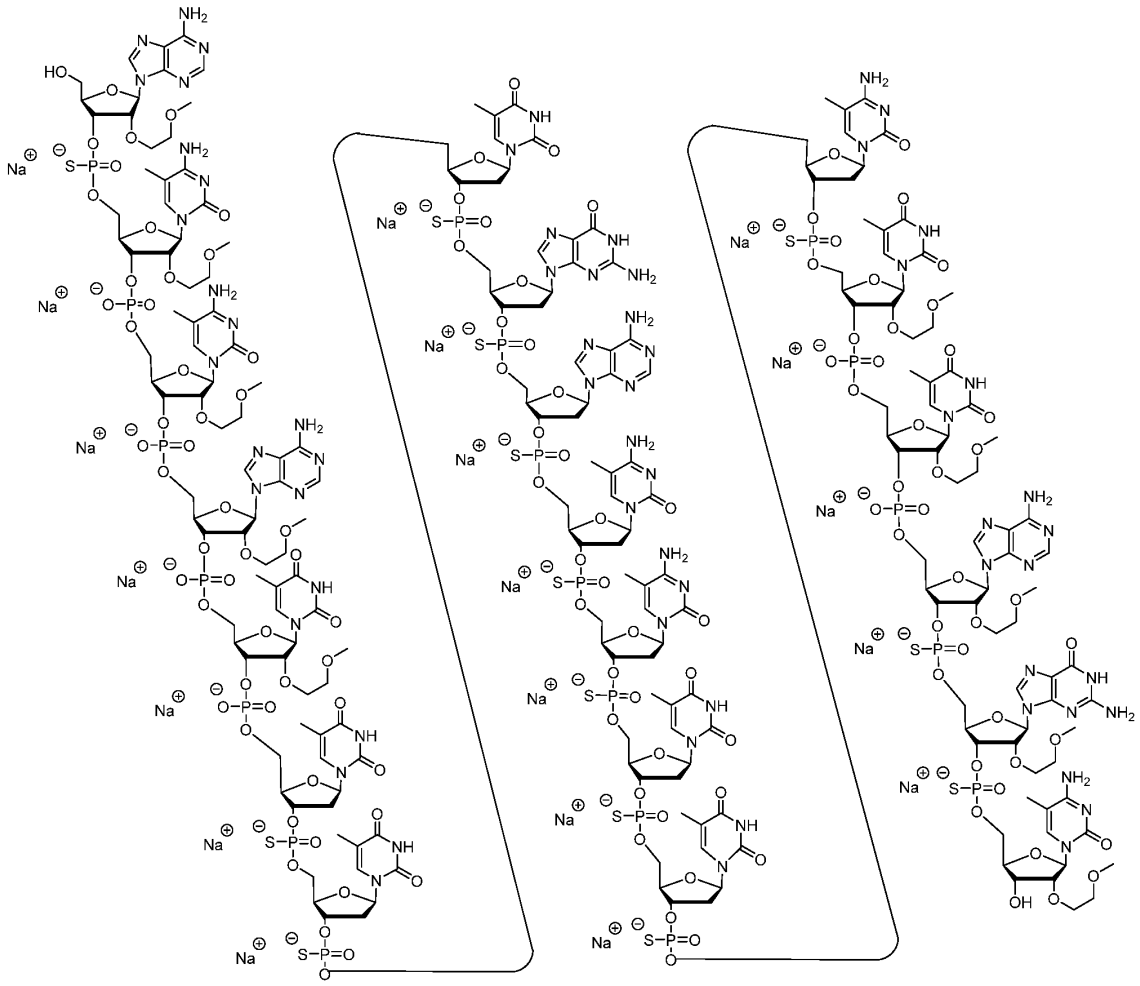
(SEQ ID NO: 2866).

Embodiment 65. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 2873), or a salt thereof.

Embodiment 66. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 2873).

Embodiment 67. The modified oligonucleotide of any of embodiments 55, 57, 59, 61, 63, or 65, which is a sodium salt of the chemical structure.

Embodiment 68. A pharmaceutical composition comprising the modified oligonucleotide of any of embodiments 55-67 and a pharmaceutically acceptable carrier or diluent.

Embodiment 69. The pharmaceutical composition of embodiment 68, wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid.

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

Embodiment 71. A compound comprising a modified oligonucleotide according to the following chemical notation: $^{m}C_{es}A_{eo}T_{eo}{}^{m}C_{eo}A_{eo}T_{ds}G_{ds}A_{ds}T_{ds}{}^{m}C_{ds}T_{ds}T_{ds}G_{ds}G_{ds}T_{ds}A_{eo}A_{eo}G_{es}G_{es}{}^{m}C_{e}$ (SEQ ID NO: 1949), wherein:

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

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

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

Embodiment 72. A compound comprising a modified oligonucleotide according to the following chemical notation: $T_{es}{}^{m}C_{eo}A_{eo}{}^{m}C_{eo}{}^{m}C_{eo}A_{eo}T_{ds}T_{ds}T_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{ds}{}^{m}C_{eo}T_{es}T_{es}A_{e}$ (SEQ ID NO: 2751), wherein:

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

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

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

Embodiment 73. A compound comprising a modified oligonucleotide according to the following chemical notation: $T_{es}T_{eo}{}^{m}C_{eo}A_{eo}{}^{m}C_{eo}{}^{m}C_{eo}A_{ds}T_{ds}T_{ds}T_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{eo}{}^{m}C_{es}T_{es}T_{e}$ (SEQ ID NO: 2752), wherein:

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

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

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

Embodiment 74. A compound comprising a modified oligonucleotide according to the following chemical notation: $G_{es}{}^{m}C_{eo}A_{eo}T_{eo}A_{eo}{}^{m}C_{eo}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}G_{ds}G_{ds}G_{ds}T_{ds}A_{ds}G_{ds}G_{ds}A_{eo}T_{es}T_{es}{}^{m}C_{e}$ (SEQ ID NO: 765), wherein:

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

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

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

Embodiment 75. A compound comprising a modified oligonucleotide according to the following chemical notation: $A_{es}{}^{m}C_{eo}G_{eo}{}^{m}C_{es}A_{ds}A_{ds}T_{ds}G_{ds}T_{ds}A_{ds}T_{ds}{}^{m}C_{ds}A_{eo}G_{eo}G_{eo}{}^{m}C_{es}A_{es}A_{e}$ (SEQ ID NO: 2866), wherein:

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

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

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

Embodiment 76. A compound comprising a modified oligonucleotide according to the following chemical notation: $A_{es}{}^{m}C_{eo}{}^{m}C_{eo}A_{eo}T_{eo}T_{ds}T_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{ds}{}^{m}C_{ds}T_{eo}T_{eo}A_{es}G_{es}{}^{m}C_{e}$ (SEQ ID NO: 2873), wherein:

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

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

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

Embodiment 77. The compound of any of embodiments 71-76, comprising the modified oligonucleotide covalently linked to a conjugate group.

Embodiment 78. A pharmaceutical composition of any of embodiments 71-77, and a pharmaceutically acceptable diluent or carrier.

Embodiment 79. The pharmaceutical composition of embodiment 78, wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid.

Embodiment 80. The pharmaceutical composition of embodiment 79, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide and artificial cerebrospinal fluid.

Embodiment 81. A chirally enriched population of modified oligonucleotides of any of embodiments 55-67, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having a particular setereochemical configuration.

Embodiment 82. The chirally enriched population of embodiment 81, wherein the population is enriched for modified oligonucleotides comprising at least one particular phorphorothioate internucleoside linkage having the (Sp) configuration.

Embodiment 83. The chirally enriched population of embodiment 81, wherein the population is enriched for modified oligonucleotides comprising at least one particular phorphorothioate internucleoside linkage having the (Rp) configuration.

Embodiment 84. The chirally enriched population of embodiment 81, wherein the population is enriched for modified oligonucleotides having a particular, independently selected stereochemical configuration at each phosphorothioate internucleoside linkage

Embodiment 85. The chirally enriched population of embodiment 84, wherein the population is enriched for modified oligonucleotides having the (Sp) configuration at each phosphorothioate internucleoside linkage.

Embodiment 86. The chirally enriched population of embodiment 84, wherein the population is enriched for modified oligonucleotides having the (Rp) configuration at each phosphorothioate internucleoside linkage.

Embodiment 87. The chirally enriched population of embodiment 84, wherein the population is enriched for modified oligonucleotides having the (Rp) configuration at one particular phosphorothioate internucleoside linkage and the (Sp) configuration at each of the remaining phosphorothioate internucleoside linkages.

Embodiment 88. The chirally enriched population of embodiment 81 or embodiment 84 wherein the population is enriched for modified oligonucleotides having at least 3 contiguous phosphorothioate internucleoside linkages in the Sp, Sp, and Rp configurations, in the 5' to 3' direction.

Embodiment 89. A chirally enriched population of modified oligonucleotides of any of embodiments 55-67, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom.

I. Certain Oligonucleotides

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

A. Certain Modified Nucleosides

Modified nucleosides comprise a modified sugar moiety or a modified nucleobase or both a modifed sugar moiety and a modified nucleobase.

1. Certain Sugar Moieties

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

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

halogen, alkyl, aryl, alkenyl and alkynyl. Examples of 4'-substituent groups suitable for non-bicyclic modified sugar moieties include but are not limited to alkoxy (*e.g.*, methoxy), alkyl, and those described in Manoharan et al., WO 2015/106128. Examples of 5'-substituent groups suitable for non-bicyclic modified sugar moieties include but are not limited to: 5-methyl (R or S), 5'-vinyl, and 5'-methoxy. In certain embodiments, non-bicyclic modified sugar moieties comprise more than one non-bridging sugar substituent, for example, 2'-F-5'-methyl sugar moieties and the modified sugar moieties and modified nucleosides described in Migawa et al., WO 2008/101157 and Rajeev et al., US2013/0203836.

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

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

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

Certain modifed sugar moieties comprise a substituent that bridges two atoms of the furanosyl ring to form 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. Examples of such 4' to 2' bridging sugar substituents include but are not limited to: 4'-CH_2-2', 4'-$(CH_2)_2$-2', 4'-$(CH_2)_3$-2', 4'-CH_2-O-2' ("LNA"), 4'-CH_2-S-2', 4'-$(CH_2)_2$-O-2' ("ENA"), 4'-$CH(CH_3)$-O-2' (referred to as "constrained ethyl" or "cEt"), 4'-CH_2-O-CH_2-2', 4'-CH_2-N(R)-2', 4'-$CH(CH_2OCH_3)$-O-2' ("constrained MOE" or "cMOE") and analogs thereof (*see, e.g.,* Seth et al., U.S. 7,399,845, Bhat et al., U.S. 7,569,686, Swayze et al., U.S. 7,741,457, and Swayze et al., U.S. 8,022,193), 4'-$C(CH_3)(CH_3)$-O-2' and analogs thereof (*see, e.g.,*Seth et al., U.S. 8,278,283), 4'-CH_2-$N(OCH_3)$-2' and analogs thereof (*see, e.g.,* Prakash et al., U.S. 8,278,425), 4'-CH_2-O-$N(CH_3)$-2' (*see, e.g.,* Allerson et al., U.S. 7,696,345 and Allerson et al., U.S. 8,124,745), 4'-CH_2-$C(H)(CH_3)$-2' (*see, e.g.,* Zhou, *et al., J. Org. Chem.,*2009, *74*, 118-134), 4'-CH_2-$C(=CH_2)$-2' and analogs thereof (*see e.g.*, Seth et al., U.S. 8,278,426), 4'-$C(R_aR_b)$-N(R)-O-2', 4'-$C(R_aR_b)$-O-N(R)-2', 4'-CH_2-O-N(R)-2', and 4'-CH_2-N(R)-O-2', wherein each R, R_a, and R_b is, independently, H, a protecting group, or C_1-C_{12} alkyl (*see, e.g.* Imanishi et al., U.S. 7,427,672).

In certain embodiments, such 4' to 2' bridges independently comprise from 1 to 4 linked groups independently selected from: $-[C(R_a)(R_b)]_n-$, $-[C(R_a)(R_b)]_n-O-$, $-C(R_a)=C(R_b)-$, $-C(R_a)=N-$, $-C(=NR_a)-$, $-C(=O)-$, $-C(=S)-$, $-O-$, $-Si(R_a)_2-$, $-S(=O)_x-$, and $-N(R_a)-$;

wherein:

x is 0, 1, or 2;

n is 1, 2, 3, or 4;

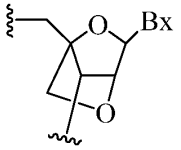
each R_a and R_b is, independently, H, a protecting group, hydroxyl, C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, substituted C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, substituted C_2-C_{12} alkynyl, C_5-C_{20} aryl, substituted C_5-C_{20} aryl, heterocycle radical, substituted heterocycle radical, heteroaryl, substituted heteroaryl, C_5-C_7 alicyclic radical, substituted

C_5-C_7 alicyclic radical, halogen, OJ_1, NJ_1J_2, SJ_1, N_3, $COOJ_1$, acyl (C(=O)-H), substituted acyl, CN, sulfonyl ($S(=O)_2$-J_1), or sulfoxyl ($S(=O)$-J_1); and

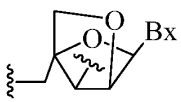
each J_1 and J_2 is, independently, H, C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, substituted C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, substituted C_2-C_{12} alkynyl, C_5-C_{20} aryl, substituted C_5-C_{20} aryl, acyl (C(=O)-H), substituted acyl, a heterocycle radical, a substituted heterocycle radical, C_1-C_{12} aminoalkyl, substituted C_1-C_{12} aminoalkyl, or a protecting group.

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.*, 2007, *129,* 8362-8379;Wengel et a., 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; 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'-CH_2-O-2'



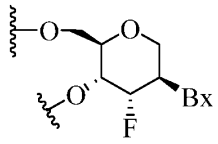
α-*L*-LNA (α-*L*-configuration)
bridge = 4'-CH_2-O-2'

α-L-methyleneoxy (4'-CH_2-O-2') or α-L-LNA bicyclic nucleosides have been incorporated into oligonucleotides that showed antisense activity (Frieden et al., *Nucleic Acids Research,* 2003, *21*, 6365-6372). Herein, general descriptions of bicyclic nucleosides include both isomeric configurations. When the positions of specific bicyclic nucleosides (*e.g.*, LNA or cEt) are identified in exemplified embodiments herein, they are in the β-D configuration, unless otherwise specified.

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

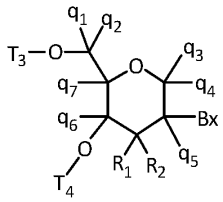
In certain embodiments, modified sugar moieties are sugar surrogates. In certain such embodiments, the oxygen atom of the sugar moiety is replaced, *e.g.,* with a sulfur, carbon or nitrogen atom. In certain such embodiments, such modified sugar moieties also comprise bridging and/or non-bridging substituents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

In certain embodiments, sugar surrogates comprise rings having other than 5 atoms. For example, in certain embodiments, a sugar surrogate comprises a six-membered tetrahydropyran ("THP"). Such tetrahydropyrans may be further modified or substituted. Nucleosides comprising such modified tetrahydropyrans include but are not limited to hexitol nucleic acid ("HNA"), anitol nucleic acid ("ANA"), manitol nucleic acid ("MNA") (*see, e.g.,* Leumann, CJ. *Bioorg. & Med. Chem.* 2002, *10*, 841-854), fluoro HNA:



F-HNA

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



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

Bx is a nucleobase moiety;

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

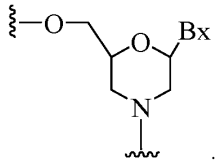
q_1, q_2, q_3, q_4, q_5, q_6 and q_7 are each, independently, H, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_2-C_6 alkenyl, substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl, or substituted C_2-C_6 alkynyl; and

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

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

In certain embodiments, sugar surrogates comprise rings having more than 5 atoms and more than one heteroatom. For example, nucleosides comprising morpholino sugar moieties and their use in oligonucleotides have been reported (*see, e.g.,* Braasch et al., Biochemistry, 2002, *41*, 4503-4510 and Summerton et al., U.S. 5,698,685;

Summerton et al., U.S. 5,166,315; Summerton et al., U.S. 5,185,444; and Summerton et al., U.S. 5,034,506). As used here, the term "morpholino" means a sugar surrogate having the following structure:



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

In certain embodiments, sugar surrogates comprise acyclic moieites. Examples of nucleosides and oligonucleotides comprising such acyclic sugar surrogates include but are not limited to: peptide nucleic acid ("PNA"), acyclic butyl nucleic acid (*see, e.g.,* Kumar et al., *Org. Biomol. Chem.*, 2013, *11*, 5853-5865), and nucleosides and oligonucleotides described in Manoharan et al., WO2011/133876.

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

2. Certain Modified Nucleobases

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

In certain embodiments, modified nucleobases are selected from: 5-substituted pyrimidines, 6-azapyrimidines, alkyl or alkynyl substituted pyrimidines, alkyl substituted purines, and N-2, N-6 and O-6 substituted purines. In certain embodiments, modified nucleobases are selected from: 2-aminopropyladenine, 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-N-methylguanine, 6-N-methyladenine, 2-propyladenine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-propynyl (-C≡C-CH_3) uracil, 5-propynylcytosine, 6-azouracil, 6-azocytosine, 6-azothymine, 5-ribosyluracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl, 8-aza and other 8-substituted purines, 5-halo, particularly 5-bromo, 5-trifluoromethyl, 5-halouracil, and 5-halocytosine, 7-methylguanine, 7-methyladenine, 2-F-adenine, 2-aminoadenine, 7-deazaguanine, 7-deazaadenine, 3-deazaguanine, 3-deazaadenine, 6-N-benzoyladenine, 2-N-isobutyrylguanine, 4-N-benzoylcytosine, 4-N-benzoyluracil, 5-methyl 4-N-benzoylcytosine, 5-methyl 4-N-benzoyluracil, universal bases, hydrophobic bases, promiscuous bases, size-expanded bases, and fluorinated bases. Further modified nucleobases include tricyclic pyrimidines, such as 1,3-diazaphenoxazine-2-one, 1,3-diazaphenothiazine-2-one and 9-(2-aminoethoxy)-1,3-diazaphenoxazine-2-one (G-clamp). Modified nucleobases may also include those in which the purine or pyrimidine base is replaced with other heterocycles, for example 7-deaza-adenine, 7-deazaguanosine, 2-aminopyridine and 2-pyridone. Further nucleobases include those disclosed in Merigan et al., U.S. 3,687,808, those disclosed in *The Concise Encyclopedia Of Polymer Science And Engineering*, Kroschwitz, J.I., Ed., John Wiley & Sons, 1990, 858-859; Englisch *et al.*, *Angewandte Chemie*, International Edition, 1991, *30*, 613; Sanghvi, Y.S., Chapter 15, *Antisense Research and Applications*, Crooke, S.T. and Lebleu, B., Eds., CRC Press, 1993, 273-288; and those disclosed in Chapters 6 and 15, *Antisense Drug Technology*, Crooke S.T., Ed., CRC Press, 2008, 163-166 and 442-443.

Publications that teach the preparation of certain of the above noted modified nucleobases as well as other

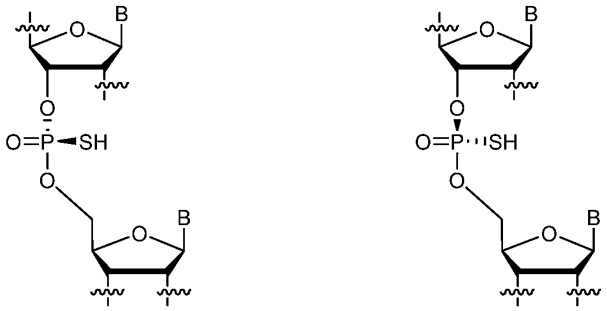
modified nucleobases include without limitation, Manoharan et al., US2003/0158403; Manoharan et al., US2003/0175906; Dinh et al., U.S. 4,845,205; Spielvogel et al., U.S. 5,130,302; Rogers et al., U.S. 5,134,066; Bischofberger et al., U.S. 5,175,273; Urdea et al., U.S. 5,367,066; Benner et al., U.S. 5,432,272;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

3. **Certain Modified Internucleoside Linkages**

In certain embodiments, nucleosides of modified oligonucleotides may be linked together using any internucleoside linkage. The two main classes of internucleoside linking groups are defined by the presence or absence of a phosphorus atom. Representative phosphorus-containing internucleoside linkages include but are not limited to phosphodiesters, which contain a phosphodiester bond ("$P(O_2)=O$") (also referred to as unmodified or naturally occurring linkages), phosphotriesters, methylphosphonates, phosphoramidates, and phosphorothioates ("$P(O_2)=S$"), and phosphorodithioates ("HS-P=S"). Representative non-phosphorus containing internucleoside linking groups include but are not limited to methylenemethylimino ($-CH_2-N(CH_3)-O-CH_2-$), thiodiester, thionocarbamate (-O-C(=O)(NH)-S-); siloxane ($-O-SiH_2-O-$); and N,N'-dimethylhydrazine ($-CH_2-N(CH_3)-N(CH_3)-$). Modified internucleoside linkages, compared to naturally occurring phosphate linkages, can be used to alter, typically increase, nuclease resistance of the oligonucleotide. In certain embodiments, internucleoside linkages having a chiral atom can be prepared as a racemic mixture, or as separate enantiomers. Methods of preparation of phosphorous-containing and non-phosphorous-containing internucleoside linkages are well known to those skilled in the art.

Representative internucleoside linkages having a chiral center include but are not limited to alkylphosphonates and phosphorothioates. Modified oligonucleotides comprising internucleoside linkages having a chiral center can be prepared as populations of modified oligonucleotides comprising stereorandom internucleoside linkages, or as populations of modified oligonucleotides comprising phosphorothioate linkages in particular stereochemical configurations. In certain embodiments, populations of modified oligonucleotides comprise phosphorothioate internucleoside linkages wherein all of the phosphorothioate internucleoside linkages are stereorandom. Such modified oligonucleotides can be generated using synthetic methods that result in random selection of the stereochemical configuration of each phosphorothioate linkage. Nonetheless, 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 (*S*p) configuration. In certain embodiments, a population of modified oligonucleotides is enriched for modified oligonucleotides having at least one phosphorothioate in the (*R*p) configuration. In certain embodiments, modified oligonucleotides comprising (*R*p) and/or (*S*p) phosphorothioates comprise one or more of the following formulas, respectively, wherein "B" indicates a nucleobase:



(R_p) (S_p)

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

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

B. <u>Certain Motifs</u>

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

1. **Certain Sugar Motifs**

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

In certain embodiments, modified oligonucleotides have a gapmer motif, which is defined by two external regions or "wings" and a central or internal region or "gap." The three regions of a gapmer motif (the 5'-wing, the gap, and the 3'-wing) form a contiguous sequence of nucleosides wherein at least some of the sugar moieties of the nucleosides of each of the wings differ from at least some of the sugar moieties of the nucleosides of the gap. Specifically, at least the sugar moieties of the nucleosides of each wing that are closest to the gap (the 3'-most nucleoside of the 5'-wing and the 5'-most nucleoside of the 3'-wing) differ from the sugar moiety of the neighboring gap nucleosides, thus defining the boundary between the wings and the gap (i.e., the wing/gap junction). In certain embodiments, the sugar moieties within the gap are the same as one another. In certain embodiments, the gap includes one or more nucleoside having a sugar moiety that differs from the sugar moiety of one or more other nucleosides of the gap. In certain embodiments, the sugar motifs of the two wings are the same as one another (symmetric gapmer). In certain embodiments, the sugar motif of the 5'-wing differs from the sugar motif of the 3'-wing (asymmetric gapmer).

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

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

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

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

Herein, the lengths (number of nucleosides) of the three regions of a gapmer may be provided using the notation [# of nucleosides in the 5'-wing] – [# of nucleosides in the gap] – [# of nucleosides in the 3'-wing]. Thus, a 3-10-3 gapmer consists of 3 linked nucleosides in each wing and 10 linked nucleosides in the gap. Where such nomenclature is followed by a specific modification, that modification is the modification in each sugar moiety of each wing and the gap nucleosides comprise 2'-β-D-deoxyribosyl sugar moieties. Thus, a 5-10-5 MOE gapmer consists of 5 linked 2'-MOE nucleosides in the 5'-wing, 10 linked 2'- β-D-deoxynucleosides in the gap, and 5 linked 2'-MOE nucleosides in the 3'-wing. A 3-10-3 cEt gapmer consists of 3 linked cEt nucleosides in the 5'-wing, 10 linked 2'- β-D-deoxynucleosides in the gap, and 3 linked cEt nucleosides in the 3'-wing. A 5-8-5 gapmer consists of 5 linked nucleosides comprising a modified sugar moiety in the 5'-wing, 8 linked 2'-β-D-deoxynucleosides in the gap, and 5 linked nucleosides comprising a modified sugar moiety in the 3'-wing. A 5-8-5 mixed gapmer has at least two different modified sugar moieties in the 5'- and/or the 3'-wing.

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

2. Certain Nucleobase Motifs

In certain embodiments, oligonucleotides comprise modified and/or unmodified nucleobases arranged along the oligonucleotide or portion thereof in a defined pattern or motif. In certain embodiments, each nucleobase is modified. In certain embodiments, none of the nucleobases are modified. In certain embodiments, each purine or each pyrimidine is modified. In certain embodiments, each adenine is modified. In certain embodiments, each guanine is modified. In certain embodiments, each thymine is modified. In certain embodiments, each uracil is modified. In certain embodiments, each cytosine is modified. In certain embodiments, some or all of the cytosine nucleobases in a modified oligonucleotide are 5-methyl cytosines. In certain embodiments, all of the cytosine nucleobases are 5-methyl cytosines and all of the other nucleobases of the modified oligonucleotide are unmodified nucleobases.

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

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

3. Certain Internucleoside Linkage Motifs

In certain embodiments, oligonucleotides comprise modified and/or unmodified internucleoside linkages arranged along the oligonucleotide or portion thereof in a defined pattern or motif. In certain embodiments, each internucleoside linking group is a phosphodiester internucleoside linkage ($P(O_2)=O$). In certain embodiments, each

internucleoside linking group of a modified oligonucleotide is a phosphorothioate internucleoside linkage ($P(O_2)$=S). In certain embodiments, each internucleoside linkage of a modified oligonucleotide is independently selected from a phosphorothioate internucleoside linkage and phosphodiester internucleoside linkage. In certain embodiments, each phosphorothioate internucleoside linkage is independently selected from a stereorandom phosphorothioate, a (*S*p) phosphorothioate, and a (*R*p) phosphorothioate. In certain embodiments, the sugar motif of a modified oligonucleotide is a gapmer and the internucleoside linkages within the gap are all modified. In certain such embodiments, some or all of the internucleoside linkages in the wings are unmodified phosphodiester internucleoside linkages. In certain embodiments, the terminal internucleoside linkages are modified. In certain embodiments, the sugar motif of a modified oligonucleotide is a gapmer, and the internucleoside linkage motif comprises at least one phosphodiester internucleoside linkage in at least one wing, wherein the at least one phosphodiester linkage is not a terminal internucleoside linkage, and the remaining internucleoside linkages are phosphorothioate internucleoside linkages. In certain such embodiments, all of the phosphorothioate linkages are stereorandom. In certain embodiments, all of the phosphorothioate linkages in the wings are (Sp) phosphorothioates, and the gap comprises at least one Sp, Sp, Rp motif. In certain embodiments, populations of modified oligonucleotides are enriched for modified oligonucleotides comprising such internucleoside linkage motifs.

In certain embodiments, modified nucleotides have an internucleoside linkage motif of soooosssssssssooss, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage. In certain embodiments, modified nucleotides have an internucleoside linkage motif of sooooossssssssssoss, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage. In certain embodiments, modified nucleotides have an internucleoside linkage motif of sooooossssssssoss, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage. In certain embodiments, modified nucleotides have an internucleoside linkage motif of soooosssssssooss, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage. In certain embodiments, modified nucleotides have an internucleoside linkage motif of sooosssssssssooss, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage. In certain embodiments, modified nucleotides have an internucleoside linkage motif of soossssssssssooss, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage.

C. Certain Lengths

It is possible to increase or decrease the length of an oligonucleotide without eliminating activity. For example, in Woolf et al. (Proc. Natl. Acad. Sci. USA 89:7305-7309, 1992), a series of oligonucleotides 13-25 nucleobases in length were tested for their ability to induce cleavage of a target RNA in an oocyte injection model. Oligonucleotides 25 nucleobases in length with 8 or 11 mismatch bases near the ends of the oligonucleotides were able to direct specific cleavage of the target RNA, albeit to a lesser extent than the oligonucleotides that contained no mismatches. Similarly, target specific cleavage was achieved using 13 nucleobase oligonucleotides, including those with 1 or 3 mismatches.

In certain embodiments, oligonucleotides (including modified oligonucleotides) can have any of a variety of ranges of lengths. In certain embodiments, oligonucleotides consist of X to Y linked nucleosides, where X represents the fewest number of nucleosides in the range and Y represents the largest number nucleosides in the range. In certain such embodiments, X and Y are each independently selected from 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22,

23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, and 50; provided that X≤Y. For example, in certain embodiments, oligonucleotides consist of 12 to 13, 12 to 14, 12 to 15, 12 to 16, 12 to 17, 12 to 18, 12 to 19, 12 to 20, 12 to 21, 12 to 22, 12 to 23, 12 to 24, 12 to 25, 12 to 26, 12 to 27, 12 to 28, 12 to 29, 12 to 30, 13 to 14, 13 to 15, 13 to 16, 13 to 17, 13 to 18, 13 to 19, 13 to 20, 13 to 21, 13 to 22, 13 to 23, 13 to 24, 13 to 25, 13 to 26, 13 to 27, 13 to 28, 13 to 29, 13 to 30, 14 to 15, 14 to 16, 14 to 17, 14 to 18, 14 to 19, 14 to 20, 14 to 21, 14 to 22, 14 to 23, 14 to 24, 14 to 25, 14 to 26, 14 to 27, 14 to 28, 14 to 29, 14 to 30, 15 to 16, 15 to 17, 15 to 18, 15 to 19, 15 to 20, 15 to 21, 15 to 22, 15 to 23, 15 to 24, 15 to 25, 15 to 26, 15 to 27, 15 to 28, 15 to 29, 15 to 30, 16 to 17, 16 to 18, 16 to 19, 16 to 20, 16 to 21, 16 to 22, 16 to 23, 16 to 24, 16 to 25, 16 to 26, 16 to 27, 16 to 28, 16 to 29, 16 to 30, 17 to 18, 17 to 19, 17 to 20, 17 to 21, 17 to 22, 17 to 23, 17 to 24, 17 to 25, 17 to 26, 17 to 27, 17 to 28, 17 to 29, 17 to 30, 18 to 19, 18 to 20, 18 to 21, 18 to 22, 18 to 23, 18 to 24, 18 to 25, 18 to 26, 18 to 27, 18 to 28, 18 to 29, 18 to 30, 19 to 20, 19 to 21, 19 to 22, 19 to 23, 19 to 24, 19 to 25, 19 to 26, 19 to 29, 19 to 28, 19 to 29, 19 to 30, 20 to 21, 20 to 22, 20 to 23, 20 to 24, 20 to 25, 20 to 26, 20 to 27, 20 to 28, 20 to 29, 20 to 30, 21 to 22, 21 to 23, 21 to 24, 21 to 25, 21 to 26, 21 to 27, 21 to 28, 21 to 29, 21 to 30, 22 to 23, 22 to 24, 22 to 25, 22 to 26, 22 to 27, 22 to 28, 22 to 29, 22 to 30, 23 to 24, 23 to 25, 23 to 26, 23 to 27, 23 to 28, 23 to 29, 23 to 30, 24 to 25, 24 to 26, 24 to 27, 24 to 28, 24 to 29, 24 to 30, 25 to 26, 25 to 27, 25 to 28, 25 to 29, 25 to 30, 26 to 27, 26 to 28, 26 to 29, 26 to 30, 27 to 28, 27 to 29, 27 to 30, 28 to 29, 28 to 30, or 29 to 30 linked nucleosides.

D. Certain Modified Oligonucleotides

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

E. Certain Populations of Modified Oligonucleotides

Populations of modified oligonucleotides in which all of the modified oligonucleotides of the population have the same molecular formula can be stereorandom populations or chirally enriched populations. All of the chiral centers of all of the modified oligonucleotides are stereorandom in a stereorandom population. In a chirally enriched population, at least one particular chiral center is not stereorandom in the modified oligonucleotides of the population. In certain embodiments, the modified oligonucleotides of a chirally enriched population are enriched for β-D ribosyl sugar moieties, and all of the phosphorothioate internucleoside linkages are stereorandom. In certain embodiments, the modified oligonucleotides of a chirally enriched population are enriched for both β-D ribosyl sugar moieties and at least one, particular phosphorothioate internucleoside linkage in a particular stereochemical configuration.

F. Nucleobase Sequence

In certain embodiments, oligonucleotides (unmodified or modified oligonucleotides) are further described by their nucleobase sequence. In certain embodiments oligonucleotides have a nucleobase sequence that is complementary

to a second oligonucleotide or an identified reference nucleic acid, such as a target nucleic acid. In certain such embodiments, a portion of an oligonucleotide has a nucleobase sequence that is complementary to a second oligonucleotide or an identified reference nucleic acid, such as a target nucleic acid. In certain embodiments, the nucleobase sequence of a portion or entire length of an oligonucleotide is at least 50%, at least 60%, at least 70%, at least 80%, at least 85%, at least 90%, at least 95%, or 100% complementary to the second oligonucleotide or nucleic acid, such as a target nucleic acid.

II. Certain Oligomeric Compounds

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

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

A. Certain Conjugate Groups

In certain embodiments, oligonucleotides are covalently attached to one or more conjugate groups. In certain embodiments, conjugate groups modify one or more properties of the attached oligonucleotide, including but not limited to pharmacodynamics, pharmacokinetics, stability, binding, absorption, tissue distribution, cellular distribution, cellular uptake, charge and clearance. In certain embodiments, conjugate groups impart a new property on the attached oligonucleotide, *e.g.*, fluorophores or reporter groups that enable detection of the oligonucleotide. Certain conjugate groups and conjugate moieties have been described previously, for example: cholesterol moiety (Letsinger et al., Proc. Natl. Acad. Sci. USA, 1989, 86, 6553-6556), cholic acid (Manoharan et al., *Bioorg. Med. Chem. Lett.*, 1994, *4*, 1053-1060), a thioether, *e.g.,* hexyl-S-tritylthiol (Manoharan et al., *Ann. N.Y. Acad. Sci.*, 1992, *660*, 306-309; Manoharan et al., *Bioorg. Med. Chem. Lett.,* 1993, *3*, 2765-2770), a thiocholesterol (Oberhauser et al., *Nucl. Acids Res.*, 1992, *20*, 533-538), an aliphatic chain, *e.g.,* do-decan-diol or undecyl residues (Saison-Behmoaras et al., *EMBO J.,* 1991, *10*, 1111-1118; Kabanov et al., *FEBS Lett.*, 1990, *259*, 327-330; Svinarchuk et al., *Biochimie*, 1993, *75*, 49-54), a phospholipid, e.g., di-hexadecyl-rac-glycerol or triethyl-ammonium 1,2-di-O-hexadecyl-rac-glycero-3-H-phosphonate (Manoharan et al., *Tetrahedron Lett.*, 1995, *36*, 3651-3654; Shea et al., *Nucl. Acids Res.*, 1990, *18*, 3777-3783), a polyamine or a polyethylene glycol chain (Manoharan et al., *Nucleosides & Nucleotides*, 1995, *14*, 969-973), or adamantane acetic acid a palmityl moiety (Mishra et al., *Biochim. Biophys. Acta*, 1995, *1264,* 229-237), an octadecylamine or hexylamino-carbonyl-oxycholesterol moiety (Crooke et al., *J. Pharmacol. Exp. Ther.,* 1996, *277*, 923-937), a tocopherol group (Nishina et al., *Molecular Therapy Nucleic Acids*, 2015**,** *4*, e220; and Nishina et al., *Molecular Therapy,* 2008, *16*, 734-

740), or a GalNAc cluster (*e.g.*, WO2014/179620).

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

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

1. **Conjugate Moieties**

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

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

2. **Conjugate Linkers**

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

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

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

Examples of conjugate linkers include but are not limited to pyrrolidine, 8-amino-3,6-dioxaoctanoic acid

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

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

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

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

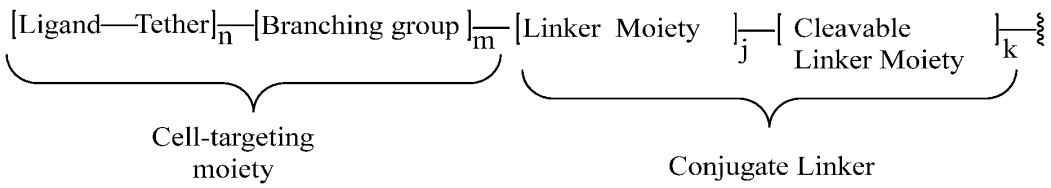
embodiments, a cleavable moiety is selectively cleaved inside a cell or subcellular compartment, such as a lysosome. In certain embodiments, a cleavable moiety is selectively cleaved by endogenous enzymes, such as nucleases.

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

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

3. **Cell-Targeting Moieties**

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



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

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

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

B. Certain Terminal Groups

In certain embodiments, oligomeric compounds comprise one or more terminal groups. In certain such embodiments, oligomeric compounds comprise a stabilized 5'-phosphate. Stabilized 5'-phosphates include, but are not limited to 5'-phosphanates, including, but not limited to 5'-vinylphosphonates. In certain embodiments, terminal groups comprise one or more abasic nucleosides and/or inverted nucleosides. In certain embodiments, terminal groups

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

III. Oligomeric Duplexes

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

IV. Antisense Activity

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

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

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

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

Antisense activities may be observed directly or indirectly. In certain embodiments, observation or detection of

an antisense activity involves observation or detection of a change in an amount of a target nucleic acid or protein encoded by such target nucleic acid, a change in the ratio of splice variants of a nucleic acid or protein and/or a phenotypic change in a cell or subject.

V. Certain Target Nucleic Acids

In certain embodiments, oligomeric compounds comprise or consist of an oligonucleotide comprising a portion that is complementary to a target nucleic acid. In certain embodiments, the target nucleic acid is an endogenous RNA molecule. In certain embodiments, the target nucleic acid encodes a protein. In certain such embodiments, the target nucleic acid is selected from: an endogenous antisense transcript that does not encode a protein (e.g., UBE3A-ATS), a mature mRNA, and a pre-mRNA, including intronic, exonic and untranslated regions. In certain embodiments, the target RNA is an antisense transcript. In certain embodiments, the target RNA is a mature mRNA. In certain embodiments, the target nucleic acid is a pre-mRNA. In certain such embodiments, the target region is entirely within an intron. In certain embodiments, the target region spans an intron/exon junction. In certain embodiments, the target region is at least 50% within an intron. In certain embodiments, the target nucleic acid is the RNA transcriptional product of a retrogene. In certain embodiments, the target nucleic acid is a non-coding RNA. In certain such embodiments, the target non-coding RNA is selected from: a long non-coding RNA, a short non-coding RNA, an intronic RNA molecule.

A. Complementarity/Mismatches to the Target Nucleic Acid

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

In certain embodiments, oligonucleotides are complementary to the target nucleic acid over the entire length of the oligonucleotide. In certain embodiments, oligonucleotides are 99%, 95%, 90%, 85%, or 80% complementary to the target nucleic acid. In certain embodiments, oligonucleotides are at least 80% complementary to the target nucleic acid over the entire length of the oligonucleotide and comprise a portion that is 100% or fully complementary to a target nucleic acid. In certain embodiments, the portion of full complementarity is 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 nucleobases in length.

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

mismatch is at position 4, 3, 2, or 1 from the 3'-end of the wing region.

B. UBE3A-ATS

In certain embodiments, oligomeric compounds comprise or consist of an oligonucleotide, or portion thereof, that is complementary to a target nucleic acid, wherein the target nucleic acid is UBE3A-ATS. In certain embodiments, UBE3A-ATS nucleic acid has the sequence set forth in SEQ ID NO: 1 (GENBANK Accession No: NC_000015.10_TRUNC_24821647_25441028), SEQ ID NO: 2915 (Ensemble Gene ID ENSG00000224078), or SEQ ID NO: 2916 (the cDNA of Ensemble transcript ENST00000554726.1).

In certain embodiments, an oligomeric compound complementary to SEQ ID NO: 1, SEQ ID NO: 2915, or SEQ ID NO: 2916 is capable of reducing UBE3A-ATS in a cell. In certain embodiments, an oligomeric compound complementary to SEQ ID NO: 1 is capable of increasing UBE3A RNA or protein in a cell. In certain embodiments, an oligomeric compound complementary to SEQ ID NO: 1, SEQ ID NO: 2915, or SEQ ID NO: 2916 is capable of increasing paternal UBE3A RNA or protein in a cell. In certain embodiments, the cell is *in vitro*. In certain embodiments, the cell is in a subject. In certain embodiments, the oligomeric compound consists of a modified oligonucleotide. In certain embodiments, an oligomeric compound complementary to SEQ ID NO: 1, SEQ ID NO: 2915, or SEQ ID NO: 2916 is capable of ameliorating one or more symptom or hallmark of a neurogenetic disorder when administered to a subject. In certain embodiments, the neurogenetic disorder is AS. In certain embodiments, the symptoms or hallmarks are selected from developmental delays, ataxia, speech impairment, sleep problems, seizures, and EEG abnormalities.

In certain embodiments, an oligomeric compound complementary to SEQ ID NO: 1, SEQ ID NO: 2915, or SEQ ID NO: 2916 is capable of reducing the detectable amount of UBE3A-ATS RNA *in vitro* by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%. In certain embodiments, an oligomeric compound complementary to SEQ ID NO: 1, SEQ ID NO: 2915, or SEQ ID NO: 2916 is capable of increasing the detectable amount of UBE3A protein *in vitro* by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%. In certain embodiments, an oligomeric compound complementary to SEQ ID NO: 1, SEQ ID NO: 2915, or SEQ ID NO: 2916 is capable of reducing the detectable amount of UBE3A-ATS RNA in the CSF of a subject by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%. In certain embodiments, an oligomeric compound complementary to SEQ ID NO: 1, SEQ ID NO: 2915, or SEQ ID NO: 2916 is capable of increasing the detectable amount of UBE3A protein in the CSF of a subject by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%.

C. Certain Target Nucleic Acids in Certain Tissues

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

VI. Certain Pharmaceutical Compositions

In certain embodiments, described herein are pharmaceutical compositions comprising one or more oligomeric compounds. In certain embodiments, the one or more oligomeric compounds each consists of a modified oligonucleotide. In certain embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable

diluent or carrier. In certain embodiments, a pharmaceutical composition comprises or consists of a sterile saline solution and one or more oligomeric compound. In certain embodiments, the sterile saline is pharmaceutical grade saline. In certain embodiments, a pharmaceutical composition comprises or consists of one or more oligomeric compound and sterile water. In certain embodiments, the sterile water is pharmaceutical grade water. In certain embodiments, a pharmaceutical composition comprises or consists of one or more oligomeric compound and phosphate-buffered saline (PBS). In certain embodiments, the sterile PBS is pharmaceutical grade PBS. In certain embodiments, a pharmaceutical composition comprises or consists of one or more oligomeric compound and artificial cerebrospinal fluid. In certain embodiments, the artificial cerebrospinal fluid is pharmaceutical grade.

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

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

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

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

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

In certain embodiments, pharmaceutical compositions comprise a delivery system. Examples of delivery systems include, but are not limited to, liposomes and emulsions. Certain delivery systems are useful for preparing

certain pharmaceutical compositions including those comprising hydrophobic compounds. In certain embodiments, certain organic solvents such as dimethylsulfoxide are used.

In certain embodiments, pharmaceutical compositions comprise one or more tissue-specific delivery molecules designed to deliver the one or more pharmaceutical agents of the present invention to specific tissues or cell types. For example, in certain embodiments, pharmaceutical compositions include liposomes coated with a tissue-specific antibody.

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

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

Under certain conditions, certain compounds disclosed herein act as acids. Although such compounds may be drawn or described in protonated (free acid) form, or ionized and in association with a cation (salt) form, aqueous solutions of such compounds exist in equilibrium among such forms. For example, a phosphate linkage of an oligonucleotide in aqueous solution exists in equilibrium among free acid, anion and salt forms. Unless otherwise indicated, compounds described herein are intended to include all such forms. Moreover, certain oligonucleotides have several such linkages, each of which is in equilibrium. Thus, oligonucleotides in solution exist in an ensemble of forms at multiple positions all at equilibrium. The term “oligonucleotide” is intended to include all such forms. Drawn structures necessarily depict a single form. Nevertheless, unless otherwise indicated, such drawings are likewise intended to include corresponding forms. Herein, a structure depicting the free acid of a compound followed by the term

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

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

Herein, certain specific doses are described. A dose may be in the form of a dosage unit. For clarity, a dose (or dosage unit) of a modified oligonucleotide or an oligomeric compound in milligrams indicates the mass of the free acid form of the modified oligonucleotide or oligomeric compound. As described above, in aqueous solution, the free acid is in equilibrium with anionic and salt forms. However, for the purpose of calculating dose, it is assumed that the modified oligonucleotide or oligomeric compound exists as a solvent-free, sodium-acetate free, anhydrous, free acid. For example, where a modified oligonucleotide or an oligomeric compound is in solution comprising sodium (e.g., saline), the modified oligonucleotide or oligomeric compound may be partially or fully de-protonated and in association with Na+ ions. However, the mass of the protons is nevertheless counted toward the weight of the dose, and the mass of the Na+ ions are not counted toward the weight of the dose. Thus, for example, a dose, or dosage unit, of 100 mg of Compound No. 1263518 equals the number of fully protonated molecules that weighs 100 mg. This would be equivalent to 106 mg of solvent-free, sodium-acetate free, anhydrous sodiated Compound No. 1263518. When an oligomeric compound comprises a conjugate group, the mass of the conjugate group is included in calculating the dose of such oligomeric compound. If the conjugate group also has an acid, the conjugate group is likewise assumed to be fully protonated for the purpose of calculating dose.

VII. Certain Compositions

1. Compound No. 1065645

In certain embodiments, Compound No. 1065645 is characterized as a 5-10-5 MOE gapmer having a sequence (from 5' to 3') of CATCATGATCTTGGTAAGGC (SEQ ID NO: 1949), wherein each of nucleosides 1-5 and 16-20 (from 5' to 3') are 2'-MOE nucleosides and each of nucleosides 6-15 are 2'-β-D-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 5 to 6, 16 to 17, and 17 to 18 are phosphodiester internucleoside linkages and the internucleoside linkages between nucleosides 1 to 2, 6 to 7, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages, and wherein each cytosine is a 5-methyl cytosine.

In certain embodiments, Compound No. 1065645 is represented by the following chemical notation: $^{m}C_{es}A_{eo}T_{eo}{}^{m}C_{eo}A_{eo}T_{ds}G_{ds}A_{ds}T_{ds}{}^{m}C_{ds}T_{ds}T_{ds}G_{ds}G_{ds}T_{ds}A_{eo}A_{eo}G_{es}G_{es}{}^{m}C_{e}$ (SEQ ID NO: 1949), wherein:

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

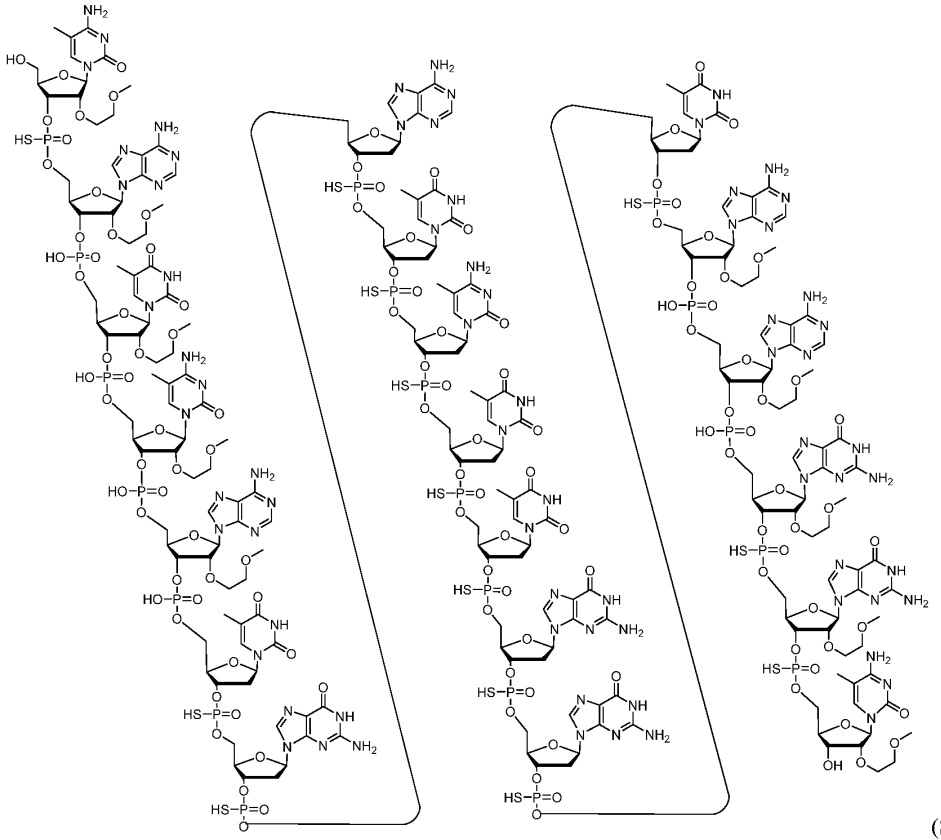
e = a 2'-MOE sugar moiety,

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

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

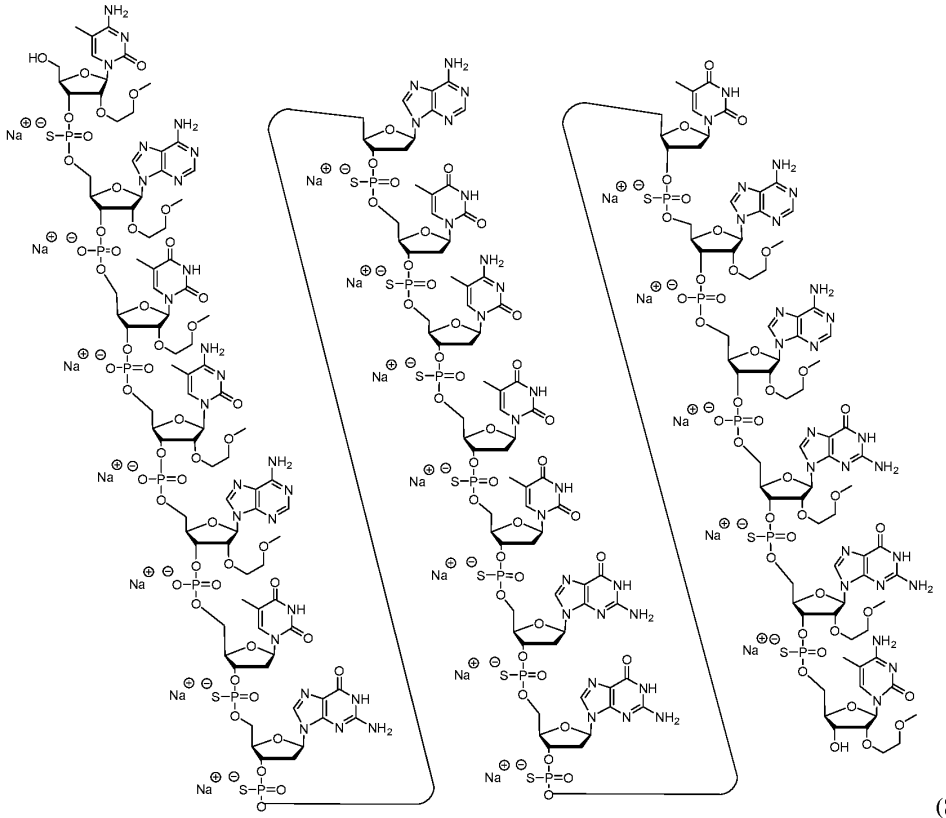
In certain embodiments, Compound No. 1065645 is represented by the following chemical structure:



(SEQ ID NO: 1949).

Structure 1. Compound No. 1065645

In certain embodiments, the sodium salt of Compound No. 1065645 is represented by the following chemical structure:



(SEQ ID NO: 1949).

Structure 2. The sodium salt of Compound No. 1065645

2. Compound No. 1263517

In certain embodiments, Compound No. 1263517 is characterized as a 6-10-4 MOE gapmer having a sequence (from 5' to 3') of TCACCATTTTGACCTTCTTA (SEQ ID NO: 2751), wherein each of nucleosides 1-6 and 17-20 (from 5' to 3') are 2'-MOE nucleosides and each of nucleosides 7-16 are 2'-β-D-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 5 to 6, 6 to 7, and 17 to 18 are phosphodiester internucleoside linkages and the internucleoside linkages between nucleosides 1 to 2, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 16 to 17, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages, and wherein each cytosine is a 5-methyl cytosine.

In certain embodiments, Compound No. 1263517 is represented by the following chemical notation: $T_{es}{}^{m}C_{eo}A_{eo}{}^{m}C_{eo}{}^{m}C_{eo}A_{eo}T_{ds}T_{ds}T_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{ds}{}^{m}C_{eo}T_{es}T_{es}A_{e}$ (SEQ ID NO: 2751), wherein:

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

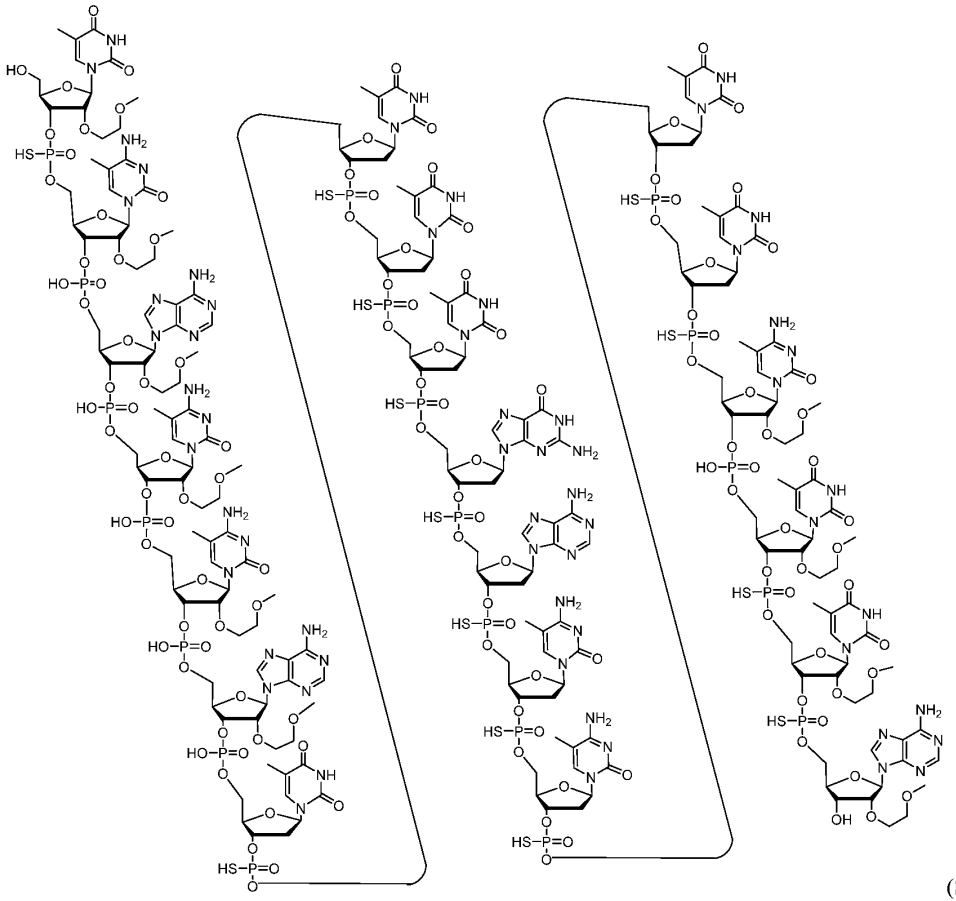
e = a 2'-MOE sugar moiety,

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

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

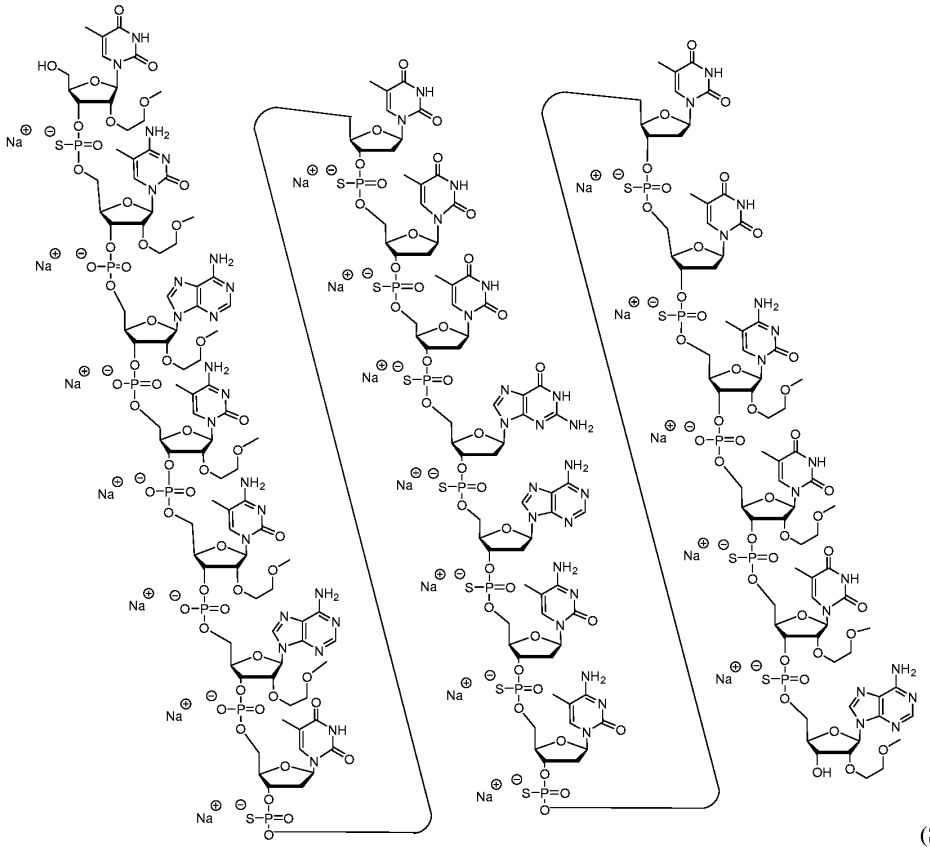
In certain embodiments, Compound No. 1263517 is represented by the following chemical structure:



(SEQ ID NO: 2751).

Structure 3. Compound No. 1263517

In certain embodiments, the sodium salt of Compound No. 1263517 is represented by the following chemical structure:



(SEQ ID NO: 2751).

Structure 4. The sodium salt of Compound No. 1263517

3. Compound No. 1263518

In certain embodiments, Compound No. 1263518 is characterized as a 6-10-4 MOE gapmer having a sequence (from 5' to 3') of TTCACCATTTTGACCTTCTT (SEQ ID NO: 2752), wherein each of nucleosides 1-6 and 17-20 (from 5' to 3') are 2'-MOE nucleosides and each of nucleosides 7-16 are 2'-β-D-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 5 to 6, 6 to 7, and 17 to 18 are phosphodiester internucleoside linkages and the internucleoside linkages between nucleosides 1 to 2, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 16 to 17, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages, and wherein each cytosine is a 5-methyl cytosine.

In certain embodiments, Compound No. 1263518 is represented by the following chemical notation: $T_{es}T_{eo}{}^{m}C_{eo}A_{eo}{}^{m}C_{eo}{}^{m}C_{eo}A_{ds}T_{ds}T_{ds}T_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{eo}{}^{m}C_{es}T_{es}T_{e}$ (SEQ ID NO: 2752), wherein:

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

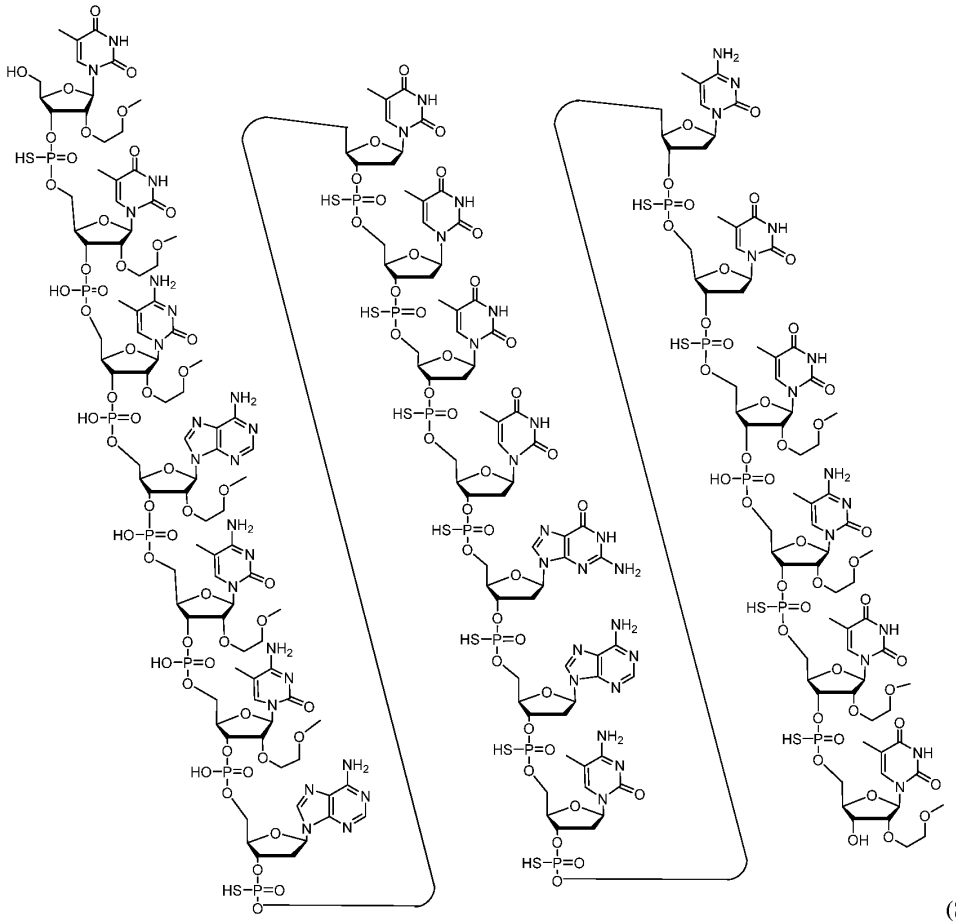
e = a 2'-MOE sugar moiety,

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

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

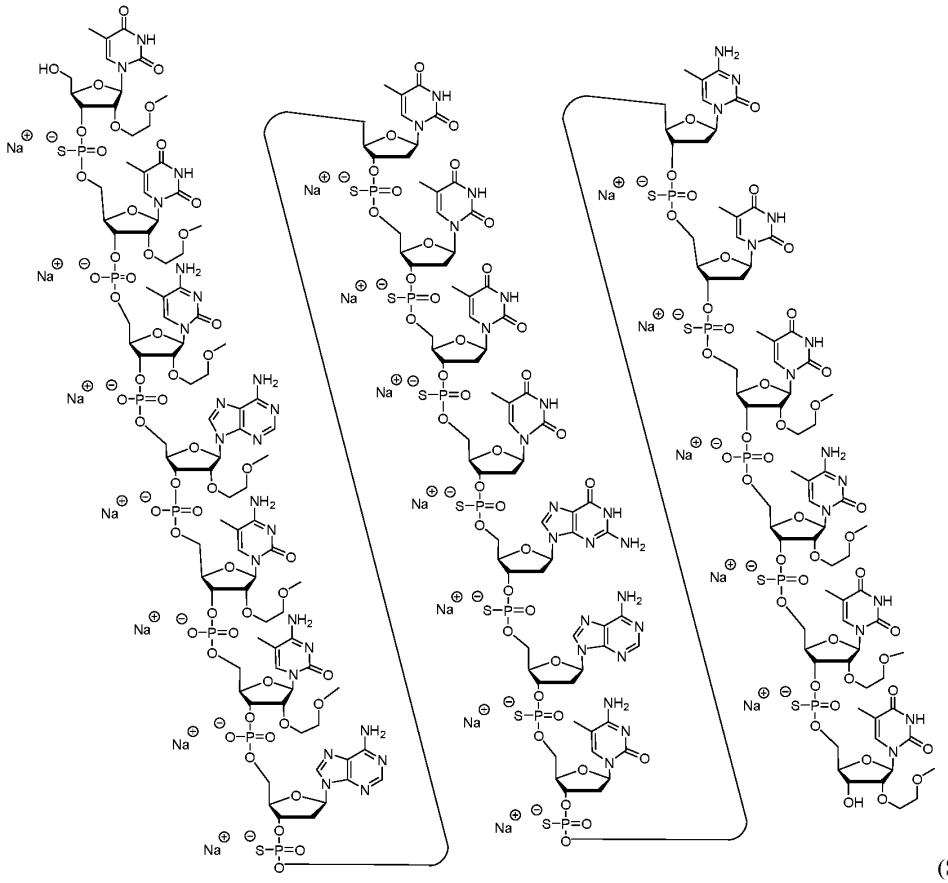
In certain embodiments, Compound No. 1263518 is represented by the following chemical structure:



(SEQ ID NO: 2752).

Structure 5. Compound No. 1263518

In certain embodiments, the sodium salt of Compound No. 1263518 is represented by the following chemical structure:



(SEQ ID NO: 2752).

Structure 6. The sodium salt of Compound No. 1263518

4. Compound No. 1263533

In certain embodiments, Compound No. 1263533 is characterized as a 6-10-4 MOE gapmer having a sequence (from 5' to 3') of GCATACCCAGGGTAGGATTC (SEQ ID NO: 765), wherein each of nucleosides 1-6 and 17-20 (from 5' to 3') are 2'-MOE nucleosides and each of nucleosides 7-16 are 2'-β-D-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 5 to 6, 6 to 7, and 17 to 18 are phosphodiester internucleoside linkages and the internucleoside linkages between nucleosides 1 to 2, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 16 to 17, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages, and wherein each cytosine is a 5-methyl cytosine.

In certain embodiments, Compound No. 1263533 is represented by the following chemical notation: $G_{es}{}^{m}C_{eo}A_{eo}T_{eo}A_{eo}{}^{m}C_{eo}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}G_{ds}G_{ds}G_{ds}T_{ds}A_{ds}G_{ds}G_{ds}A_{eo}T_{es}T_{es}{}^{m}C_{e}$ (SEQ ID NO: 765), wherein:

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

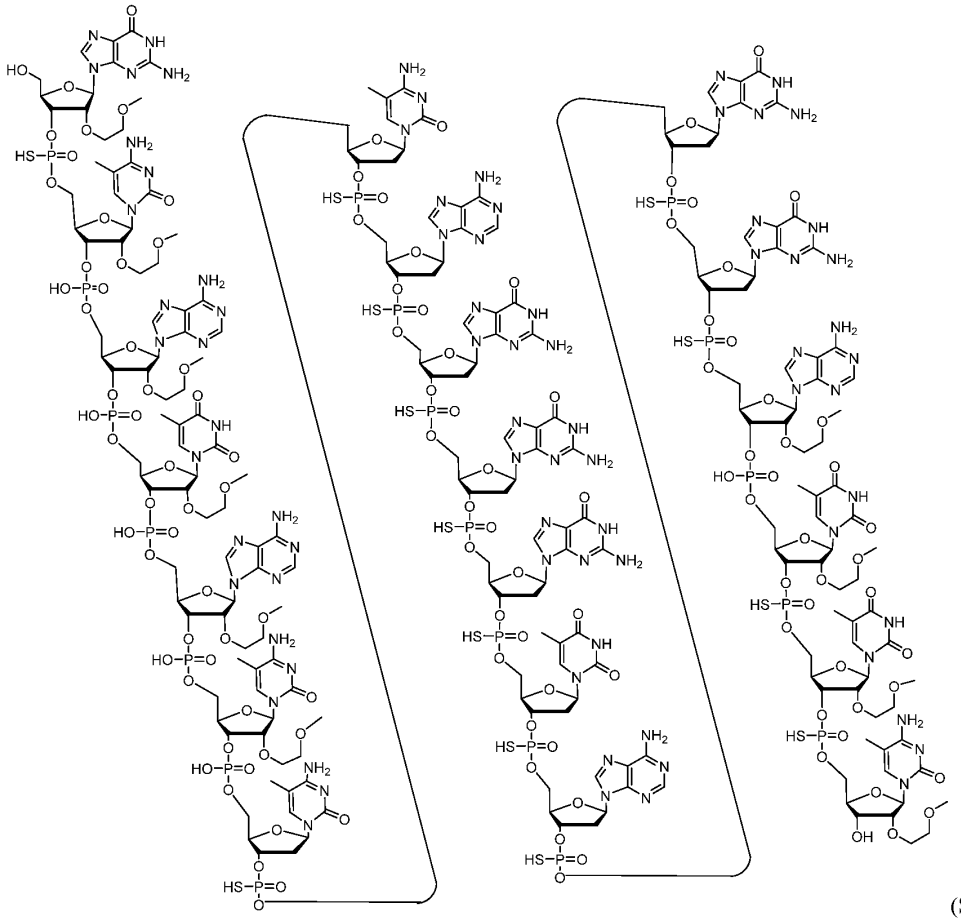
e = a 2'-MOE sugar moiety,

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

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

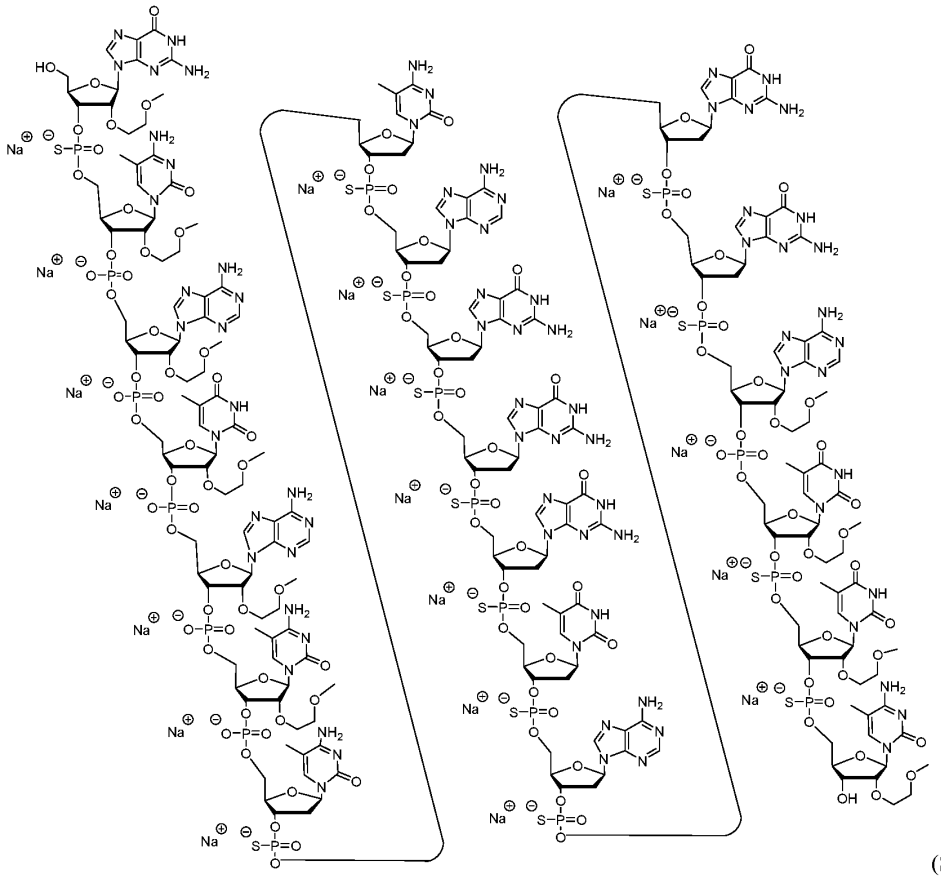
In certain embodiments, Compound No. 1263533 is represented by the following chemical structure:



(SEQ ID NO: 765).

Structure 7. Compound No. 1263533

In certain embodiments, the sodium salt of Compound No. 1263533 is represented by the chemical structure:



(SEQ ID NO: 765).

Structure 8. The sodium salt of Compound No. 1263533

5. Compound No. 1273039

In certain embodiments, Compound No. 1273039 is characterized as a 4-8-6 MOE gapmer having a sequence (from 5' to 3') of ACGCAATGTATCAGGCAA (SEQ ID NO: 2866), wherein each of nucleosides 1-4 and 13-18 (from 5' to 3') are 2'-MOE nucleosides and each of nucleosides 5-12 are 2'-β-D-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 13 to 14, 14 to 15, and 15 to 16 are phosphodiester internucleoside linkages and the internucleoside linkages between nucleosides 1 to 2, 4 to 5, 5 to 6, 6 to 7, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 16 to 17, and 17 to 18 are phosphorothioate internucleoside linkages, and wherein each cytosine is a 5-methyl cytosine.

In certain embodiments, Compound No. 1273039 is represented by the following chemical notation: $A_{es}{}^{m}C_{eo}G_{eo}{}^{m}C_{es}A_{ds}A_{ds}T_{ds}G_{ds}T_{ds}A_{ds}T_{ds}{}^{m}C_{ds}A_{eo}G_{eo}G_{eo}{}^{m}C_{es}A_{es}A_{e}$ (SEQ ID NO: 2866), wherein:

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

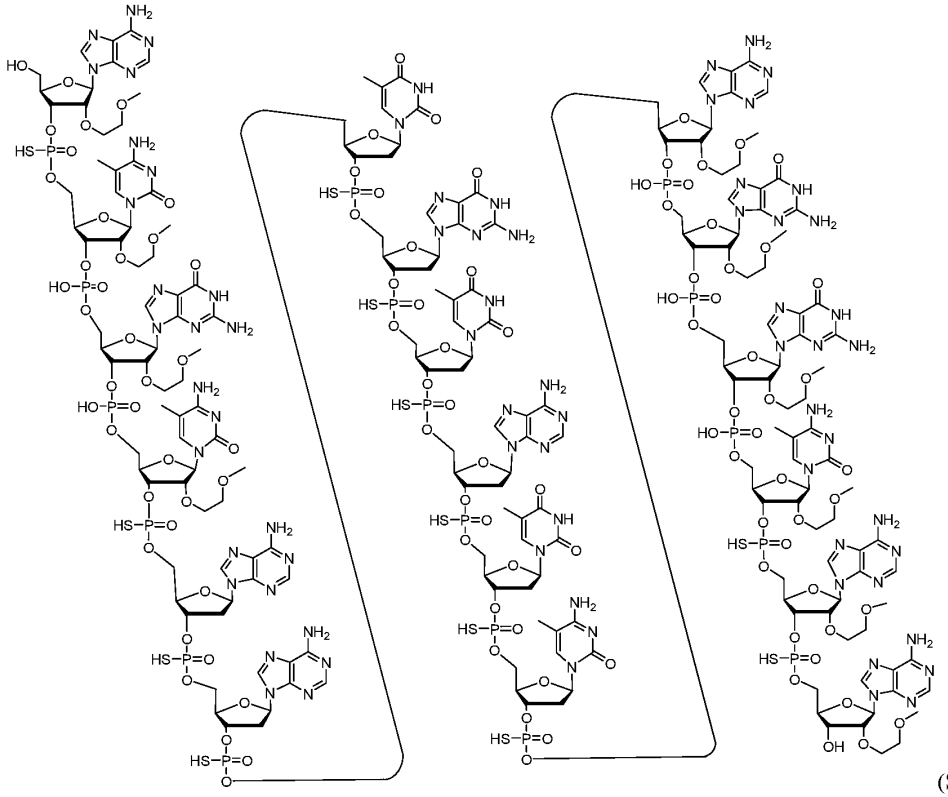
e = a 2'-MOE sugar moiety,

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

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

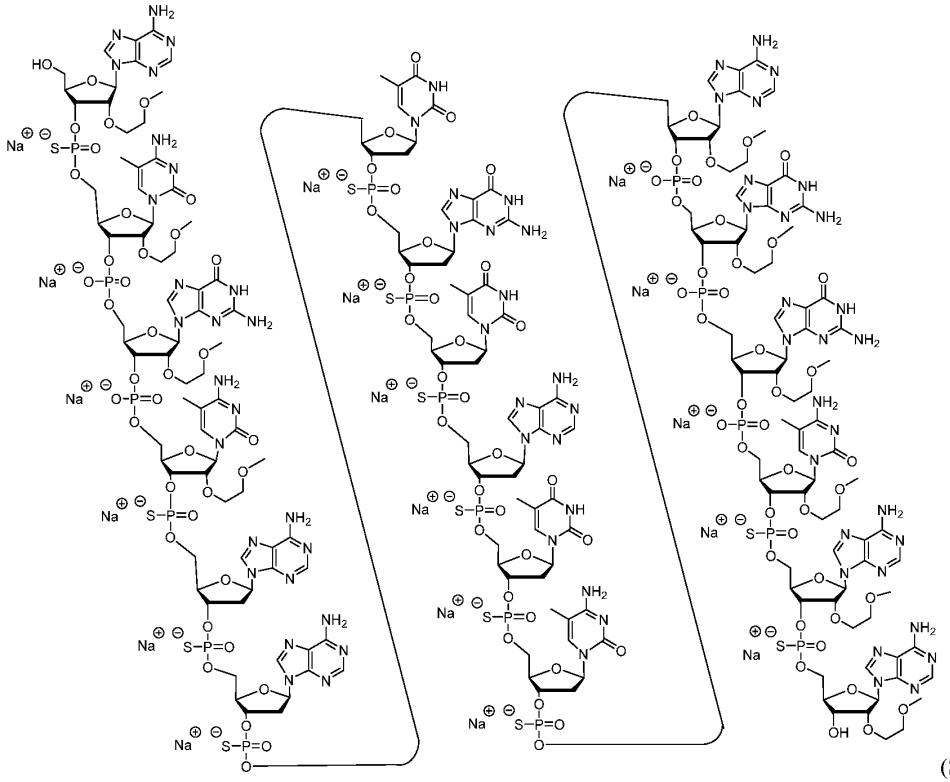
In certain embodiments, Compound No. 1273039 is represented by the following chemical structure:



(SEQ ID NO: 2866).

Structure 9. Compound No. 1273039

In certain embodiments, the sodium salt of Compound No. 1273039 is represented by the following chemical structure:



(SEQ ID NO: 2866).

Structure 10. The sodium salt of Compound No. 1273039

6. Compound No. 1273062

In certain embodiments, Compound No. 1273062 is characterized as a 5-10-5 MOE gapmer having a sequence (from 5' to 3') of ACCATTTTGACCTTCTTAGC (SEQ ID NO: 2873), wherein each of nucleosides 1-5 and 16-20 (from 5' to 3') are 2'-MOE nucleosides and each of nucleosides 6-15 are 2'-β-D-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 5 to 6, 16 to 17, and 17 to 18 are phosphodiester internucleoside linkages and the internucleoside linkages between nucleosides 1 to 2, 6 to 7, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages, and wherein each cytosine is a 5-methyl cytosine.

In certain embodiments, Compound No. 1273062 is represented by the following chemical notation: $A_{es}{}^{m}C_{eo}{}^{m}C_{eo}A_{eo}T_{eo}T_{ds}T_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{ds}{}^{m}C_{ds}T_{eo}T_{eo}A_{es}G_{es}{}^{m}C_{e}$ (SEQ ID NO: 2873), wherein:

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

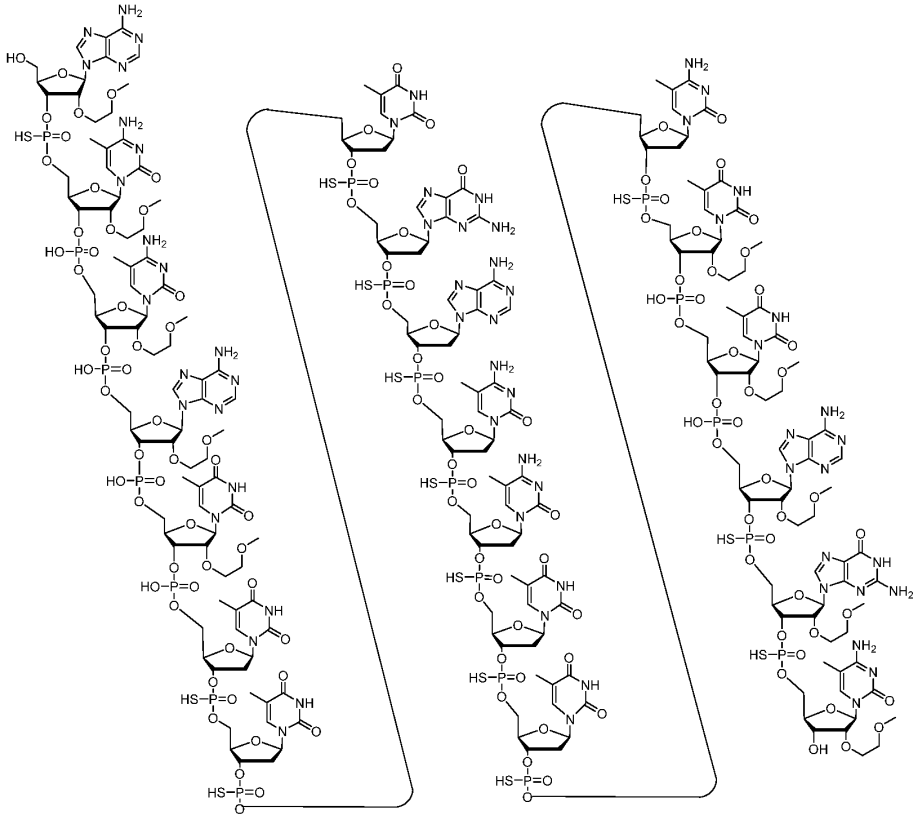
e = a 2'-MOE sugar moiety,

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

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

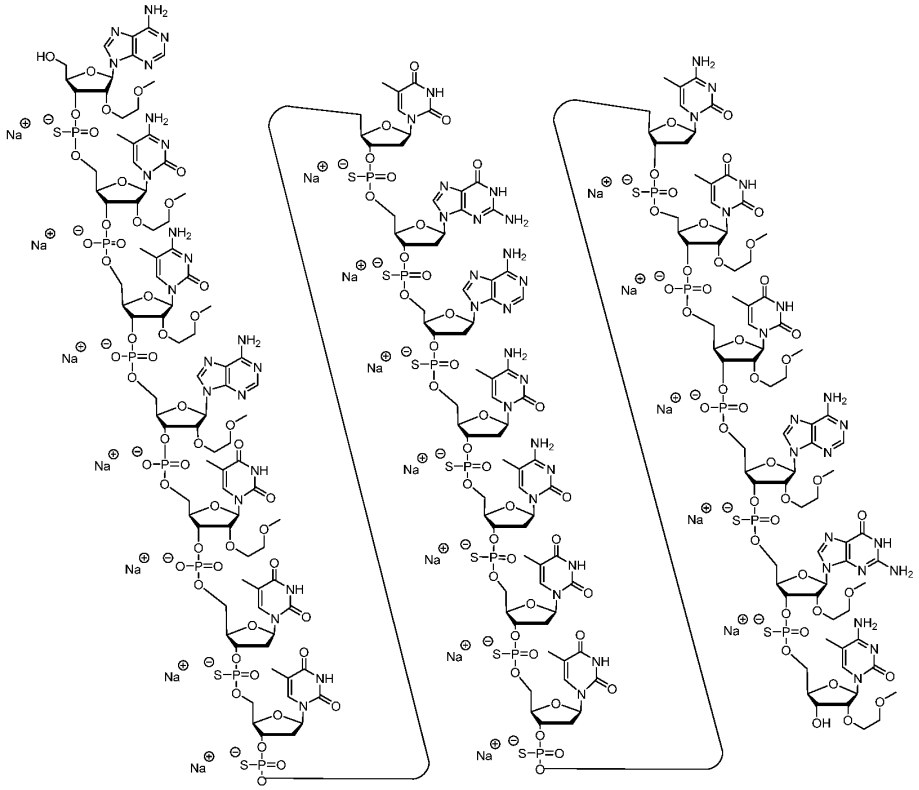
In certain embodiments, Compound No. 1273062 is represented by the following chemical structure:



(SEQ ID NO: 2873).

Structure 11. Compound No. 1273062

In certain embodiments, the sodium salt of Compound No. 1273062 is represented by the following chemical structure:



(SEQ ID NO: 2873).

Structure 12. The sodium salt of Compound No. 1273062

VIII. Certain Comparator Compounds

In certain embodiments, Compound No. 1219022, a surrogate of which (Compound #586_9) is provided in WO2017/081223 (incorporated herein by reference), was used as a comparator compound. Compound No. 1219022 is a mixed LNA/DNA oligonucleotide having a sugar motif of (from 5' to 3') llddldlddddddddddllll, wherein each "l" represents an LNA sugar moiety and each "d" represents a 2'-β-D-deoxyribosyl sugar moiety; having a sequence of (from 5' to 3') AAATTATTTATACACCATCA (SEQ ID NO: 2905), wherein each "C" is a 5-methyl cytosine; and wherein each internucleoside linkage is a phosphorothioate internucleoside linkage. Compound #586_9 has cytosines at positions 13, 15, and 16 whereas Compound No. 1219022 5-methyl cytosines at those positions. According to Wan and Seth, "[i]ntroduction of the 5-methyl group on cytosine reduces the immunostimulatory profile of certain DNA oligonucleotides and also enhances nuclease stability" (J. Med. Chem. 2016, 59, 9645-9667).

In certain embodiments, Compound No. 1219023, a surrogate of which (Compound #572_7) is provided in WO2017/081223 (incorporated herein by reference), was used as a comparator compound. Compound No. 1219023 is a mixed LNA/DNA oligonucleotide having a sugar motif of (from 5' to 3') lllddlddddddddddlll, wherein each "l" represents an LNA sugar moiety and each "d" represents a 2'-ß-D-deoxyribosyl sugar moiety; having a sequence of (from 5' to 3') TTTATCAATATCTTCTCA (SEQ ID NO: 2906), wherein each "C" is a 5-methyl cytosine; and wherein each internucleoside linkage is a phosphorothioate internucleoside linkage. Compound #572_7 has cytosines at

positions 12 and 15 whereas Compound No. 1219023 has 5-methyl cytosines at those positions.

In certain embodiments, Compound No. 1219024, a surrogate of which (Compound #591_1) is provided in WO2017/081223 (incorporated herein by reference), was used as a comparator compound. Compound No. 1219024 is a mixed LNA/DNA oligonucleotide having a sugar motif of (from 5' to 3') ldldlddddddddddddll, wherein each "l" represents an LNA sugar moiety and each "d" represents a 2'-ß-D-deoxyribosyl sugar moiety; having a sequence of (from 5' to 3') GCACATTCTTTCTATACCT (SEQ ID NO: 2907), wherein each "C" is a 5-methyl cytosine; and wherein each internucleoside linkage is a phosphorothioate internucleoside linkage. Compound #591_1 has cytosines at positions 2, 4, 8, 12 and 17 whereas Compound No. 1219024 has 5-methyl cytosines at those positions.

In certain embodiments, Compound No. 1219025, a surrogate of which (Compound #169_52) is provided in WO2017/081223 (incorporated herein by reference), was used as a comparator compound. Compound No. 1219025 is a mixed LNA/DNA oligonucleotide having a sugar motif of (from 5' to 3') lldlldddddddddddll, wherein each "l" represents an LNA sugar moiety and each "d" represents a 2'-ß-D-deoxyribosyl sugar moiety; having a sequence of (from 5' to 3') TTATAGCCATTCTATCT (SEQ ID NO: 2908), wherein each "C" is a 5-methyl cytosine; and wherein each internucleoside linkage is a phosphorothioate internucleoside linkage. Compound #169_52 has cytosines at positions 7, 8, and 12 whereas Compound No. 1219025 has 5-methyl cytosines at those positions.

In certain embodiments, Compound No. 1219026, a surrogate of which (Compound #624_5) is provided in WO2017/081223 (incorporated herein by reference), was used as a comparator compound. Compound No. 1219026 is a mixed LNA/DNA oligonucleotide having a sugar motif of (from 5' to 3') ldlllddddddddllll, wherein each "l" represents an LNA sugar moiety and each "d" represents a 2'-ß-D-deoxyribosyl sugar moiety; having a sequence of (from 5' to 3') CTCAAAGATCATTCTCA (SEQ ID NO: 2909), wherein each "C" is a 5-methyl cytosine; and wherein each internucleoside linkage is a phosphorothioate internucleoside linkage. Compound # 624_5 has a cytosine at position 10 whereas Compound No. 1219026 has a 5-methyl cytosine at that position.

In certain embodiments, Compound No. 1219027, a surrogate of which (Compound #626_8) is provided in WO2017/081223 (incorporated herein by reference), was used as a comparator compound. Compound No. 1219027 is a mixed LNA/DNA oligonucleotide having a sugar motif of (from 5' to 3') ldldldlddddddddddldll, wherein each "l" represents an LNA sugar moiety and each "d" represents a 2'-ß-D-deoxyribosyl sugar moiety; having a sequence of (from 5' to 3') TTACACTTAATTATACTTCC (SEQ ID NO: 2910), wherein each "C" is a 5-methyl cytosine; and wherein each internucleoside linkage is a phosphorothioate internucleoside linkage. Compound #626_8 has cytosines at positions 4, 6, and 16 whereas Compound No. 1219027 has 5-methyl cytosines at those positions.

In certain embodiments, Compound No. 1219028, a surrogate of which (Compound #639_5) is provided in WO2017/081223 (incorporated herein by reference), was used as a comparator compound. Compound No. 1219028 is a mixed LNA/DNA oligonucleotide having a sugar motif of (from 5' to 3') lddddddddddddlldlll, wherein each "l" represents an LNA sugar moiety and each "d" represents a 2'-ß-D-deoxyribosyl sugar moiety; having a sequence of (from 5' to 3') GTTTCCATCTACTATTAA (SEQ ID NO: 2911), wherein each "C" is a 5-methyl cytosine; and wherein each internucleoside linkage is a phosphorothioate internucleoside linkage. Compound #639_5 has cytosines at positions 5, 6, 9 and 12 whereas Compound No. 1219028 has 5-methyl cytosines at those positions.

In certain embodiments, Compound No. 1219029, a surrogate of which (Compound #642_12) is provided in WO2017/081223 (incorporated herein by reference), was used as a comparator compound. Compound No. 1219029 is a

mixed LNA/DNA oligonucleotide having a sugar motif of (from 5' to 3') llddlddddddddddll, wherein each "l" represents an LNA sugar moiety and each "d" represents a 2'-ß-D-deoxyribosyl sugar moiety; having a sequence of (from 5' to 3') CTGTATACACCATCCCA (SEQ ID NO: 2912), wherein each "C" is a 5-methyl cytosine; and wherein each internucleoside linkage is a phosphorothioate internucleoside linkage. Compound #642_12 has cytosines at positions 8, 10, 11, 14 and 15 whereas Compound No. 1219029 has 5-methyl cytosines at those positions.

In certain embodiments, Compound No. 1219030, a surrogate of which (Compound #304_6) is provided in WO2017/081223 (incorporated herein by reference), was used as a comparator compound. Compound No. 1219030 is a mixed LNA/DNA oligonucleotide having a sugar motif of (from 5' to 3') lddlllddddddddllll, wherein each "l" represents an LNA sugar moiety and each "d" represents a 2'-ß-D-deoxyribosyl sugar moiety, having a sequence of (from 5' to 3') AGTTCTACTATACTTTC (SEQ ID NO: 2913), wherein each "C" is a 5-methyl cytosine; and wherein each internucleoside linkage is a phosphorothioate internucleoside linkage. Compound #304_6 has cytosines at positions 8 and 13 whereas Compound No. 1219030 has 5-methyl cytosines at those positions.

In certain embodiments, Compound No. 1219031, a surrogate of which (Compound #573_8) is provided in WO2017/081223 (incorporated herein by reference), was used as a comparator compound. Compound No. 1219031 is a mixed LNA/DNA oligonucleotide having a sugar motif of (from 5' to 3') llddldlddddddddddddll, wherein each "l" represents an LNA sugar moiety and each "d" represents a 2'-ß-D-deoxyribosyl sugar moiety; having a sequence of (from 5' to 3') TATACCTTTCTTTAACCCTT (SEQ ID NO: 2914), wherein each "C" is a 5-methyl cytosine; and wherein each internucleoside linkage is a phosphorothioate internucleoside linkage. Compound #573_8 has cytosines at positions 6, 10, 16, 17, and 18 whereas Compound No. 1219031 has cytosines at those positions.

Compound Nos. 1219022-1219031 (relating to Compound Nos. #586_9, #572_7, #591_1, #169_52, #624_5, #626_8, #639_5 #642_12, #304_6, #573_8, respectively) were selected as comparator compounds from Example 7 of WO2017/081223, which provides a subset of active compounds "selected for potency and efficacy testing."

In certain embodiments, compounds described herein are superior relative to compounds described in WO2017/081223 because they demonstrate one or more improved properties, such as *in vivo* tolerability.

For example, as described herein, certain compounds Compound No. 1263517, Compound No. 1263518, Compound No. 1263533, Compound No. 1273039, and Compound No. 1273062 achieved 3-hour FOB scores in mice of 1.0 (Table 88), 0.0 (Table 88), 1.0 (Table 88), 1.0 (Table 96), and 0.0 (Table 96), respectively, whereas each of comparator compounds Compound No. 1219022, Compound No. 1219024, Compound No. 1219025, Compound No. 1219028, Compound No. 1219029, Compound No. 1219030, and Compound No. 1219031 achieved 3-hour FOB scores in mice of 7.0, 5.3, 4.0, 6.0, 6.3, 5.0, and 5.3 (Table 119), respectively. Therefore, certain compounds described herein are more tolerable than comparator compounds Compound No. 1219022, Compound No. 1219024, Compound No. 1219025, Compound No. 1219028, Compound No. 1219029, Compound No. 1219030, and Compound No. 1219031 in this assay.

For example, as described herein, certain compounds Compound No. 1065645, Compound No. 1263517, Compound No. 1263518, Compound No. 1263533, Compound No. 1273039, and Compound No. 1273062 each achieved 2-week FOB scores in mice of 0.0 (Example 12, Table 112), whereas Compound No. 1219023, Compound No. 1219024, Compound No. 1219025, Compound No. 1219026, Compound No. 1219028, Compound No. 1219029, Compound No. 1219030, and Compound No. 1219031 achieved 2-week delayed FOB scores in mice of 3.5, 6.5, 6.0, 6.0, 6.0, 6.0, 6.0, 5.0, and 6.0, respectively (Table 119). Therefore, certain compounds described herein are more

tolerable than comparator compounds Compound No. 1219023 and Compound No. 1219026 in this assay.

For example, as described herein, certain compounds Compound No. 1065645, Compound No. 1263517, Compound No. 1263518, Compound No. 1263533, Compound No. 1273039, and Compound No. 1273062 do not cause a significant difference in body weight as compared to PBS-treated rats in an 8-week study, whereas treatment with Compound No. 1219027 leads to a greater than 10% weight loss compared to PBS-treated rats (p-value <0.05, Table 120). Therefore, certain compounds described herein are more tolerable than comparator Compound No. 1219027 in this assay.

IX. Certain Hotspot Regions

In certain embodiments, nucleobases in the ranges specified below comprise a hotspot region of UBE3A-ATS. In certain embodiments, modified oligonucleotides that are complementary to a hotspot region of UBE3A-ATS achieve an average of more than 50% reduction of UBE3A-ATS RNA *in vitro* in the standard cell assay.

1. Nucleobases 461,413-461,487 of SEQ ID NO: 1

In certain embodiments, nucleobases 461,413-461,487 of SEQ ID NO: 1 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to a portion of nucleobases 461,413-461,487 of SEQ ID NO: 1. In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are 18 nucleobases in length. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, the gapmers are MOE gapmers. In certain embodiments, the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages. In certain embodiments, the phosphodiester ("o") and phosphorothioate ("s") internucleoside linkages are arranged in order from 5' to 3': soooossssssssssooss, soooooossssssssssoss, soooossssssssssoss, sooossssssssssooss, sooossssssssssoooss, or soossssssssssooss.

The nucleobase sequences of SEQ ID Nos: 1053, 1329, 1501, 1576, 1873, 1949, 2025, 2096, 2245, 2512,2591,2680-2682, and 2844 are complementary to a portion of nucleobases 461,413-461,487 of SEQ ID NO: 1.

The nucleobase sequenc of Compound Nos: 749901-749904, 1065641-1065646, 1165562-1165563, 1165857-1165858, and 1273001 are complementary to a portion of nucleobases 461,413-461,487 of SEQ ID NO: 1.

In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 461,413-461,487 of SEQ ID NO: 1 achieve at least 36% reduction of UBE3A-ATS RNA *in vitro* in the standard cell assay. In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 461,413-461,487 of SEQ ID NO: 1 achieve an average of 60% reduction of UBE3A-ATS RNA *in vitro* in the standard cell assay.

2. Nucleobases 468,968-469,013 of SEQ ID NO: 1

In certain embodiments, nucleobases 468,968-469,013 of SEQ ID NO: 1 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to a portion of nucleobases 468,968-469,013 of SEQ ID NO: 1. In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are 18 nucleobases in length. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, the gapmers are MOE gapmers. In certain embodiments, the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages. In certain embodiments, the phosphodiester ("o") and phosphorothioate ("s") internucleoside linkages are arranged in order from 5' to 3': soooossssssssssooss, soooooossssssssssoss, soooossssssssssoss, sooossssssssssooss, sooossssssssssoooss, or

soossssssssoooss.

The nucleobase sequences of SEQ ID Nos: 376, 377, 2751-2756, 2773-2776, 2872, 2873, 2876-2878 are complementary to a portion of nucleobases 468,968-469,013 of SEQ ID NO: 1.

The nucleobase sequence of Compound Nos: 750031-750032, 1263408-1263411, 1263426, 1263441, 1263460-1263465, 1263486-1263492, 1263517-1263523, 1273061, 1273062, and 1273065-1273067 are complementary to a portion of nucleobases 468,968-469,013 of SEQ ID NO: 1.

In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 468,968-469,013 of SEQ ID NO: 1 achieve at least 75% reduction of UBE3A-ATS RNA *in vitro* in the standard cell assay. In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 468,968-469,013 of SEQ ID NO: 1 achieve an average of 78% reduction of UBE3A-ATS RNA *in vitro* in the standard cell assay. In certain embodiments, modified oligonculeotides complementary to a portion of nucleobases 468,968-469,013 of SEQ ID NO: 1 achieve an average of 410% upregulation of UBE3A-ATS RNA in vitro at 6.7 μM in cell culture.

3. Nucleobases 483,965-484,003 of SEQ ID NO: 1

In certain embodiments, nucleobases 483,965-484,003 of SEQ ID NO: 1 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to a portion of 483,965-484,003 of SEQ ID NO: 1. In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are 18 nucleobases in length. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, the gapmers are MOE gapmers. In certain embodiments, the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages. In certain embodiments, the phosphodiester ("o") and phosphorothioate ("s") internucleoside linkages are arranged in order from 5' to 3': soooossssssssssooss, sooooossssssssssoss, soooossssssssssoss, sooossssssssssooss, sooossssssssssoooss, or soossssssssssooss.

The nucleobase sequences of SEQ ID Nos: 172, 764-770, 995, 1445, 1668, 1743, 2255, 2595, 2762-2767 are complementary to a portion of nucleobases 483,965-484,003 of SEQ ID NO: 1.

The nucleobase sequence of Compound Nos: 617557, 699781, 750138-750144, 1065918-1065921, 1165621, 1165878, and 1263532-1263557 are complementary to a portion of nucleobases 483,965-484,003 of SEQ ID NO: 1.

In certain embodiments, modified oligonucleotides complementary to a portion of nucleobases 483,965-484,003 of SEQ ID NO: 1 achieve at least 24% reduction of UBE3A-ATS RNA *in vitro* in the standard cell assay. In certain embodiments, modified oligonucleotides complementary to nucleobases 483,965-484,003 of SEQ ID NO: 1 achieve an average of 65% reduction of UBE3A-ATS RNA *in vitro* in the standard cell assay. In certain embodiments, modified oligonculeotides complementary to a portion of nucleobases 468,968-469,013 of SEQ ID NO: 1 achieve an average of 330% upregulation of UBE3A-ATS RNA in vitro at 6.7 μM in cell culture.

4. **Additional Hotspot Regions**

In certain embodiments, the ranges described in the Table below comprise hotspot regions. Each hotspot region begins with the nucleobase of SEQ ID NO: 1 identified in the "Start Site SEQ ID NO: 1" column and ends with the nucleobase of SEQ ID NO: 1 identified in the "Stop Site SEQ ID NO: 1" column. In certain embodiments, modified oligonucleotides are complementary within any of the hotspot regions 1-61, as defined in the table below. In certain embodiments, modified oligonucleotides are 18 nucleobases in length. In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are gapmers. In

certain embodiments, modified oligonucleotides are 4-8-6, 6-8-4, 5-8-5, 4-10-6, 6-10-4, or 5-10-5 MOE gapmers.

The nucleobase sequence of compounds listed in the "Compound ID in range" column in the table below are complementary to SEQ ID NO: 1 within the specified hotspot region. The nucleobase sequence of the oligonucleotides listed in the "SEQ ID NO: in range" column in the table below are complementary to the target sequence, SEQ ID NO: 1, within the specified hotspot region.

In certain embodiments, modified oligonucleotides complementary to nucleobases within the hotspot region achieve at least "Min.% Red." (minimum % reduction, relative to untreated control cells) of UBE3A-ATS RNA *in vitro* in the standard cell assay, as indicated in the table below. In certain embodiments, modified oligonucleotides complementary to nucleobases within the hotspot region achieve an average of "Avg.% Red." (average % reduction, relative to untreated control cells) of UBE3A-ATS RNA *in vitro* in the standard cell assay, as indicated in the table below. In certain embodiments, modified oligonucleotides complementary to nucleobases within the hotspot region achieve a maximum of "Max. % Red." (maximum % reduction, relative to untreated control cells) of UBE3A-ATS RNA *in vitro* in the standard cell assay, as indicated in the table below.

Table 1

UBE3A-ATS Hotspots

Hot-spot ID	Start Site SEQ ID NO: 1	Stop Site SEQ ID NO: 1	Min. % Red.	Max. % Red.	Avg. % Red.	Compound ID in range	SEQ ID NO: in range
1	461413	461487	36	89	60	749901-749904, 1065641-1065646, 1165562-1165563, 1165857-1165858, 1273001	1053, 1329, 1501, 1576, 1873, 1949, 2025, 2096, 2245, 2512, 2591, 2680-2682, 2844
2	468968	469013	75	81	78	750031-750032, 1263408-1263411, 1263426, 1263441, 1263460-1263465, 1263486-1263492, 1263517-1263523, 1273061, 1273062, 1273065-1273067	376, 377, 2751-2756, 2773-2776, 2872, 2873, 2876-2878
3	483965	484003	24	91	65	617557, 699781, 750138-750144, 1065918-1065921, 1165621, 1165878, 1263532-1263557	172, 764-770, 995, 1445, 1668, 1743, 2255, 2595, 2762-2767
4	349103#	349150#	35	82	56	750519-750533	181-195
5	457354	457405	37	85	66	749848, 1065574-1065576, 1165519-1165521, 1179839-1179840	552, 973, 1273, 1795, 2162, 2237, 2370, 2537, 2671
6	457899	457936	49	77	59	749852, 1065581-1065582	556, 1497, 1945
7	457969	458013	36	78	61	749853, 1065583-1065586, 1165523-1165525	557, 1124, 1199, 1647, 2021, 2089, 2464, 2538
8	458523	458558	64	77	71	749861-749862, 1065595	565, 566, 1050
9	458560	458627	45	81	64	749863-749867, 1065596-1065600, 1272999	567-571, 1125, 1498, 1573, 1946, 2022, 2842

10	458935	458976	30	85	60	1065602-1065605, 1165530-1165540, 1165853	901, 1425, 1648, 1724, 2091, 2092, 2164, 2165, 2239, 2240, 2392-2393, 2465, 2511, 2539, 2540
11	460105	460137	43	82	60	749882, 1065615-1065619, 1165547-1165549	586, 1126, 1201, 1649, 1725, 2023, 2093, 2467, 2542
12	460348	460381	36	77	58	1065621-1065622, 1165550-1165551	902, 976, 2167, 2242
13	460641	460686	50	67	57	617531, 1065629-1065631	107, 1500, 1948, 2024
14	460974	461021	75	91	82	749893-749894, 1165855, 1263451-1263455, 1263473-1263478, 1263504-1263509	597, 598, 2219, 2745-2749
15	461597	461627	50	85	68	1065651-1065655	904, 978, 1278, 1428, 1800
16	463502	463531	60	71	66	749931, 1065674-1065675	1503, 1578, 2708
17	463826	463872	50	71	62	749938, 749939, 1065680	1728, 2714, 2715
18	464377	464428	32	77	58	749951, 1065684-1065687, 1165572-1165577, 1273006-1273008	1280, 1356, 1802, 1876, 2097, 2172, 2247, 2398, 2471, 2546, 2727, 2849-2851
19	464522	464575	47	77	62	749952-749954, 1065690, 1165578, 1263412-1263416, 1263427-1263431, 1263442-1263446, 1263466-1263469, 1263494-1263499, 1263524-1263530, 1273068-1273070	1504, 2098, 2728-2730, 2757-2760, 2777-2781, 2879-2881
20	464994	465032	27	76	52	617457, 749957-749964, 1065698-1065702, 1165866	33, 907, 981, 1281, 1357, 1877, 2136, 2733-2739
21	465231	465266	23	83	63	749969, 1065706-1065713, 1165583-1165587, 1263403-1263407, 1263421-1263425, 1263436-1263440, 1263456, 1263479-1263485, 1263510-1263516, 1273063, 1273064	318, 908, 1132, 1207, 1432, 1655, 1730, 1953, 2028, 2174, 2248, 2400, 2473, 2548, 2750, 2768-2772, 2875
22	465372	465413	33	73	54	749972, 1065717-1065719, 1165588-1165592, 1165867-1165869	321, 1058, 1358, 1878, 2099, 2137, 2175, 2249, 2401, 2475, 2514, 2593
23	465600	465631	65	68	67	749975, 1065727-1065728, 1272944-1272947	324, 1433, 1731, 2787-2790
24	466244	466282	38	68	54	1065742-1065744, 1165595-1165598	1434, 1657, 1732, 2176, 2251, 2403, 2549
25	466529	466570	31	80	57	617460, 749989-749998, 1065760-1065762	36, 338-346, 911, 985, 1435

26	466979	467014	51	75	65	617461, 750000-750005, 1065764	37, 347-351, 1806
27	467043	467095	44	93	69	617539, 750006, 1065765-1065767, 1272943, 1272960, 1273005	115, 352, 1061, 1361, 1881, 2786, 2803, 2848
28	468335	468372	42	68	56	1065781-1065783, 1165609, 1165875	1062, 1362, 1882, 2139, 2405
29	475827	475877	39	71	57	617470, 1065830-1065834	46, 1065, 1365, 1513, 1588, 1961
30	482148	482181	49	70	68	750122, 1065889-1065890, 1165612	748, 919, 993, 2406
31	487589	487629	73	79	76	750172, 1065953-1065955, 1272973, 1272974	798, 997, 1297, 1818, 2816, 2817
32	487772	487826	44	73	62	750175-750177, 1065957	801-803, 1373
33	489873	489927	52	73	59	750195-750196, 1065989	398, 399, 1375
34	493831	493860	44	63	56	750202-750204	405-407
35	499081	499119	47	70	55	1066036-1066038	1078, 1378, 1898
36	500605	500658	36	66	58	750265-750266, 1066064-1066065	683, 684, 929, 1004
37	500846	500905	30	86	55	750269-750270, 1066073-1066077, 1165670	687-688, 1155, 1230, 1678, 1976, 2051, 2562
38	501335	501375	42	67	56	1066091-1066094, 1272975-1272977	1156, 1231, 1679, 1753, 2818-2820
39	502125	502157	65	79	72	750291, 1066119-1066121	708, 1531, 1606, 1979
40	502194	502228	51	88	65	750292, 1066124-1066125	709, 1233, 1681
41	502416	502452	49	59	54	1066130-1066132	1308, 1829, 1904
42	502580	502618	57	59	58	750295, 1066140-1066142	712, 1234, 1682, 1756
43	503427	503461	36	73	61	750301, 1066185, 1165724	718, 1983, 2197
44	503636	503675	55	72	62	750307-750308, 1066190	724, 725, 1759
45	503973	504034	20	81	56	617503-617505, 617581-617582, 750313-750324, 750383, 1066202	79-81, 155-157, 302, 731-736, 2059
46	504088	504122	45	85	65	750325-750327, 1066206	245, 246, 737, 1760
47	504431	504460	49	70	57	1066218-1066219, 1165736-1165740	1164, 2060, 2119, 2276, 2427, 2495, 2574
48	506031	506071	33	66	52	750356, 750357, 1066274-1066276	275, 276, 1317, 1838, 1913
49	508739	508780	20	83	56	617503-617504, 617580-617582, 750313-750323, 750383, 1066202	79, 80, 155-157, 302, 730-735, 2059
50	509208	509271	46	68	63	750394-750395, 1066377-1066378	313-314, 1995, 2070
51	510203	510247	36	77	60	750400-750401, 1066394-1066395, 1165828	810, 811, 1175, 2071, 2440
52	510832	510872	44	70	55	1066418-1066421	1326, 1402, 1847, 1922
53	513442	513486	66	81	72	750436-750439	846-849

#The oligonucleotides described in this section are complementary to this hotspot region at multiple sites. These sites are described in detail in Table 4b herein below (Example 1).

Nonlimiting disclosure and incorporation by reference

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

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

Although the sequence listing accompanying this filing identifies each sequence as either "RNA" or "DNA" as required, in reality, those sequences may be modified with any combination of chemical modifications. One of skill in the art will readily appreciate that such designation as "RNA" or "DNA" to describe modified oligonucleotides is, in certain instances, arbitrary. For example, an oligonucleotide comprising a nucleoside comprising a 2'-OH sugar moiety and a thymine base could be described as a DNA having a modified sugar (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^{m}CGAUCG," wherein ^{m}C indicates a cytosine base comprising a methyl group at the 5-position.

Certain compounds described herein (e.g., modified oligonucleotides) have one or more asymmetric center and thus give rise to enantiomers, diastereomers, and other stereoisomeric configurations that may be defined, in terms of absolute stereochemistry, as (*R*) or (*S*), as α or β such as for sugar anomers, or as (D) or (L), such as for amino acids, etc. Compounds provided herein that are drawn or described as having certain stereoisomeric configurations include only the indicated compounds. Compounds provided herein that are drawn or described with undefined stereochemistry include all such possible isomers, including their stereorandom and optically pure forms, unless specified otherwise. Likewise, tautomeric forms of the compounds herein are also included unless otherwise indicated. Unless otherwise indicated, compounds described herein are intended to include corresponding salt forms.

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

EXAMPLES

The following examples illustrate certain embodiments of the present disclosure and are not limiting.

Moreover, where specific embodiments are provided, the inventors have contemplated generic application of those specific embodiments. For example, disclosure of an oligonucleotide having a particular motif provides reasonable support for additional oligonucleotides having the same or similar motif. And, for example, where a particular high-affinity modification appears at a particular position, other high-affinity modifications at the same position are considered suitable, unless otherwise indicated.

Example 1: Effect of 5-10-5 MOE gapmer modified oligonucleotides on human UBE3A-ATS RNA *in vitro*, single dose

Modified oligonucleotides complementary to human UBE3A-ATS nucleic acid were tested for their effect on UBE3A-ATS RNA levels *in vitro*.

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

Each internucleoside linkage of Compound IDs 617441-617596 (in Tables 2 and 3) is a phosphorothioate internucleoside linkage. All other compounds (Tables 4-33) have an internucleoside linkage motif of (from 5' to 3'): soooosssssssssssooss, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage.

All cytosine residues are 5-methylcytosines.

"Start site" indicates the 5'-most nucleoside to which the modified oligonucleotide is complementary in the human gene sequence. "Stop site" indicates the 3'-most nucleoside to which the modified oligonucleotide is complementary in the target nucleic acid sequence. Each modified oligonucleotide listed in the Tables below is 100% complementary to SEQ ID NO: 1 (GENBANK Accession No NC_000015.10 truncated from nucleotides 24821647 to 25441028). Selected compounds in the table below are complementary to the target nucleic acid sequence at more than three specific sites. For these compounds, the "start site" and "stop site" values in the Tables below are indicated with a hashtag (#) and indicate only the first site to which the compound is complementary. Additional sites to which these compounds are complementary are indicated in Table 4b below.

Human IPSC cell derived iCell GABANeurons (Cellular Dynamics) were cultured per manufacturer instructions at 20,000-60,000 cells per well (as indicated in the table heading) and were treated with 5,000-10,000 nM of modified oligonucleotide (as indicated in the table heading) by free uptake. After a treatment period of approximately 6 days, total RNA was isolated from the cells and UBE3A-ATS RNA levels were measured by quantitative real-time RTPCR. Human UBE3A-ATS primer probe set RTS4796 (forward sequence CTCCCCCAGTTCTGGAATGA, designated herein as SEQ ID NO: 2; reverse sequence TACACAGGGATTTGAGCCTGCTA, designated herein as SEQ ID NO: 3; probe sequence CCCACAGATCAAGCATTCCCCAAAGA, designated herein as SEQ ID NO: 4) was used to measure RNA levels. UBE3A-ATS RNA levels were normalized to total RNA content, as measured by RIBOGREEN®. Reduction of UBE3A-ATS RNA is presented in the tables below as percent UBE3A-ATS RNA amount relative to untreated control (UTC) cells. Each table represents results from an individual assay plate. The values marked with an asterisk (*) indicate that the modified oligonucleotide is complementary to the amplicon region of the primer probe set. Additional assays may be used to measure the potency and efficacy of the modified

oligonucleotides complementary to the amplicon region. "N.D." indicates that a value was not determined in this experiment due to experimental error. However, activities of selected modified oligonucleotides, including those that are not defined in Example 1, are successfully demonstrated in dose-response studies herein below.

Table 2

Reduction of UBE3A-ATS RNA by 7,000 nM 5-10-5 MOE gapmers with PS internucleoside linkages *in vitro* (60,000 cells/well)

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence (5' to 3')	UBE3A-ATS (%UTC)	SEQ ID NO
617441	449466	449485	ATGTTGCTTGCACTCCATCA	85	17
617442	449945	449964	ACAACATAAGGTCTTATTGT	87	18
617443	450581	450600	TTTTCAACTCCAGAATTTTC	87	19
617444	451644	451663	TTCAGTCTTATACAGAAATG	94	20
617445	452473	452492	GGACTGACACAGAAAACTGG	115	21
617446	454843	454862	AGGGTAGAAGACTAGCATAC	111	22
617447	455272	455291	GGCCATTCATTCAGCCACAC	95	23
617448	455405	455424	TAAAGATTTTATGAAAATAC	104	24
617449	456040	456059	TTTAGAACATGTGAATTTCA	109	25
617450	457025	457044	AGACATATCACAGTTGCTTG	89	26
617451	457601	457620	AATATAATGTAGTATGACCA	59	27
617452	458989	459008	GAGGACACTGGCACATCTAT	59	28
617453	459376	459395	TTAAATAATAAAATATATTT	108	29
	459401	459420			
617454	461190	461209	ATTGGAGCAAAAAGGGATCA	45	30
617455	462327	462346	AATTATTCCCTATATCCTGT	45	31
617456	463905	463924	CAACTGTTACCAAGACTTCA	24	32
617457	465003	465022	ATCTGCGAATAGAGGCCCTC	44	33
617458	465460	465479	AAGGTTTTTATTTCATCACT	68	34
617459	465872	465891	GCCCATGGATGGTTGTCAAA	34	35
617460	466539	466558	TAGGTTGCATAAAGCCAGGC	23	36
617461	466981	467000	CACACATCTTGTTCCCTCAA	23	37
617462	467508	467527	TTTTTTTAATCCTCTGATGA	123	38
617463	467914	467933	AGTCTCTTTTCTTTCGGTGC	34	39
617464	468085	468104	GGAAAGTTCTTCTCTCTCCT	69	40
617465	469204	469223	ATTTGGTCTAAAGTGAAGTT	91	41
617466	470003	470022	TTTTGTGAGATTTTTGAATA	101	42
617467	471815	471834	TGTTAAATGCTTTTCTAAAT	80	43
617468	472985	473004	CTGATGATTGATTGTTTCCT	71	44
617469	474868	474887	TATGATAATGTGTAGTTTTT	110	45
617470	475850	475869	AAGGGTAATACGGACCTCAT	29	46
617471	476475	476494	CTATTTTTTGCTTCCCTTAT	56	47
617472	479448	479467	GAATTCTTAGAAAGTTAATT	118	48

617473	479585	479604	TGCCATCTTCAAGACTAAGG	33	49
617474	480527	480546	AATGGAAAAGATGTATCACG	92	50
617475	481063	481082	AACTTTGGCAGCTATTCAAT	88	51
617476	481522	481541	GACACTAGGTTTTGCAAAAG	63	52
617477	481663	481682	TATGAATTTTCAATTCAATG	155	53
617478	483415	483434	CACTTAAGGGAACTTTCAGA	84	54
617479	483933	483952	GAGATGATGTTAAGCTTTCA	75	55
617480	484344	484363	TAAGACAAGTGGCCATGAAG	92	56
617481	484760	484779	CTCTGTTCTGTCTCAAAACA	47	57
617482	485496	485515	TATAAGAAAGAAGATTACAG	132	58
617483	486358	486377	AAATGTTAATAGACTGCGAT	93	59
617484	486941	486960	TTAAACTCCCCAGTCAAAAG	108	60
617485	488180	488199	ATTTACTTCAAACAGGAGCT	42	61
617486	489476	489495	TCAGGAAATTAAAGCATTCA	81	62
617487	489630	489649	CCTAACCTGGATCTCAGATA	57	63
617488	493552	493571	TACAGCAACCCTAGAAAACT	121	64
617489	493893	493912	ATCTTTGGCAGATGTAACCT	63	65
617490	495750	495769	GAGTATTATCCAAAAGAACA	83	66
617491	497275	497294	AAAGCCCAGGATTAGGCAGC	63	67
617492	497366	497385	CTACAAAGAGTGAATCATGA	130	68
617493	498003	498022	TAATCTTAAGTTTAAGTGGA	68	69
617494	498883	498902	AAAAAGACATAGAATGACAG	100	70
617495	499237	499256	AGATACAAATTTAAAAAAGT	119	71
617496	499672	499691	GGTAGCCCCAATACAGATTC	62	72
617497	500044	500063	CTTCAACAGCAGACTTGATC	65	73
617498	501513	501532	GGTCCACACAGAGTTCAAAT	73	74
617499	501703	501722	CTTTGGGACATCCCAAAGTT	113	75
617500	502388	502407	TACACATCTTGTATACAAGG	60	76
617501	503258	503277	TAATACTTTCTTGAGTAATA	124	77
617502	503904	503923	GGGTGGTTGGATTGCTTTAT	47	78
617503	503977	503996	CTGCACACTGTACAGGAGGG	80	79
	508743	508762			
617504	503985	504004	TTGATTCACTGCACACTGTA	67	80
	508751	508770			
617505	504015	504034	GTGCAGGAAGGAGGTTTTGT	55	81
617506	504943	504962	ATACAGTATATACATCATCC	42	82
617507	505266	505285	AAGTTTAAAACAAAAAAAGG	119	83
617508	507068	507087	AATGTCTGTTCTTTGTGGTA	91	84
617509	507897	507916	ATACCTGCTTTTGTGACAAT	75	85
617510	508556	508575	GAGTGTAGCTCATTTCAGAA	74	86
617511	509785	509804	TTTCTCAATGTCAACTCTCA	68	87
617512	510721	510740	CAAGCCGAATCTTGACATAC	73	88
617513	511227	511246	GACCAGAAAAGCTACATAGC	87	89

617514	512575	512594	ATTTTGTATATTGTAGCTTT	105	90
617515	513295	513314	CCATCTTTCTGTTATCTTGT	51	91
617516	513982	514001	CTTTGTTTCTTTTTAAGAAA	108	92
617517	514259	514278	ACCTTGACAACACCCTAGCT	89	93
617518	515123	515142	AAAAAGGAACCATAAACTAA	117	94

Table 3

Reduction of UBE3A-ATS RNA by 7,000 nM 5-10-5 MOE gapmers with PS internucleoside linkages *in vitro* (60,000 cells/well)

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence (5' to 3')	UBE3A-ATS (%UTC)	SEQ ID NO
617461	466981	467000	CACACATCTTGTTCCCTCAA	29	37
617519	449812	449831	GGTGTGTCAGCTGTGCTGGT	62	95
617520	450498	450517	ATCATACCTTCACTTTTTTT	101	96
617521	450896	450915	TTCATTGAGCTTCCTGGATA	100	97
617522	451804	451823	TTACTTCTTTTTCATTAAGT	86	98
617523	454628	454647	AGTAAACACTCCAACAAAAA	126	99
617524	455049	455068	GGTCTAAGCAAAATGTGAAG	137	100
617525	455323	455342	CAGTTAGGCCTGCTCCGAAT	102	101
617526	455499	455518	ACTCTGAAAATAGCCAATTT	134	102
617527	456944	456963	AGTATCTATCTACAATTAAA	112	103
617528	457237	457256	AATGGCTTAGCTACTCACCC	72	104
617529	458254	458273	CCTCTCTGCAAAACAAGAGA	74	105
617530	459153	459172	ATTACTCATTCTGGGAATGC	35	106
617531	460667	460686	GTTTTCAGCATGATTCTAAC	46	107
617532	461259	461278	CATATATAAAAATTAGAATG	122	108
617533	463621	463640	AATGCCACAAAGCTGGCTGT	97	109
617534	464514	464533	GTGCACAGATAATGACTAGA	69	110
617535	465402	465421	CAGTGAGAAGTCAATTGTCA	67	111
617536	465580	465599	TCCTTTAGCATTTCTATTAG	28	112
617537	466423	466442	AACATGTGCTTGCAAGCCAT	46	113
617538	466701	466720	AAATAACTGGATCTCATAAC	55	114
617539	467064	467083	CTTAGGAGAGAAACACTTTC	56	115
617540	467546	467565	TACATCCTGTAGGCTTTCTT	55	116
617541	467961	467980	ACTGAGAAATCTCTTGAATG	92	117
617542	468624	468643	TTGCTCTTTTTACTTTGTTC	37	118
617543	469731	469750	ACTCTAAGTTTTATTAATAG	105	119
617544	470091	470110	TTTGGAAGAGCTTAATAAAG	110	120
617545	472023	472042	TAGCTAGAATTTCAACTACT	63	121
617546	474443	474462	ATGTAGTATTTATTTCATTT	120	122
617547	474957	474976	GCCTAATATGTGTCATCCTG	28	123
617548	475998	476017	CCTCAATTCTATGGTTAGTT	52	124

617549	479376	479395	TCTTGGAGATGACTTCTCTG	75	125
617550	479580	479599	TCTTCAAGACTAAGGTAGGG	54	126
617551	479654	479673	AGTAAGGTCTGTTATTCTCC	35	127
617552	480998	481017	GCTATACAACAAAAAGAATT	123	128
617553	481073	481092	ACTGTGGAAAAACTTTGGCA	54	129
617554	481582	481601	ATAATCTACATGTATAGACC	85	130
617555	481984	482003	AAAAGCCAATTCTGAAATTC	44	131
617556	483689	483708	ATTCTCCTACCTCTCAGCCT	107	132
617558	484654	484673	AACTGTAGCAAATATACTAC	110	133
617559	485236	485255	AAATTACTGCTCTGTAAAAG	93	134
617560	485886	485905	GATTCAATGAAATAAAAAAT	144	135
617561	486894	486913	AATGACATAGCTTATGCTGT	104	136
617562	488162	488181	CTAGAAATTAAGACATCCCT	63	137
617563	488563	488582	GCCACACCATCAAAAGAACC	77	138
617564	489518	489537	TGGACCACCTAAGACCTCAA	62	139
617565	489731	489750	ACCGGTTCCCAATTTTCTCC	82	140
617566	493655	493674	GAGAGAATACGGCCCTGATG	77	141
617567	494790	494809	AACTTCAATCAGAGTAATAT	117	142
617568	496045	496064	GGCAAAGGAATGAAGAGACC	69	143
617569	497328	497347	GCCAATAACAAGAAAAGAGA	96	144
617570	497416	497435	ATCAAATTGGATGACCTAAA	122	145
617571	498140	498159	CAATGGATTTCAATTACACT	54	146
617572	498893	498912	ATTCTCCAACAAAAAGACAT	93	147
617573	499276	499295	GTAGCTACAAGAAGTAATTG	117	148
617574	499958	499977	AAAGAATGCCTATAAGAATT	118	149
617575	500578	500597	CTACTGGCATCAGTCAAAAC	60	150
617576	501578	501597	AAAAGGCAAGGCTAAGGAGT	69	151
617577	502305	502324	CCCACACAGGTCATTCATTC	52	152
617578	503150	503169	TGTATACACCATCCCAGAAA	93	153
617579	503795	503814	AAAATGCCAGTTTGTTGTAC	60	154
617580	503973	503992	ACACTGTACAGGAGGGTGTC	69	155
	508739	508758			
617581	503981	504000	TTCACTGCACACTGTACAGG	70	156
	508747	508766			
617582	503993	504012	AAATGATGTTGATTCACTGC	36	157
	508759	508778			
617583	504551	504570	AGAGTTTTCATGAATTCAGG	46	158
617584	505011	505030	GGTTTCTTTCATTAAATAGC	63	159
617585	506396	506415	GAGGCAACTCCTGAGAGCTG	64	160
617586	507650	507669	TTAAATGTCAGGAGGTCCCC	57	161
617587	508201	508220	TGTCATCTGATCTCACACAT	86	162
617588	508772	508791	CAAAGTCCAAGGGAAATGAT	71	163
617589	510010	510029	CACAGTAGAGGCAAATGAGA	79	164

617590	511058	511077	GACATTTAGGATGATGATAT	72	165
617591	512158	512177	GTTGTATTAATGGACTTTTG	65	166
617592	513203	513222	ATTTTTTGCATAAGTGCATT	86	167
617593	513508	513527	ACATTTCTTAGTTGAACAGT	29	168
617594	514104	514123	AGATTCTTCCCCAATCCCAT	81	169
617595	514524	514543	CTCACTTGTCTCCTTTTACC	73	170
617596	515282	515301	ACAATAAGGAAGAGCAAAAC	104	171

Table 4

Reduction of UBE3A-ATS RNA by 5,000 nM 5-10-5 MOE gapmers with mixed PO/ PS internucleoside linkages *in vitro* (35,000 cells/well)

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence (5' to 3')	UBE3A-ATS (%UTC)	SEQ ID NO
617456	463905	463924	CAACTGTTACCAAGACTTCA	22	32
617457	465003	465022	ATCTGCGAATAGAGGCCCTC	22	33
617460	466539	466558	TAGGTTGCATAAAGCCAGGC	35	36
617461	466981	467000	CACACATCTTGTTCCCTCAA	36	37
617557	483977	483996	ATCATGTGCATACCCAGGGT	9	172
705110	229870#	229889#	TCACTCATTTTGTTCAGCTT	33	173
705112	232607#	232626#	GTTTTCACTCATTTTGTTCA	61	174
750513	220331	220350	ACAATTATTCTCATCATCGA	113	175
	456700	456719			
750514	220346	220365	CCTCAGCATCCTCAGACAAT	80	176
	456715	456734			
750515	220359	220378	TCTGGAATGAGTCCCTCAGC	73	177
	456728	456747			
750516	220371	220390	CTCAGATTGACATCTGGAAT	123	178
	456740	456759			
750517	229869#	229888#	CACTCATTTTGTTCAGCTTT	15	179
750518	232608#	232627#	AGTTTTCACTCATTTTGTTC	67	180
750519	349103#	349122#	GTCATCACCTCTCTTCAGGA	22	181
750520	349105#	349124#	AAGTCATCACCTCTCTTCAG	35	182
750521	349107#	349126#	TTAAGTCATCACCTCTCTTC	55	183
750522	349109#	349128#	TTTTAAGTCATCACCTCTCT	37	184
750523	349111#	349130#	ATTTTTAAGTCATCACCTCT	45	185
750524	349113#	349132#	TGATTTTTAAGTCATCACCT	25	186
750525	349115#	349134#	CATGATTTTTAAGTCATCAC	55	187
750526	349117#	349136#	AGCATGATTTTTAAGTCATC	65	188
750527	349119#	349138#	TGAGCATGATTTTTAAGTCA	46	189

750528	349121#	349140#	ATTGAGCATGATTTTTAAGT	56	190
750529	349123#	349142#	CTATTGAGCATGATTTTTAA	60	191
750530	349125#	349144#	TCCTATTGAGCATGATTTTT	56	192
750531	349127#	349146#	AATCCTATTGAGCATGATTT	41	193
750532	349129#	349148#	GTAATCCTATTGAGCATGAT	26	194
750533	349131#	349150#	GCGTAATCCTATTGAGCATG	34	195
750534	349133#	349152#	CAGCGTAATCCTATTGAGCA	63	196
750535	349135#	349154#	CTCAGCGTAATCCTATTGAG	50	197
750536	349137#	349156#	GCCTCAGCGTAATCCTATTG	71	198
750537	349139#	349158#	GGGCCTCAGCGTAATCCTAT	48	199
750538	349141#	349160#	CTGGGCCTCAGCGTAATCCT	28	200
750539	349143#	349162#	GGCTGGGCCTCAGCGTAATC	75	201
750540	355254#	355273#	TAGGCTGGGCCTCAGCGTAA	32	202
750541	349147#	349166#	CCTAGGCTGGGCCTCAGCGT	98	203
750542	349149#	349168#	CACCTAGGCTGGGCCTCAGC	21	204
750543	349151#	349170#	CTCACCTAGGCTGGGCCTCA	55	205
750544	349153#	349172#	TTCTCACCTAGGCTGGGCCT	24	206
750545	349155#	349174#	AATTCTCACCTAGGCTGGGC	53	207
750546	349157#	349176#	AAAATTCTCACCTAGGCTGG	39	208
750547	349159#	349178#	CCAAAATTCTCACCTAGGCT	46	209
750548	349162#	349181#	CTTCCAAAATTCTCACCTAG	95	210
750549	349165#	349184#	CCTCTTCCAAAATTCTCACC	17	211
750550	349168#	349187#	CATCCTCTTCCAAAATTCTC	75	212
750551	349171#	349190#	CAGCATCCTCTTCCAAAATT	50	213
750552	349174#	349193#	TCCCAGCATCCTCTTCCAAA	70	214
750553	349177#	349196#	GGATCCCAGCATCCTCTTCC	53	215
750554	349346	349365	GCCACCCACATGCCCTGCCC	25	216
	409462	409481			
750555	349390#	349409#	AGAGCTCACTGAAAGACACA	63	217
750556	349392#	349411#	GAAGAGCTCACTGAAAGACA	85	218
750557	349442#	349461#	GCAGGATCCACTCACCTATG	27	219
750558	349957#	349976#	CAGAGCTCAGCCTTGACCCA	45	220
750559	350910#	350929#	AGCTCAGTGCAGGAGACCAG	56	221
750560	350914#	350933#	CCACAGCTCAGTGCAGGAGA	72	222
750561	350924#	350943#	GATGTGCTCACCACAGCTCA	115	223
750562	351544#	351563#	GGAACCCTTTCCTGCCTGGA	56	224

750563	353287#	353306#	CAATATAAGGTTCTCATCAT	42	225
750564	353293#	353312#	TCAGGACAATATAAGGTTCT	115	226
750565	353305#	353324#	CATCACCTCTCTTCAGGACA	37	227
750566	353356	353375	TCTCACCTAGGCTAGGCCTC	44	228
	407396	407415			
750567	353579#	353598#	AGCTCACTGAAAGACACAAG	49	229
750568	358746#	358765#	AGGAAGGGCCTGAGCTTCAG	34	230
750569	363914	363933	CTCACCACACCTCAGTGCAG	93	231
	384545	384564			
750570	364549#	364568#	CTTTCCTGCCTGGACCACCA	68	232
750571	366064	366083	TTGGGCACCCTCCAGATGCC	63	233
	373449	373468			
750572	366247	366266	CACTCACCTATGCTGGTCAA	72	234
	370104	370123			
	386794	386813			
750573	366487	366506	TCAGCTGGGTGCTGCCCTGC	117	235
	407918	407937			
750574	366668	366687	CCATTCAGGGCCATGGGTTT	67	236
	374053	374072			
750575	391964	391983	TCCCTGCACATGCATCCAGC	97	237
	393859	393878			
	403520	403539			
750576	395822	395841	ACTCCAGGGACCAAGAGCTC	49	238
	420812	420831			
750577	397780	397799	GAGACCCACTGAGATGGCCC	26	239
	415262	415281			
750578	402885	402904	ACCCCATGACCCTGGAGGTG	63	240
	410060	410079			
750579	403932	403951	ATGACCCCAGCAGGATGCAC	57	241
	424209	424228			
750580	422678	422697	TCACCCACCACTGTCCAGAG	95	242
	426410	426429			
750581	422778	422797	GTACCACTGAGATGGCCCAT	68	243
	426510	426529			
750582	423273	423292	AATGCAGACCTGGCAGTCGC	50	244
	430180	430199			

Table 4b

SEQ ID NO:1 start sites for modified oligonucleotides complementary to repeat regions

Compound Number	# of comp. sites within SEQ ID NO:1	SEQ ID NO: 1 start sites	SEQ ID NO:
705110	20	229870, 232603, 235253, 237932, 240726, 243420, 246181, 248825, 251500, 258532, 259677, 261158, 261978, 263775, 264917, 266052, 267194, 268313, 270176, 272427	173
705112	16	232607, 237936, 243424, 252518, 254323, 258536, 259681, 261162, 261982, 263779, 264921, 266056, 267198, 268317, 270180, 272431	174
750517	21	229869, 232602, 235252, 237931, 240725, 243419, 246180, 248824, 251499, 257447, 258531, 259676, 261157, 261977, 263774, 264916, 266051, 267193, 268312, 270175, 272426	179
750518	16	232608, 237937, 243425, 252519, 254324, 258537, 259682, 261163, 261983, 263780, 264922, 266057, 267199, 268318, 270181, 272432	180
750519	20	349103, 353307, 357118, 364011, 367794, 369796, 371701, 377828, 379703, 381607, 382737, 384642, 388298, 393921, 396997, 401626, 414465, 420126, 421994, 423858, 427578	181
750520	30	349105, 353309, 355214, 357120, 358879, 364013, 365917, 367796, 369798, 371703, 373302, 375957, 377830, 379705, 381609, 382739, 384644, 386464, 388300, 393923, 396999, 400729, 401628, 410769, 414467, 420128, 421996, 423860, 425727, 427580	182
750521	33	349107, 351019, 353311, 355216, 357122, 358881, 364015, 365919, 367798, 369800, 371705, 373304, 375959, 377832, 379707, 381611, 382741, 384646, 386466, 388302, 390180, 393925, 397001, 400731, 401630, 410771, 412631, 414469, 420130, 421998, 423862, 425729, 427582	183
750522	33	349109, 351021, 353313, 355218, 357124, 358883, 364017, 365921, 367800, 369802, 371707, 373306, 375961, 377834, 379709, 381613, 382743, 384648, 386468, 388304, 390182, 393927, 397003, 400733, 401632, 410773, 412633, 414471, 420132, 422000, 423864, 425731, 427584	184
750523	31	349111, 351023, 353315, 355220, 357126, 358885, 364019, 365923, 367802, 369804, 371709, 373308, 375963, 377836, 379711, 381615, 382745, 384650, 386470, 388306, 393929, 397005, 401634, 410775, 412635, 414473, 420134, 422002, 423866, 425733, 427586	185
750524	32	349113, 351025, 353317, 355222, 357128, 358887, 364021, 365925, 367804, 369806, 371711, 373310, 375965, 377838, 379713, 381617, 382747, 384652, 386472, 388308, 393931, 397007, 401636, 405499, 410777, 412637, 414475, 420136, 422004, 423868, 425735, 427588	186
750525	30	349115, 351027, 353319, 355224, 357130, 358889, 364023, 365927, 367806, 369808, 371713, 373312, 375967, 377840, 384654, 386474, 388310, 393933, 397009, 401638, 405501, 410779, 412639, 414477, 420138, 422006, 423870, 425737, 427590, 429251	187
750526	31	349117, 351029, 353321, 355226, 357132, 358891, 362700, 364025, 365929, 367808, 369810, 371715, 373314, 375969, 377842, 384656, 386476, 388312, 397011, 401640, 405503, 410781, 412641, 414479, 418232, 420140, 422008, 423872, 425739, 427592, 429253	188
750527	31	349119, 351031, 355228, 357134, 358893, 362702, 364027, 365931, 367810, 369812, 371717, 373316, 375971, 377844, 384658, 386478, 388314, 392044, 397013, 401642, 405505, 410783, 412643, 414481, 418234, 420142, 422010, 423874, 425741, 427594, 429255	189
750528	32	349121, 351033, 355230, 357136, 358895, 360780, 362704, 364029, 365933, 367812, 369814, 371719, 373318, 375973, 377846, 384660, 386480, 388316, 392046, 397015, 401644, 405507, 410785, 412645, 414483, 418236, 420144, 422012, 423876, 425743, 427596, 429257	190
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		397017, 401646, 403603, 405509, 410787, 412647, 414485, 418238, 420146, 422014, 423878, 425745, 427598, 429259	
750530	33	349125, 349125, 351037, 355234, 357140, 358899, 362708, 364033, 365937, 367816, 369818, 371723, 373322, 375977, 377850, 384664, 386484, 388320, 392050, 397019, 401648, 403605, 405511, 410789, 412649, 414487, 418240, 420148, 422016, 423880, 425747, 427600, 429261	192
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750532	31	349129, 355238, 357144, 358903, 362712, 364037, 365941, 367820, 369822, 371727, 373326, 375981, 377854, 386488, 388324, 392054, 397023, 398903, 401652, 403609, 405515, 410793, 412653, 414491, 418244, 420152, 422020, 423884, 425751, 427604, 429265	194
750533	28	349131, 355240, 357146, 358905, 362714, 364039, 365943, 367822, 369824, 371729, 373328, 375983, 377856, 386490, 388326, 392056, 397025, 401654, 403611, 410795, 414493, 418246, 420154, 422022, 423886, 425753, 427606, 429267	195
750534	29	349133, 355242, 357148, 358907, 362716, 364041, 365945, 367824, 369826, 371731, 373330, 375985, 377858, 386492, 388328, 392058, 397027, 401656, 403613, 409248, 410797, 414495, 418248, 420156, 422024, 423888, 425755, 427608, 429269	196
750535	29	349135, 355244, 357150, 358909, 362718, 364043, 365947, 367826, 369828, 371733, 373332, 375987, 377860, 386494, 388330, 392060, 397029, 401658, 403615, 409250, 410799, 414497, 418250, 420158, 422026, 423890, 425757, 427610, 429271	197
750536	30	349137, 355246, 357152, 358911, 362720, 364045, 365949, 367828, 369830, 371735, 373334, 375989, 377862, 386496, 392062, 393955, 397031, 401660, 403617, 407381, 409252, 410801, 414499, 418252, 420160, 422028, 423892, 425759, 427612, 429273	198
750537	30	349139, 355248, 357154, 358913, 360801, 362722, 364047, 365951, 367830, 369832, 371737, 373336, 375991, 377864, 386498, 392064, 393957, 397033, 401662, 403619, 409254, 410803, 414501, 418254, 420162, 422030, 423894, 425761, 427614, 429275	199
750538	25	349141, 355250, 357156, 358915, 360803, 362724, 365953, 367832, 369834, 371739, 373338, 375993, 377866, 392066, 393959, 397035, 401664, 403621, 410805, 418256, 420164, 422032, 425763, 427616, 429277	200
750539	22	349143, 355252, 357158, 358917, 362726, 365955, 369836, 373340, 375995, 377868, 392068, 393961, 397037, 401666, 403623, 410807, 418258, 420166, 422034, 425765, 429279, 448197	201
750540	20	349145, 355254, 358919, 362728, 365957, 369838, 373342, 375997, 377870, 392070, 393963, 401668, 403625, 410809, 418260, 420168, 422036, 425767, 429281, 448199	202
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750542	17	349149, 351061, 355258, 358923, 362732, 365961, 369842, 373346, 376001, 377874, 393967, 410813, 418264, 420172, 422040, 425771, 429285	204
750543	16	349151, 351063, 355260, 358925, 362734, 365963, 369844, 373348, 376003, 377876, 393969, 418266, 420174, 422042, 425773, 429287	205
750544	15	349153, 351065, 355262, 358927, 362736, 365965, 369846, 373350, 376005, 377878, 418268, 420176, 422044, 425775, 429289	206
750545	14	349155, 351067, 355264, 358929, 362738, 365967, 369848, 373352, 376007, 377880, 418270, 420178, 425777, 429291	207
750546	13	349157, 351069, 355266, 358931, 362740, 365969, 369850, 373354, 376009, 418272, 420180, 425779, 429293	208
750547	14	349159, 351071, 355268, 358933, 362742, 365971, 369852, 373356, 376011, 407403, 418274, 420182, 425781, 429295	209

750548	17	349162, 351074, 355271, 358936, 362745, 365974, 369855, 373359, 376014, 407406, 412686, 416425, 418277, 420185, 425784, 427637, 429298	210
750549	12	349165, 351077, 357180, 358939, 362748, 365977, 373362, 376017, 412689, 418280, 425787, 429301	211
750550	9	349168, 351080, 357183, 358942, 365980, 373365, 376020, 412692, 425790	212
750551	11	349171, 351083, 357186, 358945, 365983, 373368, 376023, 381675, 405557, 412695, 425793	213
750552	14	349174, 351086, 358948, 360836, 365986, 371772, 373371, 376026, 377898, 381678, 393992, 412698, 422065, 425796	214
750553	10	349177, 351089, 358951, 371775, 377901, 381681, 384716, 412701, 422068, 425799	215
750555	23	349390, 351292, 353581, 355499, 361054, 364302, 368083, 370059, 371989, 373589, 378120, 379994, 383026, 388586, 390466, 401917, 403871, 409508, 411053, 412917, 414751, 420414, 429518	217
750556	24	349392, 351294, 353583, 355501, 361056, 364304, 368085, 370061, 371991, 373591, 376253, 378122, 383028, 388588, 390468, 401919, 403873, 409510, 411055, 412919, 420416, 422284, 426016, 429520	218
750557	13	349442, 353633, 366255, 373640, 378173, 390519, 397322, 401968, 407684, 409560, 414803, 420466, 429569	219
750558	7	349957, 359696, 374917, 376821, 383615, 389153, 411626	220
750559	12	350910, 358772, 365811, 373197, 375845, 403478, 407243, 410663, 423753, 425620, 427479, 429146	221
750560	12	350914, 358776, 365815, 373201, 375849, 390074, 403482, 410667, 423757, 425624, 427483, 429150	222
750561	10	350924, 358786, 360674, 365825, 375859, 390084, 401536, 409127, 425634, 427493	223
750562	10	351544, 353840, 361305, 363233, 397528, 399421, 413175, 415009, 418768, 424402	224
750563	20	353287, 357098, 358857, 363991, 365896, 367774, 369776, 379683, 381587, 382717, 384622, 388278, 398857, 401606, 403563, 414445, 416346, 425705, 427558, 429219	225
750564	20	353293, 357104, 360748, 363997, 367780, 369782, 379689, 381593, 382723, 384628, 388284, 393907, 396983, 398863, 401612, 405475, 414451, 416352, 427564, 429225	226
750565	17	353305, 357116, 364009, 367792, 369794, 379701, 381605, 382735, 384640, 388296, 393919, 396995, 401624, 414463, 420124, 423856, 427576	227
750567	12	353579, 361052, 370057, 378118, 388584, 390464, 401915, 409506, 412915, 414749, 420412, 429516	229
750568	11	358746, 362555, 365785, 369656, 375819, 381477, 382607, 386333, 390044, 416238, 421864	230
750570	11	364549, 385176, 392568, 397522, 399415, 404124, 407883, 413169, 415003, 418762, 428112	232

Table 5

Reduction of UBE3A-ATS RNA by 7,000 nM 5-10-5 MOE gapmers with mixed PO/ PS internucleoside linkages *in vitro* (35,000 cells/well)

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence (5' to 3')	UBE3A-ATS (%UTC)	SEQ ID NO
617456	463905	463924	CAACTGTTACCAAGACTTCA	40	32
617457	465003	465022	ATCTGCGAATAGAGGCCCTC	30	33
617460	466539	466558	TAGGTTGCATAAAGCCAGGC	40	36
617461	466981	467000	CACACATCTTGTTCCCTCAA	41	37

617557	483977	483996	ATCATGTGCATACCCAGGGT	26	172
750326	504100	504119	CTTCAACTAACAGTATCTTA	20	245
750327	504103	504122	AGTCTTCAACTAACAGTATC	51	246
750328	504126	504145	CTATTTCATTAAGTCACCCC	53	247
750329	504179	504198	GGACAGCTGTGTGGAGGGAT	26	248
750330	504218	504237	ACCACCAGGGAGACCAGCCT	68	249
750331	504228	504247	CAGCCTTTCTACCACCAGGG	55	250
750332	504229	504248	TCAGCCTTTCTACCACCAGG	32	251
750333	504334	504353	ACAGAGTGTTTACTGTGAGC	29	252
750334	504503	504522	TCCATGGAATGGCTGTCATG	39	253
750335	504731	504750	TTCCTTCAGAGTTATTTCTT	73	254
750336	504740	504759	TTATTCTCCTTCCTTCAGAG	70	255
750337	504741	504760	GTTATTCTCCTTCCTTCAGA	41	256
750338	504817	504836	GAAGTAGTCCTGCCCTTTCC	60	257
750339	504923	504942	ATATCCTTTCCTCTCCTACT	78	258
750340	504958	504977	GACTGATGGTTACCCATACA	40	259
750341	504987	505006	CATTTAACAACTATTATCTT	27	260
750342	505003	505022	TCATTAAATAGCTAACCATT	91	261
750343	505043	505062	CCACTTTGCAACTCAAGATT	31	262
750344	505046	505065	CAGCCACTTTGCAACTCAAG	20	263
750345	505051	505070	GACTCCAGCCACTTTGCAAC	62	264
750346	505073	505092	CCAGAAATTTAGTCTGTTGT	59	265
750347	505096	505115	CATAAGCTGCTGGATTTGTT	51	266
750348	505241	505260	GAAGAGAACGAGGATATAAA	35	267
750349	505306	505325	GTGATATATTAGAACTGTAT	28	268
750350	505443	505462	AGAGGATTTAGAGTTAAAAT	22	269
750351	505569	505588	ACTGAAAGGTCTGTATGTTT	73	270
750352	505656	505675	CAGGCCTAGCTTCCACCTAA	108	271
750353	505837	505856	TCTGTCAAAGACCTGTGAGG	56	272
750354	505922	505941	TCTGCTTGTGGTTCTTCCCT	71	273
750355	505985	506004	CAAATATGGAATAGCACTTG	54	274
750356	506040	506059	GTTGAGAACGGTATTGAGTA	56	275
750357	506052	506071	CTCTTGTTTTCAGTTGAGAA	42	276
750358	506097	506116	ATTTCTCCATGGACTCCAGA	47	277
750359	506109	506128	CATTGGCTTCATATTTCTCC	11	278
750360	506306	506325	TATTGCCTTCACTGCTGCCT	9	279
750361	506518	506537	ACTGACTTGCTCTGCCTACT	71	280
750362	506617	506636	GAGAAGTCTCTCATGGCACC	40	281
750363	506731	506750	GGAGTGCTCCACACTTCTGT	27	282
750364	506776	506795	CTCCAGGTTGTGGAGGTTGT	75	283
750365	506783	506802	GTATATACTCCAGGTTGTGG	23	284
750366	506881	506900	ACTTCTCATTCTCTCCACCA	17	285
750367	507189	507208	AAAGCATTTTCTACCAGAGC	45	286

750368	507198	507217	TAGACAAGGAAAGCATTTTC	54	287
750369	507312	507331	CACCTGCCCTGCTTTTGCTT	41	288
750370	507324	507343	TGGTCCTAGCTTCACCTGCC	89	289
750371	507357	507376	AGATCCAACCTGTGTGGAAA	61	290
750372	507534	507553	AGAAATTAGAGCCAGGTTCC	36	291
750373	507635	507654	TCCCCCCAGAAGGCTTGACT	71	292
750374	507755	507774	TCGCTGGCCATTTCATATAT	44	293
750375	507978	507997	AAAACATGTTAACTGTTATC	40	294
750376	508159	508178	TTAGCCATGTGCTTTGTGAC	68	295
750377	508208	508227	TCCCTTCTGTCATCTGATCT	59	296
750378	508218	508237	AAGGTAGTTCTCCCTTCTGT	93	297
750379	508426	508445	TTCCATTGCACTCCTTTCTA	113	298
750380	508530	508549	TAAAAGGAAAACCCACTTGT	72	299
750381	508700	508719	TACAGAAATTACCAGTAAAG	38	300
750382	508710	508729	TCCAGATTTCTACAGAAATT	102	301
750383	503980	503999	TCACTGCACACTGTACAGGA	78	302
	508746	508765			
750384	508890	508909	TGCCTAGTTCCCTCCTGAAA	98	303
750385	508908	508927	TTATGTTTACTTCATGACTG	91	304
750386	508945	508964	CTTCATTATTCTCTAGTGCC	14	305
750387	509013	509032	CTATTCCCCTTCAACATGTG	44	306
750388	509060	509079	CATACCCAACATGCTTGCAT	44	307
750389	509079	509098	AATGCATTACCCTACAATGC	105	308
750390	509127	509146	CTCATCACAACTGGGTGGTA	76	309
750391	509134	509153	ATCCCAGCTCATCACAACTG	88	310
750392	509167	509186	TCCAAGTGCTTCAAGCTGAG	100	311
750393	509189	509208	CACCCACAGCAGGCAGATAA	58	312
750394	509208	509227	TACCTTGCTCCAAAATAATC	37	313
750395	509230	509249	CTGTTTCTTGAGGCAAATGA	54	314
750396	509787	509806	CTTTTCTCAATGTCAACTCT	48	315
750397	510028	510047	AGAGTTATACACGGAACCCA	71	316

Table 6

Reduction of UBE3A-ATS RNA by 8,000 nM 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages *in vitro* (40,000 cells/well)

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence (5' to 3')	UBE3A-ATS (%UTC)	SEQ ID NO
617456	463905	463924	CAACTGTTACCAAGACTTCA	26	32
617457	465003	465022	ATCTGCGAATAGAGGCCCTC	46	33
617460	466539	466558	TAGGTTGCATAAAGCCAGGC	8	36
617461	466981	467000	CACACATCTTGTTCCCTCAA	21	37
617557	483977	483996	ATCATGTGCATACCCAGGGT	23	172

749968	465163	465182	TTCTAGGGCTCCAGTTTATG	86	317
749969	465238	465257	TGGTCATCTCGGGTATATAA	20	318
749970	465341	465360	CTTACTATCTTCAAGAATTC	68	319
749971	465346	465365	TTTTTCTTACTATCTTCAAG	56	320
749972	465394	465413	AGTCAATTGTCAGACTTATT	37	321
749973	465587	465606	AAGGAGTTCCTTTAGCATTT	27	322
749974	465594	465613	CAGACCGAAGGAGTTCCTTT	50	323
749975	465612	465631	TCCAGTGCCTTTCTATTTCA	33	324
749976	465686	465705	ACTTTGTTTTAAACTTACAC	46	325
749977	465765	465784	CATCAACACAAGTTTATAAT	47	326
749978	465892	465911	AACTCCCACAAGGTACTCTT	32	327
749979	465906	465925	ACTGTCAACTCCTGAACTCC	54	328
749980	465956	465975	CAATGAATCTATTCTTAGAT	122	329
749981	465978	465997	GTGAAACTGTTTATACCCTT	25	330
749982	465996	466015	GTTGGTGATGCAGGTAAAGT	24	331
749983	466024	466043	TTGTTACTGAGCTGTGCCAC	48	332
749984	466119	466138	AAGTGGATCTCTTGGGCAGG	22	333
749985	466182	466201	TTTACCCTCTCCCAACCACT	51	334
749986	466217	466236	GGCTGCTGTTTGAGTCCCCA	40	335
749987	466220	466239	ATGGGCTGCTGTTTGAGTCC	58	336
749988	466221	466240	TATGGGCTGCTGTTTGAGTC	55	337
749989	466529	466548	AAAGCCAGGCCAGGTGCTGA	64	338
749990	466532	466551	CATAAAGCCAGGCCAGGTGC	30	339
749991	466534	466553	TGCATAAAGCCAGGCCAGGT	20	340
749992	466537	466556	GGTTGCATAAAGCCAGGCCA	36	341
749993	466539	466558	TAGGTTGCATAAAGCCAGGC	46	36
749994	466541	466560	TCTAGGTTGCATAAAGCCAG	52	342
749995	466544	466563	TTCTCTAGGTTGCATAAAGC	33	343
749996	466546	466565	CCTTCTCTAGGTTGCATAAA	28	344
749997	466549	466568	TCACCTTCTCTAGGTTGCAT	34	345
749998	466551	466570	TATCACCTTCTCTAGGTTGC	44	346
749999	466701	466720	AAATAACTGGATCTCATAAC	55	114
750000	466979	466998	CACATCTTGTTCCCTCAAGG	26	347
750001	466981	467000	CACACATCTTGTTCCCTCAA	26	37
750002	466983	467002	TTCACACATCTTGTTCCCTC	26	348
750003	466986	467005	TGCTTCACACATCTTGTTCC	43	349
750004	466988	467007	CCTGCTTCACACATCTTGTT	49	350
750005	466991	467010	GAACCTGCTTCACACATCTT	36	351
750006	467049	467068	CTTTCATCAGTTAGTCAGGT	23	352
750007	467200	467219	GGAGTTGGTTATTGGAAAAT	48	353
750008	467289	467308	TCTATTGGTGTTCCTTTTAG	48	354
750009	467296	467315	AGAGTAGTCTATTGGTGTTC	22	355
750010	467363	467382	CTTTTAAGATAATTTTTCTC	90	356

750011	467417	467436	TACGCTCCTTCATTTCATGC	55	357
750012	467506	467525	TTTTTAATCCTCTGATGAAT	102	358
750013	467508	467527	TTTTTTTAATCCTCTGATGA	62	38
750014	467604	467623	CTCTCTTCTCCTTTATGACT	41	359
750015	467628	467647	CTTAAATAAGTTTTCTACCC	42	360
750016	467639	467658	AGCCATTATTTCTTAAATAA	56	361
750017	467669	467688	CATATCTTTTCCTAGATTTG	110	362
750018	467813	467832	AGAATCCTGTCTCCCTCTTA	34	363
750019	467916	467935	TGAGTCTCTTTTCTTTCGGT	41	364
750020	467919	467938	TGATGAGTCTCTTTTCTTTC	35	365
750021	467921	467940	TGTGATGAGTCTCTTTTCTT	30	366
750022	467962	467981	TACTGAGAAATCTCTTGAAT	77	367
750023	468277	468296	TAAAATTATTTATACACCAT	73	368
750024	468359	468378	TTTATACTGTAGTATGCATT	53	369
750025	468410	468429	TTACTTCCCTACCCTTGCAT	75	370
750026	468413	468432	CTTTTACTTCCCTACCCTTG	67	371
750027	468464	468483	ATTTATTTTAAGCTGATAAC	52	372
750028	468733	468752	AAATCCATTTGTCCAGTCTG	14	373
750029	468888	468907	TATCTGCATGCAATATCTTT	70	374
750030	468924	468943	CTGTAAGTATAGATGCCTCT	15	375
750031	468968	468987	TTAGCCTTTTGATATAGTTT	25	376
750032	468988	469007	GCTTCACCATTTTGACCTTC	19	377
750033	469140	469159	TTTTGAAAGGGAGGCACTGA	27	378
750034	469604	469623	TGAGGTGTAATGTTGTTTAT	32	379
750035	469717	469736	TAATAGTCTCTATTGTTTTT	50	380
750036	469884	469903	CAAGTTAACTAATATGTTGG	71	381
750037	469985	470004	TATTGATTCAATTCCCTTAT	23	382
750038	469988	470007	GAATATTGATTCAATTCCCT	37	383
750039	470062	470081	AATTTTTTTAAATGGTTGGC	51	384

Table 7

Reduction of UBE3A-ATS RNA by 8,000 nM 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages *in vitro* (40,000 cells/well)

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence (5' to 3')	UBE3A-ATS (%UTC)	SEQ ID NO
617456	463905	463924	CAACTGTTACCAAGACTTCA	18	32
617457	465003	465022	ATCTGCGAATAGAGGCCCTC	36	33
617460	466539	466558	TAGGTTGCATAAAGCCAGGC	12	36
617461	466981	467000	CACACATCTTGTTCCCTCAA	16	37
617557	483977	483996	ATCATGTGCATACCCAGGGT	27	172
750182	488205	488224	AACAGAGAATTGTATATCCA	43	385
750183	488322	488341	ACATGAGATCTTTAATAAGA	73	386

750184	488343	488362	CAAGAGAGAAGCCACTCATG	64	387
750185	488685	488704	AGCAGATTTGAGCTGGAAGA	42	388
750186	488928	488947	AACTGGCAGAAAATATCTCT	36	389
750187	488941	488960	AAAGAAGAACATAAACTGGC	70	390
750188	489021	489040	GTTGGCTCTATTTTCAAATG	33	391
750189	489449	489468	CTGTTTAGGCTGGACACTGT	90	392
750190	489478	489497	ATTCAGGAAATTAAAGCATT	60	393
750191	489698	489717	AGCAGAACAGACCTTATTTG	41	394
750192	489712	489731	CCTTCAACCAGAGGAGCAGA	44	395
750193	489756	489775	GATCTTGGTTTGTAGAAGGT	35	396
750194	489824	489843	TTCAAAATGGTAGAAAATTG	64	397
750195	489873	489892	TGAAAGGCCTACAGCAACCA	46	398
750196	489893	489912	ATGGGAGCTCTGGAAAACAG	27	399
750197	490070	490089	TTCTGAGTATATGTGAAACA	39	400
750198	492874	492893	ATAAGGAGATTAATTTAAGA	86	401
750199	493278	493297	GAATCAAAGAAAGAAGGAAT	47	402
750200	493440	493459	GCTGTAATAATAATCATATT	41	403
750201	493678	493697	AGAATTCTTCCCTACAGGTT	51	404
750202	493831	493850	CAGTAATTAATGTTCTTATA	37	405
750203	493839	493858	CCCCAATTCAGTAATTAATG	39	406
750204	493841	493860	GGCCCCAATTCAGTAATTAA	56	407
750205	493882	493901	ATGTAACCTATTCAAGATGA	47	408
750206	493908	493927	TTATTTGGAAGAAGAATCTT	98	409
750207	494002	494021	TATAAAATACTTTTTATGGG	101	410
750208	494398	494417	GACTGTGATAAAGATGTATA	84	411
750209	494443	494462	TAAGGGTCATGTACTATACA	33	412
750210	494494	494513	GTGTGTGCAATAGCCTAAAT	27	413
750211	494554	494573	CAGAAGCAAAAGATAGCAGC	53	414
750212	494873	494892	TATTAATGTACTTGAAGATG	52	415
750213	495043	495062	ATCAGTGTGTGCAGATTCTG	45	416
750214	495050	495069	TCCCATCATCAGTGTGTGCA	27	417
750215	495201	495220	TATGAAAATTAATGTTCAAG	80	418
750216	495233	495252	AAAAAATTTTAAACCCCTAG	76	419
750217	495441	495460	TCATGAAAGTAGAGAGTAAG	68	420
750218	495659	495678	TGAAACAATTTAAGTGCCCA	64	421
750219	495718	495737	TTGAAGGGATATCTTCATTC	106	422
750220	495795	495814	TCTGAAAAAAATAGAACAAC	64	423
750221	496202	496221	AATAAAAGACCTGCACAGCA	66	424
750222	496205	496224	CAAAATAAAAGACCTGCACA	48	425
750223	496379	496398	AGACCCTTATTTACACCATA	65	426
750224	496557	496576	CTATTAATGAGCTATCTGAA	37	427

750225	496561	496580	TCTACTATTAATGAGCTATC	45	428
750226	496567	496586	TTTCCATCTACTATTAATGA	39	429
750227	496661	496680	GTCTCCACCAGAACAAAACT	69	430
750228	496691	496710	ATGACATAACCATATACAAA	35	431
750229	496697	496716	TTACTGATGACATAACCATA	71	432
750230	496869	496888	CAAAATTCAACCTGGTTTCA	39	433
750231	496927	496946	ATGGAGGGTGTAAATCAAAT	36	434
750232	497148	497167	TGTTACACTGTTATTAAAGC	28	435
750233	497197	497216	AAAACAATGAAGCAGAGGGA	37	436
750234	497299	497318	TAATAAAAAGTATCCCACCA	72	437
750235	497429	497448	GAAGTTATGCACCATCAAAT	46	438
750236	497477	497496	TTTACTACTGATATCACCAA	41	439
750237	497680	497699	AGAACAGACTAAGCCCGAAA	40	440
750238	497917	497936	AATTCTGGTGGAAAATACAG	71	441
750239	497984	498003	ACAGAAATCATATCAAATCC	69	442
750240	498096	498115	ATATATGAAACATTCCATCC	39	443
750241	498127	498146	TTACACTTTAGACCAAACGG	37	444
750242	498179	498198	GGGCAGATTGATCACCTAGA	25	445
750243	498208	498227	CGGGACCTCAATACTCTACT	37	446
750244	498432	498451	TAAATGGAAATTGAGAGCAG	61	447
750245	498842	498861	AAGTCACAACCACATACTGC	57	448
750246	498894	498913	GATTCTCCAACAAAAAGACA	50	449
750247	498942	498961	GACACTAGCAGTTTCTTACC	30	450
750248	499132	499151	GCTTAAAGTAGCCTAAGGAT	32	451
750249	499286	499305	ACAATAAGTTGTAGCTACAA	61	452
750250	499304	499323	TTAAAAACAACTGTAGCTAC	62	453
750251	499335	499354	TTCCTATTAGGAGGTTTAAA	43	454
750252	499395	499414	ATAAGTAATTCATAGTCAGA	44	455
750253	499452	499471	GGCTTAAATAAAAGACTGCT	63	456

Table 8

Reduction of UBE3A-ATS RNA by 8,000 nM 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages *in vitro* (35,000 cells/well)

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence (5' to 3')	UBE3A-ATS (%UTC)	SEQ ID NO
617456	463905	463924	CAACTGTTACCAAGACTTCA	34	32
617457	465003	465022	ATCTGCGAATAGAGGCCCTC	44	33
617460	466539	466558	TAGGTTGCATAAAGCCAGGC	45	36
617461	466981	467000	CACACATCTTGTTCCCTCAA	19	37
617557	483977	483996	ATCATGTGCATACCCAGGGT	37	172
749753	448285	448304	TAAGATTCCATTGCCAGAAT	115	457

749754	448296	448315	AAGTTTCGCAATAAGATTCC	103	458
749755	448500	448519	TTTCAGTCAGCAAAGGCAGC	80	459
749756	448681	448700	TCTCAACCCTGAAAACAATC	87	460
749757	448989	449008	CATTGGCATTATTCACAGCA	103	461
749758	449031	449050	CTGACTGTCATTCATATAAG	69	462
749759	449067	449086	TGCATAACGATAATCATGTG	161	463
749760	449112	449131	TTGTAGATCCTGGCAAGTAT	132	464
749761	449130	449149	AAAAATAAAGTTTCCCTCTT	64	465
749762	449167	449186	CAAAACTTGTCAACATTATA	129	466
749763	449218	449237	CTATATTTAGACCAAATGAG	91	467
749764	449254	449273	CTGACATATATAAATTAGAA	104	468
749765	449263	449282	CATAGCAACCTGACATATAT	109	469
749766	449279	449298	ACAAACATTGTAAAAACATA	92	470
749767	449337	449356	TTAGAACATGTAGCCATAAT	69	471
749768	449382	449401	AATTGTATTTAATTTAATGA	102	472
749769	449439	449458	ATCATACTGGAGCCAGGTGA	85	473
749770	449545	449564	AATGCAGAAATAAGACCTTC	88	474
749771	449765	449784	CAGTCATCCTTATCTAAGGG	63	475
749772	449786	449805	AAGCCAAAGAGTACTCTTCC	83	476
749773	449820	449839	GATATCTGGGTGTGTCAGCT	67	477
749774	449944	449963	CAACATAAGGTCTTATTGTT	74	478
749775	450083	450102	GGTCTTCTAGAAGCTAATAG	77	479
749776	450092	450111	TTGATAAGTGGTCTTCTAGA	64	480
749777	450204	450223	CAATTCTTTTGAGTGTGTAC	66	481
749778	450205	450224	TCAATTCTTTTGAGTGTGTA	70	482
749779	450511	450530	GTGTGACATTGTCATCATAC	87	483
749780	450710	450729	CTTTATGCTTTCTGTTCTTT	76	484
749781	450733	450752	GAGACTCTCTTTGTTTCTTT	96	485
749782	450906	450925	TTCATTGGAATTCATTGAGC	94	486
749783	450978	450997	CAAGACTTTCTTCTTGTTTT	115	487
749784	451042	451061	AGTCAGCTGTTAATCTTCCT	85	488
749785	451104	451123	TTTTTCTTTGAGCATTTTTA	104	489
749786	451250	451269	TTTAAGTATTTAGAGAACTC	122	490
749787	451286	451305	TACCTAGGCTCACTTGCTTT	91	491
749788	451306	451325	TAGTTGTTGATTTGAATAAC	87	492
749789	451308	451327	TGTAGTTGTTGATTTGAATA	93	493
749790	451389	451408	TTATTTTAAAATCACTTCAG	96	494
749791	451466	451485	TCTTCTTTGGCAAATATATT	126	495
749792	451604	451623	TCCCTTTTTGCCATCTTTTG	58	496
749793	451673	451692	AATAAGTTTCTAATTTACAC	113	497
749794	451834	451853	TCTCATGTGTTTTTGTTCCT	49	498
749795	451954	451973	TAAACCTGGAGATTTTATCC	128	499
749796	452167	452186	GGGAACACACCATTCAGCAG	38	500

749797	452222	452241	AATCTTGTTGACTAAAAGTA	114	501
749798	452255	452274	GTCTCACGCTGTGTGAATCA	104	502
749799	452257	452276	AGGTCTCACGCTGTGTGAAT	89	503
749800	452285	452304	TGCTCCTATTTCAATATGAG	100	504
749801	452324	452343	ATAAGGTTCAAAAGCCGGTG	182	505
749802	452459	452478	AACTGGTAACATAAATGCAG	99	506
749803	452485	452504	TCAGAGCAAAATGGACTGAC	142	507
749804	452517	452536	TACAAATACCCAGTCTGCAG	65	508
749805	452590	452609	AAGGCCCTTATCATATGCCA	96	509
749806	452661	452680	TCCTATAAAAGAAGATATTT	65	510
749807	452715	452734	CTGTGAGAGCTCTGCCCTCA	93	511
749808	453217	453236	GTTAATAGTGTTCTTACATC	106	512
749809	453233	453252	CAGTGGAGTCAAGTTGGTTA	135	513
749810	453350	453369	TCTACTAGCTAACTTTATCA	109	514
749811	453453	453472	AGGATCAAAGCAGAAATTAA	102	515
749812	453814	453833	AAAAACATAGACTTTACTAA	139	516
749813	453899	453918	CACAAAAAACTGATTATATA	92	517
749814	453933	453952	GATCTGTGTTGTTCTTAAGT	73	518
749815	453978	453997	AAGGTAGATTTTATGGCTAC	68	519
749816	454002	454021	GGGCAAAAATAGCAACATAA	47	520
749817	454067	454086	AAGACATAGATGATCCCATA	89	521
749818	454085	454104	TATGAGATGTAAGGAGACAA	86	522
749819	454303	454322	GATAGGAGTAATCTTTTTTT	86	523
749820	454611	454630	AAACAAAAACTCTCCTAAGT	77	524
749821	454657	454676	AGAACTAACAGAATTAAGAG	89	525
749822	454658	454677	CAGAACTAACAGAATTAAGA	111	526
749823	454661	454680	ACACAGAACTAACAGAATTA	71	527
749824	454759	454778	AAAAAGAGGAAAACCGAAAG	88	528

Table 9

Reduction of UBE3A-ATS RNA by 8,000 nM 5-10-5 MOE gapmers with a mixed PO/PS internucleoside linkages *in vitro* (35,000 cells/well)

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence (5' to 3')	UBE3A-ATS (%UTC)	SEQ ID NO
617456	463905	463924	CAACTGTTACCAAGACTTCA	40	32
617457	465003	465022	ATCTGCGAATAGAGGCCCTC	49	33
617460	466539	466558	TAGGTTGCATAAAGCCAGGC	28	36
617461	466981	467000	CACACATCTTGTTCCCTCAA	33	37
617557	483977	483996	ATCATGTGCATACCCAGGGT	42	172
749825	454828	454847	CATACAAATGTCACTAATAT	114	529
749826	454836	454855	AAGACTAGCATACAAATGTC	85	530
749827	454864	454883	ACAGGTGTATATTCCCTATC	84	531

749828	454998	455017	ATATATCTACTGAATATGAT	108	532
749829	455062	455081	CTCAGAACCCTTTGGTCTAA	66	533
749830	455110	455129	CTGACTTGACTTTAATGAAA	68	534
749831	455148	455167	GCATTCAGCTTATAGCAGAA	58	535
749832	455150	455169	CTGCATTCAGCTTATAGCAG	84	536
749833	455193	455212	AAACATTCCTCATACCACAC	73	537
749834	455230	455249	CTTATCCTTGATCCAGACAA	78	538
749835	455436	455455	AATGGGAAATGCTAAAGTTG	72	539
749836	455459	455478	AGTGACACAGTAGTTGTATC	70	540
749837	455485	455504	CAATTTCCTCTCTACCAAGC	71	541
749838	455542	455561	CTTTGTCATTTCATTTATAA	70	542
749839	455603	455622	ATACAGGCATCTCAGCCCTC	61	543
749840	455767	455786	AAAGTACCAAAGTGGCTGCT	71	544
749841	455768	455787	AAAAGTACCAAAGTGGCTGC	68	545
749842	455829	455848	GAAATAATGAACTCACAGTC	70	546
749843	455960	455979	CACAGTTGTTTAGGTCATCT	119	547
749844	457070	457089	GCATGCCATATTTCCTTCTT	91	548
749845	457076	457095	ATAGAGGCATGCCATATTTC	86	549
749846	457151	457170	AGCAAAAATAATCTTAGAAA	91	550
749847	457194	457213	GATTCCAGGCCTTCTATCTC	80	551
749848	457354	457373	GGTCTCAATGAGGAAAAGGA	34	552
749849	457424	457443	ATAAAAGCAAAAGAGAGTTA	84	553
749850	457556	457575	TCTATTCTGAAACCCCAATA	45	554
749851	457705	457724	GACATGCCATCAAGAGAAGA	59	555
749852	457917	457936	ATGTATTAACCAATATTTTG	51	556
749853	457993	458012	AGAACCCACTTGATCTATTA	53	557
749854	458199	458218	TAAAGAATTGAGTACCAAAA	64	558
749855	458268	458287	TATCACATTAATTCCCTCTC	37	559
749856	458289	458308	TAGAATAGAAAAGCATGAAG	71	560
749857	458328	458347	AACAACTATATTTGCTTGTA	39	561
749858	458346	458365	ATAATCACACTAAATCTTAA	70	562
749859	458391	458410	CCTCTATTAAGATCTATGAG	75	563
749860	458438	458457	ACTTCATCAATATTTCCCCA	31	564
749861	458537	458556	GCACTTAAATTTATCAGTTG	28	565
749862	458539	458558	AAGCACTTAAATTTATCAGT	36	566
749863	458567	458586	TTAGTATGTCGAGAACTCAA	24	567
749864	458588	458607	AAGTTGAAACACATTTTAGC	32	568
749865	458596	458615	AGGATTAAAAGTTGAAACAC	30	569
749866	458597	458616	CAGGATTAAAAGTTGAAACA	49	570
749867	458608	458627	AATCAGGGAAGCAGGATTAA	55	571
749868	458668	458687	TGATTACTCTTGGCAGTAAT	58	572
749869	458823	458842	TGATAGATACTTGTATTAGC	14	573
749870	458896	458915	CAAATCTAAAGCTCATTTAC	72	574

749871	458908	458927	CTACCAAAATGTCAAATCTA	56	575
749872	459220	459239	GTAACCTGAATATTTCATGA	37	576
749873	459228	459247	AAATAATGGTAACCTGAATA	56	577
749874	459240	459259	AATACATTACTGAAATAATG	86	578
749875	459256	459275	TTTACCTTGACATTCTAATA	40	579
749876	459450	459469	TTAACCTATTTTAATAATAT	89	580
749877	459567	459586	TTAAGTGATTGGAAATAAAA	82	581
749878	459580	459599	CAATTAGGAATATTTAAGTG	97	582
749879	459633	459652	CCAGGCAATGGCTCTTTCAA	66	583
749880	459645	459664	TGTATAGTTTACCCAGGCAA	37	584
749881	460066	460085	CTTTATCAATCTAATCAATT	65	585
749882	460115	460134	ACTTTATAGTGTGGATGGTA	22	586
749883	460146	460165	TTTTAGGGAATTGTCCTGAT	39	587
749884	460211	460230	AAGGAAACACACATAATACC	46	588
749885	460213	460232	GGAAGGAAACACACATAATA	26	589
749886	460272	460291	CACTAAGGACAAAGATATGG	75	590
749887	460303	460322	TATTTGTTCATTCTCAAGAA	56	591
749888	460545	460564	CAACCTGGGCTCTCATCTAA	41	592
749889	460709	460728	AATGCTTGATCTGTGGGCTC	32*	593
749890	460749	460768	ATTGTGTACACAGGGATTTG	22*	594
749891	460792	460811	AACTGTATACTTTGAAAGTA	68	595
749892	460870	460889	GAAGCAAGTAAGTAAATAAT	81	596
749893	460981	461000	CTTAGATGTGTTTATCCAAA	25	597
749894	460999	461018	GTGTTTTTCCATTTTTCTCT	9	598
749895	461027	461046	TGGCTCTATCAAGGCTTCCC	39	599
749896	461039	461058	AATCCTATATTTTGGCTCTA	34	600

Table 10

Reduction of UBE3A-ATS RNA by 10,000 nM 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages *in vitro* (40,000 cells/well)

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence (5' to 3')	UBE3A-ATS (%UTC)	SEQ ID NO
617456	463905	463924	CAACTGTTACCAAGACTTCA	47	32
617457	465003	465022	ATCTGCGAATAGAGGCCCTC	70	33
617460	466539	466558	TAGGTTGCATAAAGCCAGGC	51	36
617461	466981	467000	CACACATCTTGTTCCCTCAA	45	37
617557	483977	483996	ATCATGTGCATACCCAGGGT	29	172
699780	479654	479673	AGTAAGGTCTGTTATTCTCC	122	127
750040	470321	470340	GAACTATCCTGCATCCGAGG	41	601
750041	470398	470417	CAACCATCGAGATGATCATA	70	602
750042	471812	471831	TAAATGCTTTTCTAAATCTA	100	603
750043	471892	471911	GCTTTTATAGTGTTGAGGCA	81	604

750044	472153	472172	TTAAGCTCTAATTAAAACAG	113	605
750045	473241	473260	TATTTCACTGGAGCTTTGAT	107	606
750046	473564	473583	AATCATCTACTGATGAACAC	99	607
750047	473573	473592	TCTTTATCTAATCATCTACT	90	608
750048	473576	473595	TTCTCTTTATCTAATCATCT	111	609
750049	473697	473716	AGTTCCTGGAAACCGCCATT	63	610
750050	473789	473808	ATGCTGTTGTACACTAGATC	82	611
750051	473955	473974	GTACACTATTGTTTTGATAT	44	612
750052	474053	474072	CACCCCTAATTTATATTACT	56	613
750053	474069	474088	CATAGGTCAATTCCTTCACC	47	614
750054	474103	474122	TTAATTTAAATAGTTTACAA	100	615
750055	474123	474142	CTAGCTTGAATGGATACCAA	71	616
750056	474169	474188	TAGTGGTTGCCTTAGTATTA	52	617
750057	474198	474217	CAAGTGCTATATTTTTTTAA	95	618
750058	474230	474249	TATATATAATTGAGGGCCAC	116	619
750059	474414	474433	ATAATTATAAGATAGGGTTT	127	620
750060	474618	474637	ATTAGTATTGCTGCTCTAGC	91	621
750061	474786	474805	CCAACTGTAATCATTGATTT	79	622
750062	474865	474884	GATAATGTGTAGTTTTTTAT	82	623
750063	474878	474897	TAAGGTGTTGTATGATAATG	78	624
750064	474953	474972	AATATGTGTCATCCTGAAGA	93	625
750065	475066	475085	TCATTGTGAATTTCCCACAT	81	626
750066	475233	475252	TTAGGGATATACTGTTATAC	72	627
750067	475268	475287	AAAATTAGGTTATTGGATTG	103	628
750068	475293	475312	CTTTCACTCTCATTTCTTAA	91	629
750069	475397	475416	ACTTTCAAGTTTATTAATTT	115	630
750070	475495	475514	TACTTTCATTTATGTCTAGT	78	631
750071	475503	475522	GATATCTATACTTTCATTTA	125	632
750072	475628	475647	CATGTTTTTACACCAGCTGT	87	633
750073	475693	475712	TTACTTACTCAATTTCTTCT	97	634
750074	476072	476091	GTTTCAGCAGTTTCTGCTCC	85	635
750075	476164	476183	GGGCACTTAGGAGTTCCTAA	80	636
750076	476337	476356	CTCTGAGAGTGTTTAGAAAT	55	637
750077	476350	476369	GTGAAAGAAAATGCTCTGAG	62	638
750078	476405	476424	TACATCAGACAAGGCTCAGG	91	639
750079	476845	476864	TTCTATAATCTTATGGTTAA	77	640
750080	476851	476870	GAAGTGTTCTATAATCTTAT	74	641
750081	477296	477315	GTGAAAATTTTGTAGGTTGC	110	642
750082	478347	478366	TACAATCAGTGTCTTTCACC	78	643
750083	478472	478491	ATGGTTAGGGCTATGTTATG	96	644
750084	478542	478561	GAAATAAAACGCAATGTATC	118	645
750085	478710	478729	CTTGCATGTTGCCTTTTTCT	129	646
750086	479037	479056	AACTCTCTGCCATTATTACT	81	647

750087	479330	479349	TAATCTCACTGGATACAGAA	107	648
750088	479468	479487	AAACATTTTACCATTTTATA	133	649
750089	479644	479663	GTTATTCTCCCTCTTGAACC	82	650
750090	479647	479666	TCTGTTATTCTCCCTCTTGA	86	651
750091	479649	479668	GGTCTGTTATTCTCCCTCTT	51	652
750092	479652	479671	TAAGGTCTGTTATTCTCCCT	52	653
750093	479656	479675	AAAGTAAGGTCTGTTATTCT	92	654
750094	479659	479678	CTAAAAGTAAGGTCTGTTAT	74	655
750095	479661	479680	GACTAAAAGTAAGGTCTGTT	70	656
750096	479664	479683	AATGACTAAAAGTAAGGTCT	133	657
750097	480219	480238	AAAGATATAGAACTGAAAAG	128	658
750098	480286	480305	GTTGGAGACTTCAATTTCCT	89	659
750099	480361	480380	AAACAACAGAGCCTCAAATA	114	660
750100	480441	480460	AAAATACCACAAAGATAGGC	38	661
750101	480530	480549	AAGAATGGAAAAGATGTATC	57	662
750102	480533	480552	TAAAAGAATGGAAAAGATGT	99	663
750103	480648	480667	AATTTTACCTCAGTATAAAA	106	664
750104	480698	480717	ATTACCAAATGCCACTGTAT	59	665
750105	480714	480733	GTTGCATAACATGTGTATTA	65	666
750106	480787	480806	AATTAACTGCTTAATGAGTA	145	667
750107	480898	480917	ATAAAGGTCACTTATTGTAT	89	668
750108	480968	480987	AATAAAACTGATACATACTA	101	669
750109	481010	481029	AATCAACTTTTAGCTATACA	119	670
750110	481027	481046	TATCATTATGACCTAGGAAT	69	671

Table 11

Reduction of UBE3A-ATS RNA by 8,000 nM 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages *in vitro* (40,000 cells/well)

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence (5' to 3')	UBE3A-ATS (%UTC)	SEQ ID NO
617456	463905	463924	CAACTGTTACCAAGACTTCA	16	32
617457	465003	465022	ATCTGCGAATAGAGGCCCTC	21	33
617460	466539	466558	TAGGTTGCATAAAGCCAGGC	24	36
617461	466981	467000	CACACATCTTGTTCCCTCAA	15	37
617557	483977	483996	ATCATGTGCATACCCAGGGT	12	172
750254	499480	499499	ACTGGAATTACTAAAAGGGA	62	672
750255	499621	499640	AGTAGAGAGTGGGATGGTAT	53	673
750256	499691	499710	TAAGAAACATCACATTCAAG	67	674
750257	500139	500158	TGAACAGAATGAGAAGTTTA	82	675
750258	500141	500160	TCTGAACAGAATGAGAAGTT	69	676
750259	500285	500304	TGGTGTACATTGGATATGAA	24	677
750260	500319	500338	TTTCTAACATTTACTGTGGA	83	678

750261	500367	500386	TTCTAACATACTAATTAGCA	41	679
750262	500384	500403	CACCAATGCAAGCCAGCTTC	28	680
750263	500526	500545	TGTTTAGAGGTCAAGCCCTG	75	681
750264	500570	500589	ATCAGTCAAAACATGTTCTG	56	682
750265	500629	500648	TATTACACAAGGTATTGGTA	35	683
750266	500639	500658	ATGAAAGGTTTATTACACAA	34	684
750267	500760	500779	AATCAATTTGTGCCACAGGC	34	685
750268	500786	500805	GCAGCTTATAAAGAGAGCCA	78	686
750269	500860	500879	TTTGGTAGGTAACTACGGGT	35	687
750270	500882	500901	TCGGATATAGCTTTTACATA	14	688
750271	501004	501023	AAACTAAGCACATCCGATAG	60	689
750272	501060	501079	ATCATCTTTGATTTGACTTT	37	690
750273	501091	501110	TTCTTTATGAATCTTTGAAA	51	691
750274	501151	501170	GTAAAGAGCCACCTAAGGGA	40	692
750275	501165	501184	ATGAGATGGGCACAGTAAAG	33	693
750276	501391	501410	TCCCCAGATAATGCATAGAT	49	694
750277	501437	501456	GGTGGCATAGAAGGCAGCAC	74	695
750278	501549	501568	GGATGCAGCAGGAGAAGAAA	42	696
750279	501576	501595	AAGGCAAGGCTAAGGAGTGC	27	697
750280	501679	501698	AGAGAGCTAGAGCTAGGACT	17	698
750281	501694	501713	ATCCCAAAGTTACACAGAGA	58	699
750282	501703	501722	CTTTGGGACATCCCAAAGTT	73	75
750283	501752	501771	CACCTGTATCCAAAATTCAA	47	700
750284	501788	501807	CATATCTGAAGCACAGAGAG	39	701
750285	501860	501879	CAGTCTGCTCTGCTGCTCTG	66	702
750286	501862	501881	TCCAGTCTGCTCTGCTGCTC	67	703
750287	501882	501901	AGCTCAGAGGCAGCAGGAGC	47	704
750288	502030	502049	CTAAGCTCCATATTTAAATC	69	705
750289	502049	502068	TTCAGGCTTCCTTCACAGCC	69	706
750290	502052	502071	TTCTTCAGGCTTCCTTCACA	44	707
750291	502138	502157	GGAATCAGTGCTACCCATTA	23	708
750292	502194	502213	TTAGCCATCATTTTATTCTC	12	709
750293	502341	502360	GGCCCATTTTTTCAATCTCA	43	710
750294	502404	502423	CATGGTCTTCCTTGACTACA	40	711
750295	502580	502599	AAGCCAATGCGCAAGAAAAG	42	712
750296	503121	503140	CATCCAGTTAATCTCTGACA	31	713
750297	503125	503144	CTCGCATCCAGTTAATCTCT	38	714
750298	503145	503164	ACACCATCCCAGAAATGGTC	75	715
750299	503180	503199	TTTCTGACTCCCTATCCAGT	44	716
750300	503376	503395	TTCCCCAGGGTCATAGGAGT	71	717
750301	503442	503461	GCACTGTCCCAGTTGGATTA	27	718
750302	503490	503509	ACCCAGCAAAATGTGGGTCT	119	719
750303	503504	503523	TTGGTTGTGGTGAAACCCAG	79	720

750304	503533	503552	TGTTAAAAGAGAAAAGAATC	77	721
750305	503550	503569	TTGCAGTGATGTACTGATGT	26	722
750306	503599	503618	TTGTTTTTATAAGCAATTAG	59	723
750307	503645	503664	TATAAATATGCCCATATGCT	28	724
750308	503656	503675	CTGCCTGCAACTATAAATAT	45	725
750309	503825	503844	GTATCTCCTAGCCCAGTGCC	32	726
750310	503828	503847	ACTGTATCTCCTAGCCCAGT	64	727
750311	503895	503914	GATTGCTTTATTGCAACTAA	63	728
750312	503936	503955	CTTAAATAGTAGGAAAGCCA	14	729
750313	503973	503992	ACACTGTACAGGAGGGTGTC	25	155
	508739	508758			
750314	503975	503994	GCACACTGTACAGGAGGGTG	30	730
	508741	508760			
750315	503977	503996	CTGCACACTGTACAGGAGGG	17	79
	508743	508762			
750316	503979	503998	CACTGCACACTGTACAGGAG	41	731
	508745	508764			
750317	503981	504000	TTCACTGCACACTGTACAGG	33	156
	508747	508766			
750318	503983	504002	GATTCACTGCACACTGTACA	34	732
	508749	508768			
750319	503985	504004	TTGATTCACTGCACACTGTA	19	80
	508751	508770			
750320	503987	504006	TGTTGATTCACTGCACACTG	28	733
	508753	508772			
750321	503991	504010	ATGATGTTGATTCACTGCAC	19	734
	508757	508776			
750322	503993	504012	AAATGATGTTGATTCACTGC	43	157
	508759	508778			
750323	503995	504014	GGAAATGATGTTGATTCACT	29	735
	508761	508780			
750324	503998	504017	TGTGGAAATGATGTTGATTC	50	736
750325	504090	504109	CAGTATCTTAACTGGTGAAC	15	737

Table 12

Reduction of UBE3A-ATS RNA by 8,000nM 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages *in vitro* (40,000 cells/well)

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence (5' to 3')	UBE3A-ATS (%UTC)	SEQ ID NO
617456	463905	463924	CAACTGTTACCAAGACTTCA	25	32
617457	465003	465022	ATCTGCGAATAGAGGCCCTC	27	33
617460	466539	466558	TAGGTTGCATAAAGCCAGGC	25	36

617461	466981	467000	CACACATCTTGTTCCCTCAA	17	37
617557	483977	483996	ATCATGTGCATACCCAGGGT	13	172
699781	483977	483996	ATCATGTGCATACCCAGGGT	20	172
750111	481036	481055	ACATAGAATTATCATTATGA	49	738
750112	481073	481092	ACTGTGGAAAAACTTTGGCA	38	129
750113	481398	481417	ATGGGTTAAAATACTTATAA	79	739
750114	481451	481470	TAAAACCTTTGTGCATAATG	32	740
750115	481487	481506	CAACAACAAAAGCGGATAAA	50	741
750116	481524	481543	ATGACACTAGGTTTTGCAAA	34	742
750117	481529	481548	ACCTCATGACACTAGGTTTT	26	743
750118	481571	481590	GTATAGACCCAAACTATAAA	35	744
750119	481573	481592	ATGTATAGACCCAAACTATA	55	745
750120	481725	481744	TGATCTCTTCAACAAATTGT	82	746
750121	482139	482158	AATGTTGCCGAAAGAAAAGA	73	747
750122	482156	482175	ACAAGTGTCATATACTAAAT	51	748
750123	482174	482193	AAATTTAACCAAGGAGTTAC	48	749
750124	482246	482265	AGCCATCTAAAAGAGAAATT	38	750
750125	482396	482415	GATCAAGAAGTAAAATTATC	74	751
750126	482685	482704	CACATGATAATCTCAATTAT	52	752
750127	482916	482935	GAAAAATTCACTCTATAGGT	58	753
750128	482988	483007	CTATAGAGAGATAGATATTA	52	754
750129	483017	483036	AGAAAAATGTCTTTCCAAAT	43	755
750130	483089	483108	CAAATACTTAAATCAACTGT	50	756
750131	483255	483274	GGAGGGAGGAAAATTATTTC	14	757
750132	483297	483316	AGCAAACAACAGCAACATGC	56	758
750133	483323	483342	AAAATACTTTAGAAAAGTCA	73	759
750134	483365	483384	CAGAATTCAATGGACCCACA	33	760
750135	483809	483828	TCGGCAAAGGCATTATTATT	32	761
750136	483920	483939	GCTTTCACCTATAGGTGGCC	45	762
750137	483928	483947	GATGTTAAGCTTTCACCTAT	25	763
750138	483967	483986	TACCCAGGGTAGGATTCATG	17	764
750139	483970	483989	GCATACCCAGGGTAGGATTC	13	765
750140	483972	483991	GTGCATACCCAGGGTAGGAT	9	766
750141	483975	483994	CATGTGCATACCCAGGGTAG	16	767
750142	483979	483998	AGATCATGTGCATACCCAGG	34	768
750143	483982	484001	AGAAGATCATGTGCATACCC	36	769
750144	483984	484003	TAAGAAGATCATGTGCATAC	44	770
750145	483987	484006	AATTAAGAAGATCATGTGCA	119	771
750146	484085	484104	GTTCAGATGAACAATAAGCA	45	772
750147	484311	484330	ACTCATGCTGGTTACTAGGG	30	773
750148	484598	484617	TCATATGGGTGGTCGCTAAT	24	774
750149	484719	484738	ACACTAACGATGAACTCTAA	55	775
750150	484721	484740	TAACACTAACGATGAACTCT	42	776

750151	485136	485155	TTAAAACTCAACCCAGTGCA	29	777
750152	485344	485363	ATTCCTAGAGAAAACCTAGG	82	778
750153	485478	485497	AGAACAATGTTTCTTATGAA	72	779
750154	485865	485884	GAAACTGGGATATTACCAAT	45	780
750155	485871	485890	AAAATGGAAACTGGGATATT	37	781
750156	486052	486071	AAAAATTAAAGGCCAACAGA	46	782
750157	486157	486176	TTATGGCAGGTAGTGAAAGG	47	783
750158	486265	486284	ACAATATGCAAAAATTAAAT	74	784
750159	486400	486419	CATTCTCCAACATAGATCCT	41	785
750160	486568	486587	CAATAATAGAGACTTTACCA	79	786
750161	486812	486831	ATATATTATGTAAATGTAAC	78	787
750162	486824	486843	AGGATGGAAAAGATATATTA	76	788
750163	486842	486861	AAACAGGTTGAAAATGAAAG	79	789
750164	487049	487068	AAAGGCAATATTGAAGGAAA	72	790
750165	487267	487286	GAATTGAGTTAATAATTCCT	57	791
750166	487304	487323	TCTCACAGAGAAAGAGGTGG	21	792
750167	487314	487333	TTTTCTATAATCTCACAGAG	43	793
750168	487341	487360	GGCTCAGAAAACATCCTTTT	35	794
750169	487437	487456	ATTTAATTTACACTTAATTA	93	795
750170	487464	487483	ACTTTCCTCTGCTTATAACT	22	796
750171	487469	487488	ACTATACTTTCCTCTGCTTA	28	797
750172	487589	487608	AGCAATTAGAAATCACATGA	21	798
750173	487724	487743	AAAGCAGTAAACAATAAGTG	53	799
750174	487739	487758	TCATATGTAAATCCAAAAGC	57	800
750175	487772	487791	CATTGTAAGGATAAGAGATA	27	801
750176	487784	487803	CAGTTTGAATTACATTGTAA	29	802
750177	487804	487823	AATTGAACTTAAATTGGCAT	32	803
750178	487831	487850	CTGCATAGGAGTAGAGTTTT	31	804
750179	487877	487896	AAGATGGAATTTGCGACATC	50	805
750180	487921	487940	ACATAAAAATGTATAAATCC	70	806
750181	488018	488037	ACTGATAAAGGTAAGCACAT	31	807

Table 13

Reduction of UBE3A-ATS RNA by 8,000nM 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages *in vitro* (40,000 cells/well)

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence (5' to 3')	UBE3A-ATS (%UTC)	SEQ ID NO
617456	463905	463924	CAACTGTTACCAAGACTTCA	13	32
617457	465003	465022	ATCTGCGAATAGAGGCCCTC	38	33
617460	466539	466558	TAGGTTGCATAAAGCCAGGC	16	36
617461	466981	467000	CACACATCTTGTTCCCTCAA	11	37
617557	483977	483996	ATCATGTGCATACCCAGGGT	13	172
750398	510078	510097	CAGAGAGGAGAGAAGGACAA	45	808

750399	510104	510123	GGCTAGGAAAATTCTCCTGG	39	809
750400	510207	510226	AGGGAGAGCTGTCCTAAGGC	27	810
750401	510214	510233	GATATCCAGGGAGAGCTGTC	23	811
750402	510269	510288	TTGAAGGGAAAATTATTAAT	43	812
750403	510319	510338	AGCTGGACGGACAGTGTTGC	47	813
750404	510407	510426	CAAGACATGCTAGGGACTCT	38	814
750405	510408	510427	CCAAGACATGCTAGGGACTC	30	815
750406	510416	510435	GCCACAGTCCAAGACATGCT	49	816
750407	510442	510461	GCAGATAATCTGAAGATAGA	43	817
750408	510515	510534	TTTATTACAAACTGAAAGAG	42	818
750409	510609	510628	GGTCAGATAATGAGGGCCTT	20	819
750410	510701	510720	AGGATAGGTGTATGTGAGTG	31	820
750411	510729	510748	ATGAAGGTCAAGCCGAATCT	50	821
750412	510798	510817	AAAAGAAGTATGTGAAAGTA	45	822
750413	510997	511016	TGTCTCTAATCCTATTCCAA	12	823
750414	511100	511119	AGTCTTCATGATTTGGTAAA	37	824
750415	511341	511360	AGTAAGAGGCAGAATTATGT	54	825
750416	511441	511460	GGGCAGCAACAGCTCTTGAA	16	826
750417	511503	511522	TAATAATTAACAGTGACTGG	24	827
750418	511529	511548	AAGTCATTCCCCACCCTGGC	ND	828
750419	511555	511574	TCCAGCAGGGTGTATTCCAG	47	829
750420	511567	511586	TCAGCTGTGGTTTCCAGCAG	34	830
750421	511579	511598	GCTTAGAGAATCTCAGCTGT	49	831
750422	511594	511613	GGTTGGAAGCTGCCAGCTTA	22	832
750423	511668	511687	AATGGACTGCCGGCCTGGAG	47	833
750424	511893	511912	TGAACTACTTGGAGACCTTC	55	834
750425	511895	511914	AGTGAACTACTTGGAGACCT	45	835
750426	512282	512301	TCTTTTATTAAACCTAGTTT	60	836
750427	512318	512337	TTAGCTAGCTGTGGGTTTGC	25	837
750428	512392	512411	ACAAGAGCAGACATCTTTTT	60	838
750429	512564	512583	TGTAGCTTTTCTAAAATTCT	34	839
750430	512570	512589	GTATATTGTAGCTTTTCTAA	16	840
750431	513010	513029	CTTGATGGCTGTAGCTTGGT	21	841
750432	513074	513093	TTTCTGGATTCTCAGTCTTA	28	842
750433	513189	513208	TGCATTGGTATCTGTATATC	23	843
750434	513219	513238	GTTTCCTATTTCATCCATTT	25	844
750435	513378	513397	CTGGAGTGTAAGTAAATTCA	33	845
750436	513442	513461	ATACTCTTTCCACATTTCAG	19	846
750437	513450	513469	TCCTCTTGATACTCTTTCCA	34	847
750438	513459	513478	CTTAGGGTCTCCTCTTGATA	32	848
750439	513467	513486	CAGAGTGTCTTAGGGTCTCC	27	849
750440	513620	513639	ATATTTCTCAAATACTCTTC	48	850
750441	513760	513779	TGTGCTAGAACACTATCTTG	62	851
750442	513793	513812	TGACTCTCATCTCCCTCTTC	70	852
750443	513796	513815	CCCTGACTCTCATCTCCCTC	50	853

750444	513875	513894	CCTTCCTTCTTTATACTGCC	46	854
750445	513944	513963	CATCAAAATCTCTCATTCCT	22	855
750446	513947	513966	AATCATCAAAATCTCTCATT	35	856
750447	513951	513970	CCCCAATCATCAAAATCTCT	70	857
750448	514039	514058	TAGTCAGTAGTCCTAAAAAC	58	858
750449	514073	514092	AGACCTCTGTCTCTGGGATT	54	859
750450	514159	514178	AAAGTCCTTACCTGTTCTTG	36	860
750451	514326	514345	TTCACCGAAAGTACAGTCTT	54	861
750452	514330	514349	TAGTTTCACCGAAAGTACAG	ND	862
750453	514439	514458	AAGTCTTTTCTCCCCTCCCC	28	863
750454	514504	514523	TCAACAGTGTTAGTGTGTAA	45	864
750455	514513	514532	CCTTTTACCTCAACAGTGTT	35	865
750456	514673	514692	AGACTAGTCCCTGTGTAGTC	27	866
750457	514676	514695	CCAAGACTAGTCCCTGTGTA	40	867
750458	514701	514720	AACTGTCAGAGGAAGAAATG	62	868
750459	514861	514880	CGAACAGAACTTGCCGATGT	37	869
750460	514920	514939	TTGTATAGGGAGATGATAGA	39	870
750461	515069	515088	TAACCTTTTATTATTATAGA	55	871
750462	515111	515130	TAAACTAAAGTAACTGGTTT	55	872
750463	515143	515162	CCAGGAAGCTCTGGAGGGAA	23	873
750464	515187	515206	ACTCTATTATATATTTTGGT	28	874
750465	515215	515234	GTTATAAAAGTACTTTTTTT	78	875
750466	515242	515261	GGATACTTCCTCTACCCCAA	30	876
750467	515247	515266	ACAGTGGATACTTCCTCTAC	40	877
750468	515318	515337	CTGCCTTTTCATTACTATTT	30	878
750469	515500	515519	GTTTTAAAGTGGTAATTGAA	44	879

Table 14

Reduction of UBE3A-ATS RNA by 7,000 nM 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages *in vitro* (37,000 cells/well)

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence (5' to 3')	UBE3A-ATS (%UTC)	SEQ ID NO
617557	483977	483996	ATCATGTGCATACCCAGGGT	44	172
699781	483977	483996	ATCATGTGCATACCCAGGGT	51	172
749882	460115	460134	ACTTTATAGTGTGGATGGTA	39	586
750519	349103#	349122#	GTCATCACCTCTCTTCAGGA	17	181
1065269	432253	432272	TCATCATCAACCTAACCGAG	92	880
1065285	433960	433979	CCATCTTGGAACCGGATGAC	65	881
1065301	442413	442432	GTAATTGAGGTGGCCATATC	101	882
1065317	443132	443151	GAGTCCTAAATGTCTCATAC	81	883
1065333	444649	444668	GGTTTTAGTCCACTGGTTCA	44	884
1065349	445540	445559	CTAGTCATGTATCTACAGCC	88	885
1065365	446609	446628	GTATATGGCTTACACAGGCT	82	886

1065381	447599	447618	GAGATTTCAGACTACCTGTA	64	887
1065397	448125	448144	ATTGACCCAGCCCATGGCAC	97	888
1065413	448713	448732	GCGCATTGAGCAAAATTCCA	73	889
1065429	449066	449085	GCATAACGATAATCATGTGG	116	890
1065445	449627	449646	GGCTATAGGCCATTTATTCA	111	891
1065461	451295	451314	TTGAATAACTACCTAGGCTC	86	892
1065477	452310	452329	CCGGTGCAGGAATCCAGGAT	98	893
1065493	453797	453816	TAACAATAAGATAAAGGCGC	123	894
1065509	454580	454599	GGCAAGCAAAGACTACACCG	55	895
1065525	455169	455188	GCTCCTAACATTGTATCCCC	94	896
1065541	455476	455495	CTCTACCAAGCTATCCAAGT	78	897
1065557	456768	456787	GTCCTATTGGAGGGCCGCAC	39	898
1065573	457320	457339	GTCCTCCAATAAGCTTCTGA	48	899
1065589	458165	458184	GGGACAATACTGCAATCCTT	63	900
1065605	458957	458976	AGAGACCTCAAGACCTATAG	15	901
1065621	460348	460367	GACTACTTCAACCTGATACC	30	902
1065637	460957	460976	GGGCATCATTAACATAAGCT	69	903
1065652	461602	461621	ACAAACGGGCTATGTGAGAT	50	904
1065667	463052	463071	CACTGAGTTTTTGTAGTTCG	32	905
1065682	463885	463904	GGCAGTTGTGATAGTCAACA	75	906
1065698	464994	465013	TAGAGGCCCTCTTGTTTCAA	44	907
1065713	465247	465266	GGATTTTATTGGTCATCTCG	30	908
1065729	465664	465683	GTAGTTACTTATACTGGTTC	62	909
1065745	466276	466295	GTGGGTTCCTGATGGAGTCC	79	910
1065761	466540	466559	CTAGGTTGCATAAAGCCAGG	64	911
1065777	467942	467961	GCCTTAAAAGGGTTCCCTGT	64	912
1065793	470287	470306	GGTCATGATGTATGCCATTA	39	913
1065809	474125	474144	ATCTAGCTTGAATGGATACC	55	914
1065825	475454	475473	GTTCTTTCTCGGTCAAACTA	41	915
1065841	476084	476103	TACGAGTTGCTGGTTTCAGC	46	916
1065857	478470	478489	GGTTAGGGCTATGTTATGTT	31	917
1065873	480382	480401	GATTCCACTTGTGTATGCAC	33	918
1065889	482148	482167	CATATACTAAATGTTGCCGA	30	919
1065905	483368	483387	ATACAGAATTCAATGGACCC	55	920
1065936	485657	485676	GCCTAGGACCAGTTGGTTCA	48	921
1065952	487409	487428	GGCTGTTGTACATTCCTAGT	65	922
1065968	489096	489115	CCCTAAGCTTAGATATACCC	88	923
1065984	489740	489759	AGGTGGGAAACCGGTTCCCA	100	924
1066000	493977	493996	GGTCGGTCCCCACCAAAGGA	58	925
1066016	496817	496836	GCCATGTACGACCCTCATCA	76	926
1066032	498218	498237	TACTATAATACGGGACCTCA	70	927
1066048	499683	499702	ATCACATTCAAGGTAGCCCC	48	928
1066064	500605	500624	TGACCAGCAATAGGCTCTGC	37	929

1066080	500895	500914	ACTGGCCTTTGGGTCGGATA	81	930
1066096	501395	501414	GGAGTCCCCAGATAATGCAT	91	931
1066112	501767	501786	GGATGGGCTAAGAGTCACCT	74	932
1066128	502370	502389	GGTATTAAGGCCCTTGGCCA	104	933
1066144	502741	502760	GGCCCGATGACACCAGCCAC	87	934
1066160	502949	502968	TAACAGTCCTGTAACCAGAC	90	935
1066176	503331	503350	CCCCCTGAGATCCATGAGGT	125	936
1066192	503867	503886	CAGTTGTGCAGTTGTTAACT	86	937
1066208	504141	504160	AACCAGATGGCTGAGCTATT	89	938
1066224	504518	504537	TTAGGCCATACCTCTTCCAT	77	939
1066240	505065	505084	TTAGTCTGTTGTGTGACTCC	73	940
1066256	505644	505663	CCACCTAAGAGCTATCCGCT	75	941
1066272	505945	505964	GGCCGACCAGCTCTGAAAGT	120	942
1066288	506275	506294	ACCAGGGTGGTATTATAAAG	102	943
1066304	506773	506792	CAGGTTGTGGAGGTTGTTCC	96	944
1066320	507371	507390	GTTGTCTGGCATGGAGATCC	60	945
1066336	507929	507948	GTTGATTGGAGGCACTGCAG	62	946
1066352	508488	508507	TGGTGAGTAAATCAATCACG	106	947
1066368	509007	509026	CCCTTCAACATGTGTTAACG	62	948
1066384	509917	509936	CGTGGCTGTACCTGCAGTGC	49	949
1066400	510393	510412	GACTCTGATTGATTCAGTGC	93	950
1066416	510817	510836	AGTACAAACCACTAAGGGTA	114	951
1066432	511629	511648	GTGCCATATAATGTTGAAGC	71	952
1066448	511804	511823	CGTGTCTGAACTGGCCTGTG	75	953

Table 15

Reduction of UBE3A-ATS RNA by 7,000 nM 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages *in vitro* (37,000 cells/well)

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence (5' to 3')	UBE3A-ATS (%UTC)	SEQ ID NO
617557	483977	483996	ATCATGTGCATACCCAGGGT	28	172
749882	460115	460134	ACTTTATAGTGTGGATGGTA	25	586
750519	349103#	349122#	GTCATCACCTCTCTTCAGGA	17	181
1065270	432284	432303	CATAACCTCTCCTCGAGACA	96	954
1065286	434182	434201	TCTGTCACGCTTCCCTTGGC	61	955
1065302	442470	442489	TCACTGGTGTGGTATCATGC	49	956
1065318	443199	443218	GATTGCATCTCTTGCAGCAC	63	957
1065334	444722	444741	CTCACCTGTGTATATGAGTC	93	958
1065350	445583	445602	ACACTGTTAGAGCCCCCACA	71	959
1065366	446657	446676	GCATAGGAATGGGACCATAG	88	960
1065382	447672	447691	GCATCATACATAGTGTATGC	80	961
1065398	448219	448238	CTTGTCTCACAATTGTTACC	83	962
1065414	448721	448740	TAACTGTAGCGCATTGAGCA	91	963

1065430	449092	449111	GCTAGTCACTCATTGAGAAG	110	964
1065446	449633	449652	TAGATAGGCTATAGGCCATT	85	965
1065462	451694	451713	GCATATATCTTAACTCACCC	56	966
1065478	452315	452334	AAAAGCCGGTGCAGGAATCC	82	967
1065494	453918	453937	TAAGTGCCCATGGCATAGTC	65	968
1065510	454719	454738	GAGTGCTGAAGAACATCCCC	75	969
1065526	455213	455232	CAAGTCTACTACCAATAAGT	89	970
1065542	455567	455586	CGTCAGCATTGCTTGATCTC	89	971
1065558	456773	456792	TATTTGTCCTATTGGAGGGC	ND	972
1065574	457363	457382	CATGGTGAGGGTCTCAATGA	40	973
1065590	458238	458257	GAGACATGTGCCAGTTCAAG	19	974
1065606	458987	459006	GGACACTGGCACATCTATAG	64	975
1065622	460362	460381	CTGTATAACTGATTGACTAC	51	976
1065638	461068	461087	GCTCATCTATGGATTGCATT	49	977
1065653	461604	461623	GTACAAACGGGCTATGTGAG	30	978
1065668	463144	463163	AGCTATAGGTACCTGAAGTT	49	979
1065683	464365	464384	CTTAGCTTGCCCAGAGCATA	57	980
1065699	464999	465018	GCGAATAGAGGCCCTCTTGT	49	981
1065714	465287	465306	GATGTGTATAGGTGTTGGTC	55	982
1065730	465808	465827	CCATTTTGGTGCTATAACCC	43	983
1065746	466283	466302	CTTATAGGTGGGTTCCTGAT	40	984
1065762	466543	466562	TCTCTAGGTTGCATAAAGCC	69	985
1065778	468007	468026	GCACTTGTATAGTTCATCCC	37	986
1065794	470316	470335	ATCCTGCATCCGAGGCATGA	76	987
1065810	474167	474186	GTGGTTGCCTTAGTATTACA	24	988
1065826	475512	475531	CTGTAAGGTGATATCTATAC	28	989
1065842	476090	476109	TGTTCATACGAGTTGCTGGT	52	990
1065858	478533	478552	CGCAATGTATCAGGCAACAG	29	991
1065874	480393	480412	GAGGGCACAATGATTCCACT	65	992
1065890	482162	482181	GGAGTTACAAGTGTCATATA	37	993
1065906	483424	483443	GGCTCTATGCACTTAAGGGA	42	994
1065921	483978	483997	GATCATGTGCATACCCAGGG	35	995
1065937	485769	485788	GGTCAGATTCCTAAATACGC	26	996
1065953	487600	487619	GTGTCATATGTAGCAATTAG	25	997
1065969	489319	489338	CACCTGTATAGGAGAATTGT	100	998
1065985	489776	489795	CCACTCCCGTGGCAACATGA	85	999
1066001	493985	494004	GGGTAAGAGGTCGGTCCCCA	48	1000
1066017	496821	496840	GGAGGCCATGTACGACCCTC	80	1001
1066033	498225	498244	GCTGCAATACTATAATACGG	56	1002
1066049	499792	499811	AGCTGAGGTCACCGATCAGA	83	1003
1066065	500610	500629	AACAGTGACCAGCAATAGGC	64	1004
1066081	500898	500917	CTAACTGGCCTTTGGGTCGG	107	1005
1066097	501399	501418	GGGAGGAGTCCCCAGATAAT	24	1006
1066113	501802	501821	GGCCCAAGTGATGACATATC	50	1007
1066129	502410	502429	GTAAGGCATGGTCTTCCTTG	79	1008

1066145	502746	502765	AATATGGCCCGATGACACCA	85	1009
1066161	502956	502975	GCAAGATTAACAGTCCTGTA	53	1010
1066177	503342	503361	TCAGCTCAACACCCCCTGAG	96	1011
1066193	503872	503891	AGGGTCAGTTGTGCAGTTGT	39	1012
1066209	504260	504279	GCAAGGAATCATGTGGCTCC	70	1013
1066225	504526	504545	CCAAAGATTTAGGCCATACC	55	1014
1066241	505106	505125	GTAACCTTCACATAAGCTGC	48	1015
1066257	505654	505673	GGCCTAGCTTCCACCTAAGA	104	1016
1066273	505949	505968	CGCTGGCCGACCAGCTCTGA	ND	1017
1066289	506280	506299	CGTCTACCAGGGTGGTATTA	41	1018
1066305	506779	506798	ATACTCCAGGTTGTGGAGGT	84	1019
1066321	507481	507500	CAAATTGGTGAATGTTCCCC	44	1020
1066337	508000	508019	TCTCATGACCACCTAATTGA	72	1021
1066353	508571	508590	CCGTGCTGCTTTCTTGAGTG	92	1022
1066369	509052	509071	ACATGCTTGCATCCAGGCCC	53	1023
1066385	510017	510036	CGGAACCCACAGTAGAGGCA	46	1024
1066401	510398	510417	CTAGGGACTCTGATTGATTC	45	1025
1066417	510827	510846	ACCAGGCATAAGTACAAACC	62	1026
1066433	511633	511652	CTGAGTGCCATATAATGTTG	71	1027
1066449	511822	511841	AAGGCTCTCAGGGTAAGACG	42	1028

Table 16

Reduction of UBE3A-ATS RNA by 7,000 nM 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages *in vitro*(37,000 cells/well)

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence (5' to 3')	UBE3A-ATS (%UTC)	SEQ ID NO
617557	483977	483996	ATCATGTGCATACCCAGGGT	52	172
749882	460115	460134	ACTTTATAGTGTGGATGGTA	22	586
750519	349103#	349122#	GTCATCACCTCTCTTCAGGA	12	181
1065259	430439	430458	CGTGGAACACTGACCCATCA	73	1029
1065275	432915	432934	CAGCATGTAACTCATGTTGT	75	1030
1065291	441514	441533	GTTCTAAAGTCGGTTGTGTC	57	1031
1065307	442648	442667	AGAGTAGGCCAGGTGTCAAA	60	1032
1065323	443577	443596	TACCAGTGAGTAAACTGGCC	89	1033
1065339	444914	444933	GTACTCCCCATGCACACTTG	48	1034
1065355	445958	445977	ACGGATTATCATACCCTCCC	115	1035
1065371	446805	446824	GTCTTGTAAACCCTTACCAG	83	1036
1065387	447818	447837	CCGTTACTTAAGCTGTGGTA	88	1037
1065403	448458	448477	TAGTGCCAGTAGGACTTACT	75	1038
1065419	448827	448846	GGACCCTTAAGTCATAAAGA	78	1039
1065435	449209	449228	GACCAAATGAGCATCACATC	69	1040
1065451	449704	449723	CCTGTATGTATGGCTTATGC	73	1041
1065467	452181	452200	ATCCATAGTGATCTGGGAAC	77	1042

1065483	453133	453152	ACTATAATTGGGAATGGTCA	77	1043
1065499	454160	454179	GATTTGACCCTTATGGAGAC	104	1044
1065515	454855	454874	TATTCCCTATCCAGGGTAGA	96	1045
1065531	455296	455315	TTATCCTGTTGCAATAGAAC	81	1046
1065547	456499	456518	ATTAGATTAAAATCTGGCCG	93	1047
1065563	456886	456905	GACTCATAAGACAGGATGCC	87	1048
1065579	457738	457757	CCAGCCAGGTGTCTTATATC	18	1049
1065595	458523	458542	CAGTTGTGTATTGACTAAGT	23	1050
1065611	459549	459568	AAGACTATCCTGGTATGACT	56	1051
1065627	460624	460643	TCGATGTTCTTGCTTCCCTG	32	1052
1065642	461446	461465	GGCAGCTCCTGACAAATTAG	22	1053
1065658	461694	461713	AGACCCCTCCCTTAATGTAA	53	1054
1065673	463249	463268	ACCTGGGTATTGCTGTCCAA	41	1055
1065688	464458	464477	CTCACCCTTTACTAAGGTGC	75	1056
1065703	465140	465159	CCATTGGTATGAGAGATGCT	72	1057
1065719	465386	465405	GTCAGACTTATTGAGGATGG	27	1058
1065735	465932	465951	TTACTCCTCTGGTGTGCTGA	29	1059
1065751	466372	466391	GCGCACTTGGGAGCCAGCCA	68	1060
1065767	467076	467095	TTACTGACTGGCCTTAGGAG	38	1061
1065783	468351	468370	GTAGTATGCATTGACAAGCT	32	1062
1065799	471923	471942	GAGTATATTACCTCCAGGTT	27	1063
1065815	474614	474633	GTATTGCTGCTCTAGCTCTA	49	1064
1065831	475841	475860	ACGGACCTCATACAGTGAGT	31	1065
1065847	476213	476232	GGGCTCTTGGAAGTCTAGTT	59	1066
1065863	479124	479143	ACATACTTGGTTGCAGACGC	26	1067
1065879	480825	480844	TAGGTTTGCGGATGCCAGTG	50	1068
1065895	482771	482790	TACACAGTGGGATTTGCCCC	59	1069
1065911	483853	483872	ATGGCCTGACTAGGCATTGA	76	1070
1065926	484302	484321	GGTTACTAGGGCCAGAGAAT	42	1071
1065942	486355	486374	TGTTAATAGACTGCGATTAT	56	1072
1065958	487839	487858	GGGCGGAGCTGCATAGGAGT	51	1073
1065974	489522	489541	ACAATGGACCACCTAAGACC	96	1074
1065990	489953	489972	CAACCCTTACTCTGCCAGGG	80	1075
1066006	494491	494510	TGTGCAATAGCCTAAATGCC	82	1076
1066022	497436	497455	CTACTATGAAGTTATGCACC	69	1077
1066038	499100	499119	GTTAGCCTTACAGCAAATAC	52	1078
1066054	500359	500378	TACTAATTAGCAAGCCACTG	52	1079
1066070	500766	500785	GTGTCAAATCAATTTGTGCC	47	1080
1066086	501001	501020	CTAAGCACATCCGATAGTCA	49	1081
1066102	501563	501582	GGAGTGCTCTTTGTGGATGC	39	1082
1066118	502117	502136	ACCCATGGCTCATCAGTGGG	91	1083
1066134	502447	502466	GGCAGCTCTTTGTAGGCCCA	60	1084
1066150	502782	502801	GGAGTGGGTTCCTATAAGGA	53	1085

1066166	503100	503119	GGACTAATAGGCCTTTCTAC	61	1086
1066182	503399	503418	CTACAGTACCAGGTCATTTG	45	1087
1066198	503946	503965	CACCACCAACCTTAAATAGT	80	1088
1066214	504395	504414	CCATGCCACAGATTGGCTTG	64	1089
1066230	504654	504673	CGGAGCCTTACGCTTGGCTG	66	1090
1066246	505185	505204	CAGTCTGTCTCTGTGTACCG	46	1091
1066262	505741	505760	GGTTGACAGGACATGCTGTC	58	1092
1066278	506119	506138	GTTAGCCGAGCATTGGCTTC	84	1093
1066294	506589	506608	CCCATGGTGGTGGAATGCTG	102	1094
1066310	506992	507011	TCCCGCACCATGCATTCTGA	43	1095
1066326	507684	507703	TCAGCTTCCTTCAGTGGGCG	65	1096
1066342	508193	508212	GATCTCACACATGGCACTGC	71	1097
1066358	508691	508710	TACCAGTAAAGGGTAGTATA	49	1098
1066374	509110	509129	GTAAATATACACTTGGGCCC	73	1099
1066390	510117	510136	TAGCTGAACCTGTGGCTAGG	60	1100
1066406	510654	510673	AGTGTCAGGCTGTAAGGGAT	59	1101
1066422	510901	510920	GCCATAGGTTTCAGGCTGAT	46	1102
1066438	511707	511726	GAGATGGGCTATGAGCCATC	84	1103

Table 17

Reduction of UBE3A-ATS RNA by 7,000 nM 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages *in vitro* (37,000 cells/well)

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence (5' to 3')	UBE3A-ATS (%UTC)	SEQ ID NO
617557	483977	483996	ATCATGTGCATACCCAGGGT	32	172
749882	460115	460134	ACTTTATAGTGTGGATGGTA	21	586
750519	349103#	349122#	GTCATCACCTCTCTTCAGGA	8	181
1065264	430601	430620	GGACCAGCGGGCCGAACGCA	101	1104
1065280	433410	433429	ATGCAAAGGTGTCGATTTGT	47	1105
1065296	441815	441834	GGTCCATAGATGTCAGTTAC	27	1106
1065312	442767	442786	ATTAATGTTCTATGGTGGAT	46	1107
1065328	443839	443858	GGAGTAGAATGCCCACTGGG	53	1108
1065344	445212	445231	GAGACCTGAATATACCTTAC	55	1109
1065360	446498	446517	GGTATGCCAGGTTTTTGACA	49	1110
1065376	447152	447171	CCGTGTAATGACACACCTCT	67	1111
1065392	447922	447941	AGGCTATAGTCAAAGGGTGG	46	1112
1065408	448614	448633	GTGTCAGTCAATCATTGAGA	75	1113
1065424	449001	449020	GGTCTTATTTACCATTGGCA	63	1114
1065440	449470	449489	TAACATGTTGCTTGCACTCC	85	1115
1065456	450017	450036	GCTCAAACTAGAATACCCCA	81	1116
1065472	452261	452280	GTCTAGGTCTCACGCTGTGT	96	1117
1065488	453235	453254	GACAGTGGAGTCAAGTTGGT	106	1118
1065504	454462	454481	GGACTCCACACACCTACTAG	107	1119

1065520	455019	455038	GTGGGATGGCTGTCAATGCT	56	1120
1065536	455341	455360	GATAATTGAGGAGTTCACCA	81	1121
1065552	220313	220332	GATCCAAACAAGCACCCTCC	85	1122
	456682	456701			
1065568	457020	457039	TATCACAGTTGCTTGACCCT	70	1123
1065584	457982	458001	GATCTATTATGAGGGCATCA	39	1124
1065600	458571	458590	AGCTTTAGTATGTCGAGAAC	20	1125
1065616	460107	460126	GTGTGGATGGTATCCTGGTC	26	1126
1065632	460711	460730	GGAATGCTTGATCTGTGGGC	25*	1127
1065647	461518	461537	GCTAGACTAGTTGAAATCGG	44	1128
1065663	462056	462075	CCCTCCCATCAGTGAAGATT	78	1129
1065677	463767	463786	GCTTTAGAGGTCAAATAGTG	50	1130
1065693	464784	464803	CTGGTCTTCCTCGAGGATAG	69	1131
1065708	465236	465255	GTCATCTCGGGTATATAAAT	30	1132
1065724	465561	465580	GGACAAGTCTTATAGAGAAC	52	1133
1065740	466229	466248	GTTCCAAGTATGGGCTGCTG	44	1134
1065756	466426	466445	GTCAACATGTGCTTGCAAGC	35	1135
1065772	467425	467444	GCTGTTGATACGCTCCTTCA	37	1136
1065788	469130	469149	GAGGCACTGAAGTTCACTAC	37	1137
1065804	472937	472956	AGGGTCCCACTTGTTTAGGT	44	1138
1065820	474883	474902	CGTATTAAGGTGTTGTATGA	40	1139
1065836	475943	475962	CCTTGTGACAATAGTAGTGA	54	1140
1065852	476443	476462	GGCTAGATGGAGCTTGAGCC	94	1141
1065868	479997	480016	CGTGAGCTATCTGTACAAAA	24	1142
1065884	481441	481460	GTGCATAATGGTCTACCACA	32	1143
1065900	482857	482876	TGAAGATAGGTCAGTTAACG	58	1144
1065916	483925	483944	GTTAAGCTTTCACCTATAGG	33	1145
1065931	484601	484620	TGATCATATGGGTGGTCGCT	46	1146
1065947	487134	487153	ATTGTCCTCCTGGTAACCAC	28	1147
1065963	488572	488591	GGGACTGGTGCCACACCATC	55	1148
1065979	489629	489648	CTAACCTGGATCTCAGATAG	75	1149
1065995	493844	493863	CTGGGCCCCAATTCAGTAAT	98	1150
1066011	495399	495418	TTGGTAAAGGAGGGAATCGG	ND	1151
1066027	498030	498049	TCCAGGATATATGTTAGTCC	46	1152
1066043	499291	499310	TAGCTACAATAAGTTGTAGC	94	1153
1066059	500494	500513	GAGGGCCATGTTAAAGGCCT	119	1154
1066075	500861	500880	TTTTGGTAGGTAACTACGGG	41	1155
1066091	501335	501354	TGTAGCTCAGCTCAATGTGT	58	1156
1066107	501628	501647	GAACTGCACTGGGTTGTCTC	58	1157
1066123	502162	502181	GTATTGCACTCACATACTGT	61	1158
1066139	502579	502598	AGCCAATGCGCAAGAAAAGT	69	1159
1066155	502824	502843	CATAGGCATAAAGCCTCCTA	79	1160
1066171	503139	503158	TCCCAGAAATGGTCCTCGCA	86	1161
1066187	503480	503499	ATGTGGGTCTGCACCAAGTT	86	1162
1066203	504077	504096	GGTGAACTCCTGTGACTGAT	52	1163

1066219	504441	504460	GTGGAGTAGGTATATTAGTC	32	1164
1066235	504825	504844	GTATTCCTGAAGTAGTCCTG	36	1165
1066251	505330	505349	AGAAATTGGGCCGCCTCTGT	58	1166
1066267	505817	505836	GTGCTTAGTGAACTGTGGGC	55	1167
1066283	506185	506204	CCGGCATGCATCAGCTCTGA	34	1168
1066299	506693	506712	TAAGAAGCTTGCCTTTCGAT	96	1169
1066315	507250	507269	GCAGTGCTACTGTGCCCTTA	58	1170
1066331	507818	507837	TCCAGCCCTCAGTATATAGA	62	1171
1066347	508285	508304	CCGAAGTGGAAGTAGTCATG	63	1172
1066363	508790	508809	TGAATGCCACCGTGATTGCA	50	1173
1066379	509416	509435	CGTAGTGTCATCACCATAAA	45	1174
1066395	510227	510246	GTTGTGTCTGAGGGATATCC	45	1175
1066411	510718	510737	GCCGAATCTTGACATACAGG	55	1176
1066427	511241	511260	GATTACCAAAAAGGGACCAG	48	1177
1066443	511766	511785	CTCCTACCAATAATGGAGTC	76	1178

Table 18

Reduction of UBE3A-ATS RNA by 7,000 nM 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages *in vitro* (37,000 cells/well)

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence (5' to 3')	UBE3A-ATS (%UTC)	SEQ ID NO
617557	483977	483996	ATCATGTGCATACCCAGGGT	38	172
749882	460115	460134	ACTTTATAGTGTGGATGGTA	32	586
750519	349103#	349122#	GTCATCACCTCTCTTCAGGA	17	181
1065265	430612	430631	CGGACACACTGGGACCAGCG	90	1179
1065281	433463	433482	GCTCCTATCAAGCTTTTCCC	46	1180
1065297	441909	441928	TGAGGTGCATTTTCTAGCCC	78	1181
1065313	442830	442849	ATCTATGGAGTCATCTCCCC	76	1182
1065329	443979	443998	GGTAGAGGTTAATCTATGTC	59	1183
1065345	445310	445329	CGTCGGTAAAGGAAGCTACT	58	1184
1065361	446510	446529	TCATAAGGACAAGGTATGCC	73	1185
1065377	447310	447329	GGACCTCATTAGATCAGTCA	90	1186
1065393	448007	448026	GGCAGTTGAGTGGTGTCAGT	99	1187
1065409	448628	448647	GGATTGCATCACATGTGTCA	55	1188
1065425	449017	449036	TATAAGTGTCCATAAAGGTC	90	1189
1065441	449475	449494	GGCATTAACATGTTGCTTGC	66	1190
1065457	450095	450114	GAATTGATAAGTGGTCTTCT	86	1191
1065473	452266	452285	GGGAAGTCTAGGTCTCACGC	ND	1192
1065489	453243	453262	CTACATATGACAGTGGAGTC	89	1193
1065505	454467	454486	TGAGTGGACTCCACACACCT	84	1194
1065521	455028	455047	GATATTGCAGTGGGATGGCT	60	1195
1065537	455360	455379	CGTGATAGTGCTATTGTGAG	60	1196
1065553	220317	220336	CATCGATCCAAACAAGCACC	74	1197
	456686	456705			

1065569	457233	457252	GCTTAGCTACTCACCCCTGT	70	1198
1065585	457989	458008	CCCACTTGATCTATTATGAG	64	1199
1065601	458790	458809	CCCTAATATAGGGCAGATGA	59	1200
1065617	460108	460127	AGTGTGGATGGTATCCTGGT	44	1201
1065633	460736	460755	GGATTTGAGCCTGCTATGTC	15*	1202
1065648	461524	461543	CATTCAGCTAGACTAGTTGA	70	1203
1065664	462061	462080	TATGGCCCTCCCATCAGTGA	49	1204
1065678	463775	463794	TAGATTGGGCTTTAGAGGTC	33	1205
1065694	464788	464807	ACATCTGGTCTTCCTCGAGG	61	1206
1065709	465237	465256	GGTCATCTCGGGTATATAAA	17	1207
1065725	465591	465610	ACCGAAGGAGTTCCTTTAGC	40	1208
1065741	466233	466252	GGCAGTTCCAAGTATGGGCT	76	1209
1065757	466438	466457	GTGGAGCCAGCTGTCAACAT	66	1210
1065773	467718	467737	TGGAATGTATCCTGTACGGG	52	1211
1065789	469377	469396	GTGTTATACTATTGTGGTGC	42	1212
1065805	472944	472963	GTTTGTTAGGGTCCCACTTG	49	1213
1065821	474901	474920	TCTGCTATTGTTGGATATCG	33	1214
1065837	475988	476007	ATGGTTAGTTTAAGAAATCG	65	1215
1065853	478295	478314	GAGTCCTGGTTGATGTGGTG	65	1216
1065869	480141	480160	ACGGGCATGCTTTATAATTA	73	1217
1065885	481448	481467	AACCTTTGTGCATAATGGTC	82	1218
1065901	482908	482927	CACTCTATAGGTTCAAGCAG	37	1219
1065917	483964	483983	CCAGGGTAGGATTCATGGTC	63	1220
1065932	484673	484692	TGTTGTATGCAGGTTCATCA	31	1221
1065948	487139	487158	GATACATTGTCCTCCTGGTA	35	1222
1065964	488637	488656	ACACTTGAAGCTGTTGAGTC	66	1223
1065980	489652	489671	CGTGAAGGAATGATCTCTCT	61	1224
1065996	493855	493874	CCTAATCTATGCTGGGCCCC	75	1225
1066012	495430	495449	GAGAGTAAGTTACTAGAGGC	59	1226
1066028	498180	498199	TGGGCAGATTGATCACCTAG	93	1227
1066044	499495	499514	TACTAGGCCTGCTCTACTGG	71	1228
1066060	500523	500542	TTAGAGGTCAAGCCCTGTGT	63	1229
1066076	500885	500904	GGGTCGGATATAGCTTTTAC	31	1230
1066092	501340	501359	GCTTATGTAGCTCAGCTCAA	33	1231
1066108	501701	501720	TTGGGACATCCCAAAGTTAC	80	1232
1066124	502205	502224	GGAACATCATGTTAGCCATC	44	1233
1066140	502588	502607	GATGCATCAAGCCAATGCGC	41	1234
1066156	502882	502901	GAACCTCTACAGAGAGACTA	65	1235
1066172	503154	503173	GTTCTGTATACACCATCCCA	56	1236
1066188	503485	503504	GCAAAATGTGGGTCTGCACC	96	1237
1066204	504082	504101	TAACTGGTGAACTCCTGTGA	98	1238
1066220	504449	504468	CCCCAGAAGTGGAGTAGGTA	ND	1239
1066236	504866	504885	CCTCAAGATCAACAGACCCC	81	1240
1066252	505543	505562	CAGTCAGGTACAGGTGTTGG	52	1241
1066268	505823	505842	GTGAGGGTGCTTAGTGAACT	54	1242

1066284	506196	506215	GTCAGAACAATCCGGCATGC	50	1243
1066300	506730	506749	GAGTGCTCCACACTTCTGTC	65	1244
1066316	507254	507273	GCTTGCAGTGCTACTGTGCC	95	1245
1066332	507900	507919	TCGATACCTGCTTTTGTGAC	69	1246
1066348	508290	508309	CATAACCGAAGTGGAAGTAG	71	1247
1066364	508901	508920	TACTTCATGACTGCCTAGTT	78	1248
1066380	509434	509453	AAGAAGGGCATATATCTACG	72	1249
1066396	510312	510331	CGGACAGTGTTGCTGTTAGG	39	1250
1066412	510724	510743	GGTCAAGCCGAATCTTGACA	68	1251
1066428	511490	511509	TGACTGGGTAAGGCAGGATC	50	1252
1066444	511770	511789	AGTACTCCTACCAATAATGG	77	1253

Table 19

Reduction of UBE3A-ATS RNA by 7,000 nM 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages *in vitro* (37,000 cells/well)

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence (5' to 3')	UBE3A-ATS (%UTC)	SEQ ID NO
617557	483977	483996	ATCATGTGCATACCCAGGGT	17	172
749882	460115	460134	ACTTTATAGTGTGGATGGTA	26	586
750519	349103#	349122#	GTCATCACCTCTCTTCAGGA	12	181
1065271	432577	432596	GGCAGTGCATTCAACTGTAG	75	1254
1065287	440156	440175	CGTGGGTTAGTCCAAGTAAC	49	1255
1065303	442546	442565	GCCCATTATGTAGTCTATAG	37	1256
1065319	443234	443253	GACGAAGGCAGTCACTCTGC	88	1257
1065335	444735	444754	GGGAGAACTACATCTCACCT	63	1258
1065351	445658	445677	CCCCATTACCACGGTCTCTT	63	1259
1065367	446675	446694	AGCAGTCTTTATCTACAGGC	85	1260
1065383	447745	447764	TTGATGACCTGGTAAGGGAT	76	1261
1065399	448290	448309	CGCAATAAGATTCCATTGCC	83	1262
1065415	448725	448744	ACGATAACTGTAGCGCATTG	70	1263
1065431	449100	449119	GCAAGTATGCTAGTCACTCA	82	1264
1065447	449637	449656	CCATTAGATAGGCTATAGGC	77	1265
1065463	452066	452085	TCGCCGCTGATTTTAAAGAT	97	1266
1065479	452320	452339	GGTTCAAAAGCCGGTGCAGG	83	1267
1065495	453926	453945	GTTGTTCTTAAGTGCCCATG	61	1268
1065511	454740	454759	GCACTTTGCATGAGAATAGG	60	1269
1065527	455219	455238	TCCAGACAAGTCTACTACCA	69	1270
1065543	455585	455604	TCTACTCCTTGCTACAAACG	84	1271
1065575	457378	457397	CAATAGTGTAGGTGACATGG	36	1273
1065591	458400	458419	GCATGTGGGCCTCTATTAAG	8	1274
1065607	459079	459098	GTATGGTATCTTGCAGTAGC	15	1275
1065623	460427	460446	ATAGCCCTTTCAGCACACTT	16	1276
1065639	461343	461362	GCTGGCAATATGTCAACCTT	36	1277
1065654	461605	461624	TGTACAAACGGGCTATGTGA	30	1278

1065669	463151	463170	CATATGAAGCTATAGGTACC	22	1279
1065684	464383	464402	GGTAGTTCACAACTCTTCCT	59	1280
1065700	465002	465021	TCTGCGAATAGAGGCCCTCT	49	1281
1065715	465301	465320	GACACGCTGACTATGATGTG	77	1282
1065731	465875	465894	CTTGCCCATGGATGGTTGTC	71	1283
1065747	466287	466306	GTGGCTTATAGGTGGGTTCC	ND	1284
1065763	466945	466964	GGTTGTATGCCTTCTGCATT	44	1285
1065779	468014	468033	CCTTGCAGCACTTGTATAGT	44	1286
1065795	470319	470338	ACTATCCTGCATCCGAGGCA	23	1287
1065811	474227	474246	ATATAATTGAGGGCCACCAT	74	1288
1065827	475597	475616	CCTTTAGAGGGATTTGTGTA	34	1289
1065843	476097	476116	CTTAACATGTTCATACGAGT	47	1290
1065859	478733	478752	GCTGATCACATTACCCATCC	24	1291
1065875	480518	480537	GATGTATCACGCAAACAATT	81	1292
1065891	482167	482186	ACCAAGGAGTTACAAGTGTC	62	1293
1065907	483587	483606	GGCCAGGATGGTCAACCTTA	50	1294
1065922	484119	484138	TTTTTGCCACAGCCGCTTGG	193	1295
1065938	485811	485830	CGAATAATTGCATGCCAACT	68	1296
1065954	487606	487625	GGTTTAGTGTCATATGTAGC	23	1297
1065970	489324	489343	GCACACACCTGTATAGGAGA	43	1298
1065986	489780	489799	CCTGCCACTCCCGTGGCAAC	95	1299
1066002	493989	494008	TTATGGGTAAGAGGTCGGTC	ND	1300
1066018	496826	496845	GGTATGGAGGCCATGTACGA	84	1301
1066034	498510	498529	GCGCCCGGCAAGAGATTCAC	ND	1302
1066050	499912	499931	TTGCATAATAGGAGGTCCTT	51	1303
1066066	500662	500681	GGGCTTACAACCTCTCAATT	74	1304
1066082	500899	500918	CCTAACTGGCCTTTGGGTCG	80	1305
1066098	501446	501465	GTCTGCACAGGTGGCATAGA	53	1306
1066114	501817	501836	GTCCAGAGGTCATATGGCCC	54	1307
1066130	502416	502435	GCATAAGTAAGGCATGGTCT	41	1308
1066146	502755	502774	CTTCGGGCAAATATGGCCCG	76	1309
1066162	503036	503055	GGTGCTACAGTCATACTATC	62	1310
1066178	503346	503365	GTGATCAGCTCAACACCCCC	65	1311
1066194	503878	503897	TAATAAAGGGTCAGTTGTGC	39	1312
1066210	504270	504289	CACTGCCTAAGCAAGGAATC	86	1313
1066226	504530	504549	TGCCCCAAAGATTTAGGCCA	69	1314
1066242	505115	505134	TCAGACATGGTAACCTTCAC	40	1315
1066258	505660	505679	ATTGCAGGCCTAGCTTCCAC	51	1316
1066274	506031	506050	GGTATTGAGTAGGACTTCTC	34	1317
1066290	506402	506421	CTTAAGGAGGCAACTCCTGA	51	1318
1066306	506781	506800	ATATACTCCAGGTTGTGGAG	66	1319
1066322	507526	507545	GAGCCAGGTTCCTGTTCACG	33	1320
1066338	508110	508129	CCGTCTTTAGGAACTTAAAT	43	1321
1066354	508581	508600	AGCACAACCCCCGTGCTGCT	88	1322
1066370	509058	509077	TACCCAACATGCTTGCATCC	58	1323

1066386	510022	510041	ATACACGGAACCCACAGTAG	70	1324
1066402	510402	510421	CATGCTAGGGACTCTGATTG	69	1325
1066418	510832	510851	GTTAGACCAGGCATAAGTAC	44	1326
1066434	511638	511657	TGCAGCTGAGTGCCATATAA	56	1327
1066450	511890	511909	ACTACTTGGAGACCTTCACC	57	1328

Table 20

Reduction of UBE3A-ATS RNA by 7,000 nm 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages *in vitro* (37,000 cells/well)

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence (5' to 3')	UBE3A-ATS (%UTC)	SEQ ID NO
617557	483977	483996	ATCATGTGCATACCCAGGGT	35	172
749882	460115	460134	ACTTTATAGTGTGGATGGTA	26	586
749902	461442	461461	GCTCCTGACAAATTAGCACT	61	1329
750519	349103#	349122#	GTCATCACCTCTCTTCAGGA	20	181
1065258	430419	430438	CGGATGCAGGGCACCCTTGG	96	1330
1065274	432770	432789	CATGATATAAGGAGAAACGC	63	1331
1065290	440729	440748	ATCTTGCGGCTGTCTCCCAG	64	1332
1065306	442613	442632	TCCCATAGTTATATGGCTCA	60	1333
1065322	443476	443495	CTGCATGTTAGATTGGGCAT	48	1334
1065338	444879	444898	GCTGTGATGCTAGGATGCAT	84	1335
1065354	445874	445893	AGACATAGACCCCAGACGGT	83	1336
1065370	446795	446814	CCCTTACCAGAATAGCATCC	81	1337
1065386	447803	447822	TGGTAGACCACTGATTCCCC	63	1338
1065402	448415	448434	AGCAAGGGTCTTAGTGCCAA	60	1339
1065418	448742	448761	GTCTGTATATTTAGACCACG	83	1340
1065434	449159	449178	GTCAACATTATATCGATGCA	64	1341
1065450	449697	449716	GTATGGCTTATGCATGCTAT	86	1342
1065466	452137	452156	TGGGCAGGTCAACTTGGTAT	66	1343
1065482	453037	453056	AAAAGGTGATTAGGCGGCCG	88	1344
1065498	454156	454175	TGACCCTTATGGAGACTTAT	74	1345
1065514	454846	454865	TCCAGGGTAGAAGACTAGCA	63	1346
1065530	455286	455305	GCAATAGAACAGATGGCCAT	97	1347
1065546	455764	455783	GTACCAAAGTGGCTGCTCAC	89	1348
1065562	456866	456885	ACTGCCCTCTTCGAAGAGAT	71	1349
1065578	457715	457734	GATTATCTCAGACATGCCAT	20	1350
1065594	458488	458507	CCTTAAGCAAGGAGTTCACT	39	1351
1065610	459543	459562	ATCCTGGTATGACTGTCAGT	45	1352
1065626	460538	460557	GGCTCTCATCTAAATAAGCC	75	1353
1065657	461674	461693	AACCCTAAGGTGAAGTCTGT	65	1354
1065672	463245	463264	GGGTATTGCTGTCCAAATGG	20	1355
1065687	464409	464428	GTGTTATGGTTCCCATTCAG	32	1356
1065702	465012	465031	CCTGCTCAAATCTGCGAATA	58	1357

1065718	465382	465401	GACTTATTGAGGATGGTGTG	53	1358
1065734	465894	465913	TGAACTCCCACAAGGTACTC	52	1359
1065750	466341	466360	AGGCATTTGGAGCATTCGGG	16	1360
1065766	467050	467069	ACTTTCATCAGTTAGTCAGG	30	1361
1065782	468343	468362	CATTGACAAGCTATTGCAGC	44	1362
1065798	470982	471001	TTTTATGGCTTATAGCAGCG	50	1363
1065814	474563	474582	CACGCCCAAATGGAACTCTA	38	1364
1065830	475827	475846	GTGAGTTATAGAGTGTTCCC	39	1365
1065846	476165	476184	TGGGCACTTAGGAGTTCCTA	73	1366
1065862	479069	479088	GCTGTATCTGTGGTTTAGCA	67	1367
1065878	480818	480837	GCGGATGCCAGTGGCCGAGA	40	1368
1065894	482519	482538	GCTATACCCCTAGGATCAGA	31	1369
1065910	483843	483862	TAGGCATTGAATGAGGGCCC	71	1370
1065925	484245	484264	GTATGGACTTGTCTTATGGC	57	1371
1065941	486351	486370	AATAGACTGCGATTATACAA	48	1372
1065957	487807	487826	CGCAATTGAACTTAAATTGG	56	1373
1065973	489517	489536	GGACCACCTAAGACCTCAAG	50	1374
1065989	489908	489927	GGCTAAAGTAATCTTATGGG	48	1375
1066005	494490	494509	GTGCAATAGCCTAAATGCCA	69	1376
1066021	497267	497286	GGATTAGGCAGCTTCACTAC	44	1377
1066037	499088	499107	GCAAATACAATGGTAATCGC	30	1378
1066053	500286	500305	CTGGTGTACATTGGATATGA	57	1379
1066069	500694	500713	GCAAGAGGTACTGTAAGCCC	70	1380
1066085	500993	501012	ATCCGATAGTCAAACTATGA	52	1381
1066101	501532	501551	AAACACCCTTCCAATGAGGG	75	1382
1066117	501986	502005	GTTCACTAGCATCTGCTACA	46	1383
1066133	502443	502462	GCTCTTTGTAGGCCCAAGGG	38	1384
1066149	502776	502795	GGTTCCTATAAGGAATAGGC	73	1385
1066165	503096	503115	TAATAGGCCTTTCTACAGCT	77	1386
1066181	503374	503393	CCCCAGGGTCATAGGAGTGT	80	1387
1066197	503944	503963	CCACCAACCTTAAATAGTAG	70	1388
1066213	504390	504409	CCACAGATTGGCTTGGAATG	74	1389
1066229	504650	504669	GCCTTACGCTTGGCTGACAT	73	1390
1066245	505179	505198	GTCTCTGTGTACCGAGCTCA	63	1391
1066261	505724	505743	GTCTGGTGGCCAAGTGCTTC	70	1392
1066277	506116	506135	AGCCGAGCATTGGCTTCATA	73	1393
1066293	506584	506603	GGTGGTGGAATGCTGTCCAC	89	1394
1066309	506869	506888	CTCCACCAAATACTTAGCCC	67	1395
1066325	507649	507668	TAAATGTCAGGAGGTCCCCC	55	1396
1066341	508126	508145	CCTTGGGTTATTCTTACCGT	55	1397
1066357	508680	508699	GGTAGTATAAGAATGGTTCC	54	1398
1066373	509104	509123	ATACACTTGGGCCCAAATGG	78	1399
1066389	510039	510058	GCTAGCATTTGAGAGTTATA	43	1400

1066405	510647	510666	GGCTGTAAGGGATTAAGATG	79	1401
1066421	510853	510872	CTGTTACAGGGAGACAATCT	56	1402
1066437	511678	511697	ACCCTGCACAAATGGACTGC	103	1403

Table 21

Reduction of UBE3A-ATS RNA by 7,000 nM 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages *in vitro* (37,000 cells/well)

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence (5' to 3')	UBE3A-ATS (%UTC)	SEQ ID NO
617557	483977	483996	ATCATGTGCATACCCAGGGT	42	172
749882	460115	460134	ACTTTATAGTGTGGATGGTA	33	586
750519	349103#	349122#	GTCATCACCTCTCTTCAGGA	21	181
1065268	432234	432253	GGGCACCCCCGTCACCGTGC	82	1404
1065284	433765	433784	AGATTTTCCGACCTATGTCA	62	1405
1065300	442386	442405	ATCGCCATGGTCACTTGCCA	63	1406
1065316	443032	443051	GGCAAAGCAAGTTCGCCACA	91	1407
1065332	444610	444629	ATCATACAGGTCACTTGGCT	63	1408
1065348	445505	445524	ATTGGACTAGGTAACAGTGA	103	1409
1065364	446595	446614	CAGGCTATTTCTTAGTGGAC	59	1410
1065380	447562	447581	CAAGGGTAACCTATAGCTGA	116	1411
1065396	448099	448118	GCATATGCACACTTGGATCA	89	1412
1065412	448676	448695	ACCCTGAAAACAATCAATCG	102	1413
1065428	449061	449080	ACGATAATCATGTGGCCTGA	85	1414
1065444	449593	449612	GACTAACTATACAGGTCTCT	107	1415
1065460	451288	451307	ACTACCTAGGCTCACTTGCT	83	1416
1065476	452297	452316	CCAGGATGCTAATGCTCCTA	69	1417
1065492	453781	453800	GCGCTTTCACCAAGAAATTT	78	1418
1065508	454575	454594	GCAAAGACTACACCGTGACA	109	1419
1065524	455153	455172	CCCCTGCATTCAGCTTATAG	85	1420
1065540	455467	455486	GCTATCCAAGTGACACAGTA	77	1421
1065556	456757	456776	GGGCCGCACATCTGGACCTC	104	1422
1065572	457293	457312	TACAAAACGACCTAAAGACC	83	1423
1065588	458156	458175	CTGCAATCCTTAAGACTTGA	37	1424
1065604	458952	458971	CCTCAAGACCTATAGGACCT	37	1425
1065620	460284	460303	ATACATTGCCAGCACTAAGG	60	1426
1065636	460849	460868	GATTTACCACACATATAGGC	36	1427
1065651	461597	461616	CGGGCTATGTGAGATAATTC	15	1428
1065666	462686	462705	GGCTGACATGCCCCTTTTAA	142	1429
1065681	463881	463900	GTTGTGATAGTCAACAATTG	89	1430
1065697	464991	465010	AGGCCCTCTTGTTTCAATTG	63	1431
1065712	465246	465265	GATTTTATTGGTCATCTCGG	30	1432
1065728	465606	465625	GCCTTTCTATTTCAGACCGA	35	1433

1065744	466263	466282	GGAGTCCATGAAGTAACTGG	62	1434
1065760	466538	466557	AGGTTGCATAAAGCCAGGCC	55	1435
1065776	467801	467820	CCCTCTTAGTGATTGGTGGT	63	1436
1065792	470049	470068	GGTTGGCAGTCTTCACCAGT	62	1437
1065808	474120	474139	GCTTGAATGGATACCAATTA	40	1438
1065824	475447	475466	CTCGGTCAAACTAATAATAC	53	1439
1065840	476015	476034	CCAGTTTTCGCCCGTTACCT	32	1440
1065856	478440	478459	GTAGCTATAGGTGTCACATA	21	1441
1065872	480351	480370	GCCTCAAATATGTGATGCAC	45	1442
1065888	482108	482127	GAATGGCAATACATCCGTGT	80	1443
1065904	483359	483378	TCAATGGACCCACATGATCA	63	1444
1065920	483971	483990	TGCATACCCAGGGTAGGATT	29	1445
1065935	485084	485103	TCTAATACTACAACGATGGA	84	1446
1065951	487204	487223	AACCTTCCTAAAATCCCCGA	52	1447
1065967	489085	489104	GATATACCCAGTTAATCAGT	63	1448
1065983	489731	489750	ACCGGTTCCCAATTTTCTCC	78	140
1065999	493889	493908	TTGGCAGATGTAACCTATTC	52	1449
1066015	496809	496828	CGACCCTCATCACTTTTTGA	73	1450
1066031	498209	498228	ACGGGACCTCAATACTCTAC	56	1451
1066047	499678	499697	ATTCAAGGTAGCCCCAATAC	89	1452
1066063	500578	500597	CTACTGGCATCAGTCAAAAC	84	150
1066079	500894	500913	CTGGCCTTTGGGTCGGATAT	86	1453
1066095	501390	501409	CCCCAGATAATGCATAGATC	98	1454
1066111	501763	501782	GGGCTAAGAGTCACCTGTAT	59	1455
1066127	502360	502379	CCCTTGGCCACCTGACTTCG	77	1456
1066143	502629	502648	TTGGCTCAGTGTTCACTTCG	52	1457
1066159	502939	502958	GTAACCAGACCCAAGGCACT	62	1458
1066175	503325	503344	GAGATCCATGAGGTATATAC	55	1459
1066191	503815	503834	GCCCAGTGCCCTATAGGTCA	67	1460
1066207	504127	504146	GCTATTTCATTAAGTCACCC	39	1461
1066223	504502	504521	CCATGGAATGGCTGTCATGC	72	1462
1066239	504974	504993	TTATCTTCTTAGGGTCGACT	38	1463
1066255	505635	505654	AGCTATCCGCTTCCCAAGGG	47	1464
1066271	505906	505925	CCCTGAGATGCTAGTTGGGC	85	1465
1066287	506256	506275	GTATGTCCTTGGAGGTGAGC	88	1466
1066303	506744	506763	GCCTTTCATTTTGGGAGTGC	48	1467
1066319	507364	507383	GGCATGGAGATCCAACCTGT	96	1468
1066335	507919	507938	GGCACTGCAGGATAGCCATT	95	1469
1066351	508470	508489	CGTTATCCTAAGAAGTGACT	58	1470
1066367	509003	509022	TCAACATGTGTTAACGGAAC	63	1471
1066383	509910	509929	GTACCTGCAGTGCATAGAGC	52	1472
1066399	510387	510406	GATTGATTCAGTGCTCATGC	49	1473
1066415	510747	510766	ACTGCAGATAGGTAGGTGAT	43	1474

1066431	511593	511612	GTTGGAAGCTGCCAGCTTAG	96	1475
1066447	511795	511814	ACTGGCCTGTGGCAGTTAAC	80	1476

Table 22

Reduction of UBE3A-ATS RNA by 7,000 nM 5-10-5 MOE gapmers with with mixed PO/PS internucleoside linkages *in vitro* (37,000 cells/well)

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence (5' to 3')	UBE3A-ATS (%UTC)	SEQ ID NO
617557	483977	483996	ATCATGTGCATACCCAGGGT	28	172
749882	460115	460134	ACTTTATAGTGTGGATGGTA	24	586
750519	349103#	349122#	GTCATCACCTCTCTTCAGGA	17	181
1065261	430489	430508	GCGCTGGCTCACGCATGCTC	65	1477
1065277	432989	433008	CCTAGAGTTTCCTTCTCCCG	79	1478
1065293	441703	441722	GGGATGCCAATGCCTCCAAC	97	1479
1065309	442707	442726	TAAATTGCCCTGGGTGCAGC	71	1480
1065325	443778	443797	GCCCTTTCAGGACCAACTGG	107	1481
1065341	445116	445135	GTTGGGCAAACAAGTTACCC	92	1482
1065357	446183	446202	GGGACCCCAATTTACTACGC	112	1483
1065373	446912	446931	CTTCTTGCAAGGATTGGCAC	69	1484
1065389	447847	447866	ACTGAGATGTGTGATACTCC	70	1485
1065405	448471	448490	CCACTCAATAGAATAGTGCC	123	1486
1065421	448838	448857	CCCAATTGCAAGGACCCTTA	80	1487
1065437	449334	449353	GAACATGTAGCCATAATGCC	65	1488
1065453	449867	449886	GAGTGGCATCCTTAAATCCT	66	1489
1065469	452204	452223	TAATTGGTCAAGTAAACAGC	73	1490
1065485	453199	453218	TCCACCGTTACTGATTATCT	51	1491
1065501	454230	454249	CAAGTCCCACCATGTTAATC	87	1492
1065517	454913	454932	GTTAGGATCTATTTGACAGC	67	1493
1065533	455318	455337	AGGCCTGCTCCGAATGTGTT	107	1494
1065549	456627	456646	GTGCATGGTTATCTAATGCA	87	1495
1065565	456917	456936	TTGGGTCACTAGGCACACTA	110	1496
1065581	457899	457918	TGACTAGTTCGATAAGTTTT	48	1497
1065597	458561	458580	TGTCGAGAACTCAAAAGGTG	31	1498
1065613	459646	459665	CTGTATAGTTTACCCAGGCA	24	1499
1065629	460641	460660	CAGAGTGCATTGGCAACTCG	50	1500
1065644	461457	461476	GATCTTGGTAAGGCAGCTCC	29	1501
1065660	461891	461910	CAATTTGGTCCCATTGTAGT	84	1502
1065675	463503	463522	TCTATCAAGGCTGTTATTGG	40	1503
1065690	464528	464547	GCTCAGTTAGGTTAGTGCAC	23	1504
1065705	465162	465181	TCTAGGGCTCCAGTTTATGT	78	1505
1065721	465442	465461	CTTTGGTTATGTACATTGCC	73	1506
1065737	466098	466117	GCCTGTATGTCTTGAGAAAC	78	1507

1065753	466388	466407	CTCGCTTTTCACAGGAGCGC	36	1508
1065769	467300	467319	TCACAGAGTAGTCTATTGGT	43	1509
1065785	468922	468941	GTAAGTATAGATGCCTCTCC	33	1510
1065801	472475	472494	GCAAACTTTAGGAGTGTGTT	60	1511
1065817	474799	474818	GGTATTGACACCTCCAACTG	18	1512
1065833	475854	475873	ATATAAGGGTAATACGGACC	39	1513
1065849	476362	476381	GCCCCCTGCCGTGTGAAAGA	72	1514
1065865	479579	479598	CTTCAAGACTAAGGTAGGGA	38	1515
1065881	480923	480942	GTATGCGAAGCGAACGAAGC	75	1516
1065897	482786	482805	CCTAAAAAACCCGTGTACAC	62	1517
1065913	483907	483926	GGTGGCCTTCAGTCAGTACA	57	1518
1065928	484317	484336	GCCCAGACTCATGCTGGTTA	96	1519
1065944	486448	486467	ATACTTCACCTAATAGCACC	86	1520
1065960	488086	488105	GGAGTTCTTTAGGTTGGAAC	62	1521
1065976	489542	489561	GCAACTATGGGTGGAGACAT	53	1522
1065992	493191	493210	TCGGGCCAGGTCCAGGCGCA	52	1523
1066008	495127	495146	GCTGTCATATGGGAACTACG	57	1524
1066024	497743	497762	CAAACCTACGCCAATAAAGA	86	1525
1066040	499138	499157	TTTATCGCTTAAAGTAGCCT	83	1526
1066056	500407	500426	CGTATATCGAATACCCTCAA	33	1527
1066072	500818	500837	GTAAGAGTTAGCTATTCCCC	30	1528
1066088	501153	501172	CAGTAAAGAGCCACCTAAGG	71	1529
1066104	501574	501593	GGCAAGGCTAAGGAGTGCTC	54	1530
1066120	502129	502148	GCTACCCATTAGACCCATGG	34	1531
1066136	502502	502521	GGAGTCCCTGTGTCATTGGA	37	1532
1066152	502803	502822	GGATGTAGCCCATCAACCCT	77	1533
1066168	503118	503137	CCAGTTAATCTCTGACATGG	57	1534
1066184	503422	503441	AGGTGATGACACCCCTACCA	57	1535
1066200	503960	503979	GGGTGTCTCTTTGACACCAC	76	1536
1066216	504419	504438	AGGCAGTCAGGGTAATGCTA	76	1537
1066232	504667	504686	CCTTCTGTCCCAACGGAGCC	111	1538
1066248	505213	505232	CTCTCGCTGAGGACACATCA	64	1539
1066264	505791	505810	ACCACAGGGTACTATTCTGG	64	1540
1066280	506126	506145	CTGCTCTGTTAGCCGAGCAT	75	1541
1066296	506634	506653	GCTTGTATGCCCCACTGGAG	59	1542
1066312	507213	507232	GCTTGCCATGTTTTATAGAC	80	1543
1066328	507762	507781	CTCAGGATCGCTGGCCATTT	62	1544
1066344	508223	508242	GCCTAAAGGTAGTTCTCCCT	57	1545
1066360	508731	508750	CAGGAGGGTGTCAACCAGAC	75	1546
1066376	509178	509197	GGCAGATAACCTCCAAGTGC	95	1547
1066392	510128	510147	CACATAGACCATAGCTGAAC	56	1548
1066408	510668	510687	GTCTAGTATGTCTGAGTGTC	87	1549
1066424	511065	511084	GACTCGGGACATTTAGGATG	72	1550

1066440	511730	511749	ATAGGCCACGCTGGTCACTG	48	1551

Table 23

Reduction of UBE3A-ATS RNA by 7,000 nM 5-10-5 MOE gapmers with with mixed PO/PS internucleoside linkages *in vitro* (37,000 cells/well)

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence (5' to 3')	UBE3A-ATS (%UTC)	SEQ ID NO
617557	483977	483996	ATCATGTGCATACCCAGGGT	39	172
749882	460115	460134	ACTTTATAGTGTGGATGGTA	16	586
750519	349103#	349122#	GTCATCACCTCTCTTCAGGA	14	181
1065260	430471	430490	TCATCCTCTATGGACCCACG	83	1552
1065276	432973	432992	CCCGACTTACATTACCTACC	69	1553
1065292	441621	441640	ATGATCTGCTGTTCAGTGCG	45	1554
1065308	442687	442706	AGGCCAAGTGGTGCTCTTCC	58	1555
1065324	443691	443710	ATTCAGATACTAGTTTACCC	36	1556
1065340	445011	445030	TCTAGGTAGGCTGAGCCTCA	89	1557
1065356	445972	445991	TTGTCTTGGAACATACGGAT	81	1558
1065372	446901	446920	GATTGGCACTATTTTGAGCC	113	1559
1065388	447835	447854	GATACTCCAAATATGACCCG	80	1560
1065404	448465	448484	AATAGAATAGTGCCAGTAGG	70	1561
1065420	448833	448852	TTGCAAGGACCCTTAAGTCA	87	1562
1065436	449328	449347	GTAGCCATAATGCCATAGTC	61	1563
1065452	449862	449881	GCATCCTTAAATCCTGGTTG	97	1564
1065468	452186	452205	GCAATATCCATAGTGATCTG	84	1565
1065484	453194	453213	CGTTACTGATTATCTTATCC	72	1566
1065500	454225	454244	CCCACCATGTTAATCAAGGC	69	1567
1065516	454863	454882	CAGGTGTATATTCCCTATCC	70	1568
1065532	455309	455328	CCGAATGTGTTATTTATCCT	58	1569
1065548	456621	456640	GGTTATCTAATGCATCATCA	71	1570
1065564	456909	456928	CTAGGCACACTAAAGTGCAC	84	1571
1065580	457802	457821	GATGCAATCACAGCAAGTAC	68	1572
1065596	458560	458579	GTCGAGAACTCAAAAGGTGA	51	1573
1065612	459639	459658	GTTTACCCAGGCAATGGCTC	70	1574
1065628	460629	460648	GCAACTCGATGTTCTTGCTT	79	1575
1065643	461453	461472	TTGGTAAGGCAGCTCCTGAC	58	1576
1065659	461886	461905	TGGTCCCATTGTAGTTGTGT	50	1577
1065674	463502	463521	CTATCAAGGCTGTTATTGGT	29	1578
1065689	464477	464496	GCTTCTAACTAACATGCCTC	61	1579
1065704	465158	465177	GGGCTCCAGTTTATGTATCC	79	1580
1065720	465418	465437	TAGCCTGCATGGTTTACAGT	72	1581
1065736	466030	466049	GGGCTCTTGTTACTGAGCTG	79	1582
1065752	466382	466401	TTTCACAGGAGCGCACTTGG	55	1583
1065768	467295	467314	GAGTAGTCTATTGGTGTTCC	27	1584
1065784	468404	468423	CCCTACCCTTGCATGCTATG	75	1585

1065800	471928	471947	CCATTGAGTATATTACCTCC	45	1586
1065816	474789	474808	CCTCCAACTGTAATCATTGA	65	1587
1065832	475846	475865	GTAATACGGACCTCATACAG	61	1588
1065848	476316	476335	ACTACTTGTCCCCTGGGCTT	45	1589
1065864	479256	479275	CTTGCTTGTATGGTCTGATG	63	1590
1065880	480830	480849	AAAAGTAGGTTTGCGGATGC	61	1591
1065896	482778	482797	ACCCGTGTACACAGTGGGAT	60	1592
1065912	483896	483915	GTCAGTACACAAGCAGGTAG	68	1593
1065927	484309	484328	TCATGCTGGTTACTAGGGCC	42	1594
1065943	486378	486397	GTTAGGCCACAAGACTTAAT	51	1595
1065959	488046	488065	CTCAAACCCGTATAAAGATG	58	1596
1065975	489527	489546	GACATACAATGGACCACCTA	70	1597
1065991	489961	489980	GGAAGTTCCAACCCTTACTC	64	1598
1066007	494921	494940	GAATCCACTACATGGGATTA	110	1599
1066023	497674	497693	GACTAAGCCCGAAAGTTAGC	79	1600
1066039	499133	499152	CGCTTAAAGTAGCCTAAGGA	41	1601
1066055	500400	500419	CGAATACCCTCAACTTCACC	59	1602
1066071	500797	500816	CAACCTTGATAGCAGCTTAT	38	1603
1066087	501007	501026	GTGAAACTAAGCACATCCGA	77	1604
1066103	501569	501588	GGCTAAGGAGTGCTCTTTGT	66	1605
1066119	502125	502144	CCCATTAGACCCATGGCTCA	21	1606
1066135	502465	502484	TACAACAGTCCCAGGCTAGG	51	1607
1066151	502799	502818	GTAGCCCATCAACCCTGGGA	72	1608
1066167	503107	503126	CTGACATGGACTAATAGGCC	47	1609
1066183	503415	503434	GACACCCCTACCATGGCTAC	54	1610
1066199	503956	503975	GTCTCTTTGACACCACCAAC	62	1611
1066215	504408	504427	GTAATGCTATCTTCCATGCC	47	1612
1066231	504661	504680	GTCCCAACGGAGCCTTACGC	62	1613
1066247	505200	505219	CACATCAGCTGTTAGCAGTC	64	1614
1066263	505749	505768	ACTCTGTAGGTTGACAGGAC	59	1615
1066279	506121	506140	CTGTTAGCCGAGCATTGGCT	88	1616
1066295	506628	506647	ATGCCCCACTGGAGAAGTCT	77	1617
1066311	506997	507016	CGTCTTCCCGCACCATGCAT	40	1618
1066327	507699	507718	CGTGTCACTTTCAGGTCAGC	59	1619
1066343	508216	508235	GGTAGTTCTCCCTTCTGTCA	73	1620
1066359	508726	508745	GGGTGTCAACCAGACTTCCA	ND	1621
1066375	509128	509147	GCTCATCACAACTGGGTGGT	35	1622
1066391	510121	510140	ACCATAGCTGAACCTGTGGC	62	1623
1066407	510659	510678	GTCTGAGTGTCAGGCTGTAA	68	1624
1066423	510905	510924	GTGTGCCATAGGTTTCAGGC	18	1625
1066439	511725	511744	CCACGCTGGTCACTGAAAGA	70	1626

Table 24

Reduction of UBE3A-ATS RNA by 7,000 nM 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages *in vitro* (37,000 cells/well)

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence (5' to 3')	UBE3A-ATS (%UTC)	SEQ ID NO
617557	483977	483996	ATCATGTGCATACCCAGGGT	49	172
749882	460115	460134	ACTTTATAGTGTGGATGGTA	25	586
750519	349103#	349122#	GTCATCACCTCTCTTCAGGA	10	181
1065266	432182	432201	CCGCTCAATGCAGGACACCA	79	1627
1065282	433495	433514	TGCTCCATAGGTAAGATGGT	82	1628
1065298	442149	442168	TAGGCACTGCCTTTGTTGCG	87	1629
1065314	442877	442896	GTCGAAGACAATATAACATC	59	1630
1065330	444418	444437	ATCAGGGCACATGGAGTTGT	21	1631
1065346	445359	445378	CCCTTAGGTGGGAGTCTTCC	128	1632
1065362	446536	446555	GGCTCTAGACCATTGACTCA	72	1633
1065378	447498	447517	GTAGTGCCTCAATGATCCAC	62	1634
1065394	448042	448061	GGTAAAGTGGACTGGATGCC	66	1635
1065410	448635	448654	CTCATGAGGATTGCATCACA	71	1636
1065426	449041	449060	AGGAACGGCCCTGACTGTCA	110	1637
1065442	449492	449511	CCATATCAATAACAATTGGC	111	1638
1065458	450273	450292	GGAACTCCAGCCAGTGAATA	96	1639
1065474	452270	452289	ATGAGGGAAGTCTAGGTCTC	80	1640
1065490	453360	453379	ACATAGGCACTCTACTAGCT	101	1641
1065506	454514	454533	TATCAGTCATAGCTACACAC	104	1642
1065522	455119	455138	GGTGGATGTCTGACTTGACT	61	1643
1065538	455426	455445	GCTAAAGTTGTGGTCTACCA	83	1644
1065554	220324	220343	TTCTCATCATCGATCCAAAC	60	1645
	456693	456712			
1065570	457238	457257	TAATGGCTTAGCTACTCACC	90	1646
1065586	457994	458013	GAGAACCCACTTGATCTATT	24	1647
1065602	458938	458957	GGACCTCAGGAGATTGTACA	35	1648
1065618	460111	460130	TATAGTGTGGATGGTATCCT	31	1649
1065634	460744	460763	GTACACAGGGATTTGAGCCT	12*	1650
1065649	461528	461547	GGAACATTCAGCTAGACTAG	40	1651
1065665	462567	462586	TAAATTGGTCTGGTTACAAG	56	1652
1065679	463779	463798	CCTATAGATTGGGCTTTAGA	48	1653
1065695	464905	464924	GTCTATATTTGGTAAGACAC	69	1654
1065710	465240	465259	ATTGGTCATCTCGGGTATAT	18	1655
1065726	465596	465615	TTCAGACCGAAGGAGTTCCT	60	1656
1065742	466244	466263	GTAGGATCTATGGCAGTTCC	59	1657
1065758	466448	466467	GTTCTACAGAGTGGAGCCAG	65	1658
1065774	467791	467810	GATTGGTGGTTTATTCATCG	47	1659
1065790	469893	469912	TACCCATTGCAAGTTAACTA	73	1660
1065806	473260	473279	TCCTAATAGTTGGAGGTGGT	ND	1661

1065822	474959	474978	CAGCCTAATATGTGTCATCC	40	1662
1065838	476003	476022	CGTTACCTCAATTCTATGGT	49	1663
1065854	478299	478318	ACTGGAGTCCTGGTTGATGT	67	1664
1065870	480146	480165	ACAAAACGGGCATGCTTTAT	63	1665
1065886	481476	481495	GCGGATAAATTGGATTTATC	37	1666
1065902	483108	483127	AGGCAATGGACTTAGTACAC	21	1667
1065918	483965	483984	CCCAGGGTAGGATTCATGGT	45	1668
1065933	484683	484702	CAAGTGATGATGTTGTATGC	87	1669
1065949	487192	487211	ATCCCCGAATGGGAGAGATT	107	1670
1065965	489067	489086	GTGAACGAATACTGTGGCAT	59	1671
1065981	489671	489690	CCAACCTGTCATGGGACTGC	45	1672
1065997	493859	493878	TAGGCCTAATCTATGCTGGG	44	1673
1066013	496023	496042	TCTCAAAAGACATTCGGTAC	137	1674
1066029	498183	498202	CCATGGGCAGATTGATCACC	102	1675
1066045	499515	499534	TGCCTAAGGGAGTTTGTCAC	73	1676
1066061	500527	500546	ATGTTTAGAGGTCAAGCCCT	91	1677
1066077	500886	500905	TGGGTCGGATATAGCTTTTA	58	1678
1066093	501347	501366	GACATCTGCTTATGTAGCTC	45	1679
1066109	501708	501727	AGTTACTTTGGGACATCCCA	68	1680
1066125	502209	502228	GTTTGGAACATCATGTTAGC	49	1681
1066141	502595	502614	TCCAACTGATGCATCAAGCC	43	1682
1066157	502904	502923	GCCTATATCCAACCAGCTAC	73	1683
1066173	503217	503236	CGTTGGAAACTTCAAAGGCA	69	1684
1066189	503506	503525	CCTTGGTTGTGGTGAAACCC	72	1685
1066205	504087	504106	TATCTTAACTGGTGAACTCC	73	1686
1066221	504477	504496	GGATGGTTGACCTCAAAATT	30	1687
1066237	504952	504971	TGGTTACCCATACAGTATAT	42	1688
1066253	505549	505568	GCTTTTCAGTCAGGTACAGG	29	1689
1066269	505828	505847	GACCTGTGAGGGTGCTTAGT	81	1690
1066285	506235	506254	GTTTGACCAGCTCCTTGTTG	76	1691
1066301	506734	506753	TTGGGAGTGCTCCACACTTC	72	1692
1066317	507331	507350	GATGCCCTGGTCCTAGCTTC	60	1693
1066333	507909	507928	GATAGCCATTCGATACCTGC	56	1694
1066349	508297	508316	GCTTCTACATAACCGAAGTG	116	1695
1066365	508933	508952	CTAGTGCCTATTACAATCTG	61	1696
1066381	509882	509901	CATGTGCTTTGTGGACCCAT	47	1697
1066397	510318	510337	GCTGGACGGACAGTGTTGCT	61	1698
1066413	510733	510752	GGTGATGAAGGTCAAGCCGA	103	1699
1066429	511561	511580	GTGGTTTCCAGCAGGGTGTA	20	1700
1066445	511777	511796	ACTAAAGAGTACTCCTACCA	110	1701

Table 25

Reduction of UBE3A-ATS RNA by 7,000 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages *in vitro* (37,000 cells/well)

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence (5' to 3')	UBE3A-ATS (%UTC)	SEQ ID NO
617557	483977	483996	ATCATGTGCATACCCAGGGT	34	172
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749921	462626	462645	GTAATGATTTGCCCTCCTAC	32	1702
750519	349103#	349122#	GTCATCACCTCTCTTCAGGA	17	181
1065267	432208	432227	CCAGCGGGACCTGGACAAGC	62	1703
1065283	433699	433718	GGTGTAGTGGCAAGAAGTTC	59	1704
1065299	442231	442250	CCCCCTAGCTTTCCAATGGG	82	1705
1065315	442923	442942	GTCTCCACATAATCCTATTG	48	1706
1065331	444553	444572	ACATCCCATTAATCATCGCT	49	1707
1065347	445388	445407	TCAGATTACCTGAAGGTGTA	104	1708
1065363	446582	446601	AGTGGACAGATACGGTCCGT	95	1709
1065379	447508	447527	TCAGTTGTGAGTAGTGCCTC	75	1710
1065395	448074	448093	GCTTACCAGAGATGGTTTCC	111	1711
1065411	448658	448677	CGTAGGGCAAAAGTAAGGAT	71	1712
1065427	449050	449069	GTGGCCTGAAGGAACGGCCC	92	1713
1065443	449532	449551	GACCTTCAATTGATCAGTCT	112	1714
1065459	450791	450810	CCTGTCTGGTACTCCCATAT	69	1715
1065475	452275	452294	TCAATATGAGGGAAGTCTAG	73	1716
1065491	453366	453385	TTAACTACATAGGCACTCTA	76	1717
1065507	454568	454587	CTACACCGTGACAAAAGAGC	76	1718
1065523	455125	455144	AGCACAGGTGGATGTCTGAC	82	1719
1065539	455450	455469	GTAGTTGTATCTTGAATGGG	65	1720
1065555	220380	220399	CATCTGGACCTCAGATTGAC	64	1721
	456749	456768			
1065571	457288	457307	AACGACCTAAAGACCTAGCA	36	1722
1065587	458044	458063	CTTGAGTAACTACTCATGAC	83	1723
1065603	458946	458965	GACCTATAGGACCTCAGGAG	33	1724
1065619	460118	460137	CTAACTTTATAGTGTGGATG	18	1725
1065635	460843	460862	CCACACATATAGGCTAGCCA	9	1726
1065650	461573	461592	GGTCATCATATTGAACCAAT	44	1727
1065680	463826	463845	GATTTCCTTACTGAGTGAGC	29	1728
1065696	464909	464928	GGTAGTCTATATTTGGTAAG	17	1729
1065711	465242	465261	TTATTGGTCATCTCGGGTAT	47	1730
1065727	465600	465619	CTATTTCAGACCGAAGGAGT	32	1731
1065743	466251	466270	GTAACTGGTAGGATCTATGG	49	1732
1065759	466496	466515	TTTTTAGGGTAGTGTCCTGA	92	1733
1065775	467797	467816	CTTAGTGATTGGTGGTTTAT	54	1734
1065791	469899	469918	GGGATTTACCCATTGCAAGT	ND	1735
1065807	473264	473283	GCCATCCTAATAGTTGGAGG	44	1736

1065823	475306	475325	GGTTAAGTCTGCTCTTTCAC	25	1737
1065839	476008	476027	TCGCCCGTTACCTCAATTCT	60	1738
1065855	478307	478326	GCTATTACACTGGAGTCCTG	45	1739
1065871	480150	480169	CAATACAAAACGGGCATGCT	94	1740
1065887	481747	481766	GATCATTCCCTGTGGTAAAG	68	1741
1065903	483112	483131	GCTTAGGCAATGGACTTAGT	11	1742
1065919	483969	483988	CATACCCAGGGTAGGATTCA	43	1743
1065934	484722	484741	ATAACACTAACGATGAACTC	37	1744
1065950	487198	487217	CCTAAAATCCCCGAATGGGA	98	1745
1065966	489079	489098	CCCAGTTAATCAGTGAACGA	77	1746
1065982	489676	489695	ATGTTCCAACCTGTCATGGG	71	1747
1065998	493867	493886	GATGAGATTAGGCCTAATCT	43	1748
1066014	496564	496583	CCATCTACTATTAATGAGCT	58	1749
1066030	498186	498205	TCACCATGGGCAGATTGATC	109	1750
1066046	499672	499691	GGTAGCCCCAATACAGATTC	26	72
1066062	500564	500583	CAAAACATGTTCTGACCTCG	93	1751
1066078	500892	500911	GGCCTTTGGGTCGGATATAG	93	1752
1066094	501356	501375	CGTCAAACTGACATCTGCTT	38	1753
1066110	501733	501752	AGTTAACACCTATCAAGTTG	58	1754
1066126	502355	502374	GGCCACCTGACTTCGGCCCA	115	1755
1066142	502599	502618	GACTTCCAACTGATGCATCA	42	1756
1066158	502919	502938	GACCCTTCTGTGAAAGCCTA	61	1757
1066174	503279	503298	GACTGCATCTCAATCCTATG	62	1758
1066190	503636	503655	GCCCATATGCTTGAACAATT	40	1759
1066206	504088	504107	GTATCTTAACTGGTGAACTC	55	1760
1066222	504484	504503	GCAGTTTGGATGGTTGACCT	43	1761
1066238	504963	504982	GGGTCGACTGATGGTTACCC	80	1762
1066254	505594	505613	ATAGGAGCTGAATAGTAGGG	37	1763
1066270	505833	505852	TCAAAGACCTGTGAGGGTGC	78	1764
1066286	506243	506262	GGTGAGCTGTTTGACCAGCT	49	1765
1066302	506739	506758	TCATTTTGGGAGTGCTCCAC	53	1766
1066318	507359	507378	GGAGATCCAACCTGTGTGGA	79	1767
1066334	507915	507934	CTGCAGGATAGCCATTCGAT	69	1768
1066350	508354	508373	CATTATTCAATTAAGGGTGG	15	1769
1066366	508999	509018	CATGTGTTAACGGAACTGAG	85	1770
1066382	509901	509920	GTGCATAGAGCAGACTGTAC	103	1771
1066398	510328	510347	GGTTTTGAGAGCTGGACGGA	57	1772
1066414	510740	510759	ATAGGTAGGTGATGAAGGTC	75	1773
1066430	511586	511605	GCTGCCAGCTTAGAGAATCT	95	1774
1066446	511781	511800	GTTAACTAAAGAGTACTCCT	92	1775

Table 26

Reduction of UBE3A-ATS RNA by 7,000 nM 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages *in vitro* (37,000 cells/well)

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence (5' to 3')	UBE3A-ATS (%UTC)	SEQ ID NO
617557	483977	483996	ATCATGTGCATACCCAGGGT	35	172
749882	460115	460134	ACTTTATAGTGTGGATGGTA	42	586
749960	465003	465022	ATCTGCGAATAGAGGCCCTC	56	33
750519	349103#	349122#	GTCATCACCTCTCTTCAGGA	16	181
1065272	432587	432606	GTAGGAGATAGGCAGTGCAT	25	1776
1065288	440174	440193	AATTATACTGTCCTACTTCG	65	1777
1065304	442560	442579	GTACCCCAGAAATAGCCCAT	45	1778
1065320	443271	443290	CATCACTAGCCTAGTGATCT	114	1779
1065336	444826	444845	GGGTGCTGTCAACTGTCCCA	45	1780
1065352	445690	445709	GGCAAAGTACATACTGATCC	54	1781
1065368	446725	446744	CCTGTGCGGTAGCACTTGCC	80	1782
1065384	447772	447791	GGGCCAAGCACATAGGTATC	74	1783
1065400	448306	448325	CGTGCAAAACAAGTTTCGCA	91	1784
1065416	448729	448748	GACCACGATAACTGTAGCGC	62	1785
1065432	449105	449124	TCCTGGCAAGTATGCTAGTC	73	1786
1065448	449643	449662	ACTGATCCATTAGATAGGCT	53	1787
1065464	452074	452093	AGAACACTTCGCCGCTGATT	76	1788
1065480	452327	452346	AACATAAGGTTCAAAAGCCG	86	1789
1065496	454063	454082	CATAGATGATCCCATAATAG	77	1790
1065512	454746	454765	CCGAAAGCACTTTGCATGAG	70	1791
1065528	455227	455246	ATCCTTGATCCAGACAAGTC	76	1792
1065544	455606	455625	ATCATACAGGCATCTCAGCC	68	1793
1065560	220447	220466	TGTCACTGAGGGATCCCCAA	83	1794
	456816	456835			
1065576	457383	457402	GGATTCAATAGTGTAGGTGA	15	1795
1065592	458407	458426	GTACAATGCATGTGGGCCTC	ND	1796
1065608	459102	459121	ACTGGCATATTCCGATTATA	24	1797
1065624	460467	460486	CGTATTGGACCTTTCAATGA	28	1798
1065640	461349	461368	ATTGAAGCTGGCAATATGTC	67	1799
1065655	461608	461627	GCATGTACAAACGGGCTATG	33	1800
1065670	463188	463207	GGAATCTTGTAGAGGATTGG	51	1801
1065685	464393	464412	TCAGCACTTAGGTAGTTCAC	27	1802
1065716	465309	465328	TGTCTTTTGACACGCTGACT	60	1803
1065732	465880	465899	GTACTCTTGCCCATGGATGG	42	1804
1065748	466292	466311	CCCCTGTGGCTTATAGGTGG	93	1805
1065764	466995	467014	GGATGAACCTGCTTCACACA	45	1806
1065780	468051	468070	CAGATTTGCCAGGTAAAGCG	58	1807
1065796	470320	470339	AACTATCCTGCATCCGAGGC	33	1808
1065812	474393	474412	GGTCAACCAATTTGCTATTC	23	1809

1065828	475722	475741	GGTCTTGGGATTATAGTTTG	32	1810
1065844	476155	476174	GGAGTTCCTAACTCTCAATC	78	1811
1065860	478826	478845	TCTACTGAGGAACCCATCAC	86	1812
1065876	480715	480734	CGTTGCATAACATGTGTATT	46	1813
1065892	482259	482278	TACACCTGCAACAAGCCATC	85	1814
1065908	483816	483835	GAGCAAATCGGCAAAGGCAT	43	1815
1065923	484156	484175	CCAAGTGGCTTGTGGTGAAA	87	1816
1065939	485817	485836	GAACTACGAATAATTGCATG	49	1817
1065955	487610	487629	CAATGGTTTAGTGTCATATG	27	1818
1065971	489454	489473	AGTAGCTGTTTAGGCTGGAC	58	1819
1065987	489784	489803	TTGCCCTGCCACTCCCGTGG	76	1820
1066003	494419	494438	GGGATATATCACTTGGAGCT	ND	1821
1066019	496833	496852	CAGATTAGGTATGGAGGCCA	49	1822
1066035	498902	498921	ACGGATTAGATTCTCCAACA	36	1823
1066051	499936	499955	AGGACACATCAAGCTAGCTA	55	1824
1066067	500680	500699	AAGCCCTTTGCTTTTTCGGG	81	1825
1066083	500908	500927	GTGTTTTGACCTAACTGGCC	65	1826
1066099	501472	501491	CGTGGGTATGGTTTTCCTCT	75	1827
1066115	501905	501924	TCCAACGAGTGATAATTCAC	81	1828
1066131	502423	502442	AATTGATGCATAAGTAAGGC	51	1829
1066147	502762	502781	ATAGGCACTTCGGGCAAATA	67	1830
1066163	503043	503062	GGATTTAGGTGCTACAGTCA	38	1831
1066179	503356	503375	GTTAGCCCAGGTGATCAGCT	57	1832
1066195	503886	503905	ATTGCAACTAATAAAGGGTC	79	1833
1066211	504295	504314	GCTCTCATGTGAGAGTATGA	81	1834
1066227	504544	504563	TCATGAATTCAGGTTGCCCC	42	1835
1066243	505149	505168	CTTTGGTTGGAAGTTAGACC	46	1836
1066259	505666	505685	CTGCTTATTGCAGGCCTAGC	69	1837
1066275	506042	506061	CAGTTGAGAACGGTATTGAG	67	1838
1066291	506447	506466	GTCTGTCTTTAGGGTCACCC	47	1839
1066307	506828	506847	GCTTTAGGATGGTGTGGATC	60	1840
1066323	507587	507606	CTCTCACTGACTAGCTTTCG	57	1841
1066339	508114	508133	CTTACCGTCTTTAGGAACTT	47	1842
1066355	508585	508604	GGACAGCACAACCCCCGTGC	94	1843
1066371	509070	509089	CCCTACAATGCATACCCAAC	58	1844
1066387	510027	510046	GAGTTATACACGGAACCCAC	56	1845
1066403	510410	510429	GTCCAAGACATGCTAGGGAC	71	1846
1066419	510839	510858	CAATCTAGTTAGACCAGGCA	31	1847
1066435	511667	511686	ATGGACTGCCGGCCTGGAGC	49	1848
1066451	511894	511913	GTGAACTACTTGGAGACCTT	50	1849

Table 27

Reduction of UBE3A-ATS RNA by 7,000 nM 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages *in vitro* (37,000 cells/well)

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence (5' to 3')	UBE3A-ATS (%UTC)	SEQ ID NO
617557	483977	483996	ATCATGTGCATACCCAGGGT	31	172
749882	460115	460134	ACTTTATAGTGTGGATGGTA	17	586
750519	349103#	349122#	GTCATCACCTCTCTTCAGGA	16	181
1065273	432754	432773	ACGCAACTGAGACAATCCAT	33	1850
1065289	440229	440248	GTGGCTGTGCTGGATATTAC	48	1851
1065305	442574	442593	GAGCAAAATGGTCAGTACCC	43	1852
1065321	443357	443376	GATAGGTCAGTCACTCACTG	40	1853
1065337	444867	444886	GGATGCATTGGTGTCAAGAG	47	1854
1065353	445763	445782	GGTTTACACATGATAGGAAC	80	1855
1065369	446772	446791	AACAACGGTTGCAGGGACAG	29	1856
1065385	447787	447806	CCCCGTGTACAGTAAGGGCC	73	1857
1065401	448408	448427	GTCTTAGTGCCAAATATCCA	52	1858
1065417	448735	448754	TATTTAGACCACGATAACTG	100	1859
1065433	449118	449137	TCCCTCTTGTAGATCCTGGC	40	1860
1065449	449666	449685	GAGATATGATTAGTACTGGA	63	1861
1065465	452079	452098	GAGATAGAACACTTCGCCGC	39	1862
1065481	453032	453051	GTGATTAGGCGGCCGGGCGC	119	1863
1065497	454151	454170	CTTATGGAGACTTATATACC	61	1864
1065513	454842	454861	GGGTAGAAGACTAGCATACA	22	1865
1065529	455233	455252	GTACTTATCCTTGATCCAGA	48	1866
1065545	455636	455655	AGCACAAGATTGGTTCCATT	47	1867
1065561	456827	456846	GGGTACTATGTTGTCACTGA	N.D	1868
1065577	457571	457590	ATGAACCATGGAGTCTCTAT	77	1869
1065593	458456	458475	GGCTTTATACTTTACCCAAC	15	1870
1065609	459265	459284	GTAGATAACTTTACCTTGAC	14	1871
1065625	460511	460530	GTTTATAGGGTGGTTGGTTC	N.D.	1872
1065641	461413	461432	GGGTTACTTTCCAATAGAGT	11	1873
1065656	461610	461629	AGGCATGTACAAACGGGCTA	73	1874
1065671	463193	463212	GTTCTGGAATCTTGTAGAGG	11	1875
1065686	464398	464417	CCCATTCAGCACTTAGGTAG	23	1876
1065701	465011	465030	CTGCTCAAATCTGCGAATAG	73	1877
1065717	465374	465393	GAGGATGGTGTGTATGTTAT	31	1878
1065733	465889	465908	TCCCACAAGGTACTCTTGCC	61	1879
1065749	466296	466315	GCATCCCCTGTGGCTTATAG	65	1880
1065765	467043	467062	TCAGTTAGTCAGGTTAGGGA	7	1881
1065781	468335	468354	AGCTATTGCAGCTATGGGTT	35	1882
1065797	470401	470420	GTTCAACCATCGAGATGATC	64	1883
1065813	474404	474423	GATAGGGTTTAGGTCAACCA	20	1884
1065829	475726	475745	ATCTGGTCTTGGGATTATAG	26	1885

1065845	476159	476178	CTTAGGAGTTCCTAACTCTC	56	1886
1065861	478935	478954	GTTTTGGAGATTGTGTTACG	57	1887
1065877	480733	480752	GGAGCCAGGTAGAGTTAACG	41	1888
1065893	482489	482508	GGATAGTTGTGAACAACTTC	70	1889
1065909	483839	483858	CATTGAATGAGGGCCCAAAC	77	1890
1065924	484241	484260	GGACTTGTCTTATGGCTGCC	N.D.	1891
1065940	485829	485848	TGATTATTCAGAGAACTACG	47	1892
1065956	487697	487716	CGTTGGCATTTAAGTCTGAG	35	1893
1065972	489491	489510	CTGGGTTGAGACTATTCAGG	64	1894
1065988	489844	489863	CCATTGAAGAAAAACCCGCG	52	1895
1066004	494452	494471	GCACTACTGTAAGGGTCATG	48	1896
1066020	497158	497177	ACAAGGGTAGTGTTACACTG	42	1897
1066036	499081	499100	CAATGGTAATCGCATATACT	53	1898
1066052	500210	500229	GACTAATCCTCTTAAGTTCA	45	1899
1066068	500689	500708	AGGTACTGTAAGCCCTTTGC	80	1900
1066084	500972	500991	AACTTTTACACGCTAGTGGG	68	1901
1066100	501490	501509	CCCTTTGTTCATACTGAACG	69	1902
1066116	501913	501932	AGCTTCCCTCCAACGAGTGA	78	1903
1066132	502433	502452	GGCCCAAGGGAATTGATGCA	45	1904
1066148	502766	502785	AGGAATAGGCACTTCGGGCA	58	1905
1066164	503051	503070	GGAACCCAGGATTTAGGTGC	50	1906
1066180	503368	503387	GGTCATAGGAGTGTTAGCCC	44	1907
1066196	503900	503919	GGTTGGATTGCTTTATTGCA	85	1908
1066212	504299	504318	GCCTGCTCTCATGTGAGAGT	47	1909
1066228	504644	504663	CGCTTGGCTGACATTTAGGG	38	1910
1066244	505169	505188	ACCGAGCTCAAGAACTGTGA	59	1911
1066260	505670	505689	TGGCCTGCTTATTGCAGGCC	73	1912
1066276	506047	506066	GTTTTCAGTTGAGAACGGTA	41	1913
1066292	506493	506512	GGGACCTCCTTATATTCACC	35	1914
1066308	506833	506852	CCCCTGCTTTAGGATGGTGT	134	1915
1066324	507637	507656	GGTCCCCCCAGAAGGCTTGA	56	1916
1066340	508118	508137	TATTCTTACCGTCTTTAGGA	39	1917
1066356	508640	508659	GGATGGAGCTGTTGTGGCAT	57	1918
1066372	509076	509095	GCATTACCCTACAATGCATA	84	1919
1066388	510035	510054	GCATTTGAGAGTTATACACG	33	1920
1066404	510596	510615	GGGCCTTATAGACCATACCA	65	1921
1066420	510844	510863	GGAGACAATCTAGTTAGACC	30	1922
1066436	511673	511692	GCACAAATGGACTGCCGGCC	89	1923
1066452	511964	511983	GAGAGTCATACTCCTGACAG	53	1924

Table 28

Reduction of UBE3A-ATS RNA by 7,000 nM 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages *in vitro* (37,000 cells/well)

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence (5' to 3')	UBE3A-ATS (%UTC)	SEQ ID NO
617557	483977	483996	ATCATGTGCATACCCAGGGT	24	172
749882	460115	460134	ACTTTATAGTGTGGATGGTA	27	586
750519	349103#	349122#	GTCATCACCTCTCTTCAGGA	7	181
1065262	430574	430593	CTCCGGGCTCACCACCTGGT	82	1925
1065278	433033	433052	TCTATACACTGCTGTTGACG	52	1926
1065294	441732	441751	GCTTGCTAAACCTGTCCATT	40	1927
1065310	442717	442736	CTGGATGGTATAAATTGCCC	43	1928
1065326	443811	443830	GTTGCCGCTTTGGTGAACCT	69	1929
1065342	445129	445148	GTGCACTGATACAGTTGGGC	31	1930
1065358	446360	446379	CCATCAAGTAGGCCAGTCAC	37	1931
1065374	446952	446971	GGAATAACCCATACCCCCCA	97	1932
1065390	447883	447902	GCATGACTCCTAATTGCTGT	59	1933
1065406	448539	448558	GAGCTCAGTCTTCACTAGTT	46	1934
1065422	448919	448938	GTCAGGCACCAGATTGCTCA	70	1935
1065438	449442	449461	ATGATCATACTGGAGCCAGG	8	1936
1065454	449875	449894	ACCTACCAGAGTGGCATCCT	47	1937
1065470	452250	452269	ACGCTGTGTGAATCAAAAGC	85	1938
1065486	453211	453230	AGTGTTCTTACATCCACCGT	62	1939
1065502	454279	454298	CATGCCAATCGCATGCAAGC	71	1940
1065518	454967	454986	GTCAGGAGTTAACTATGAAC	95	1941
1065534	455326	455345	CACCAGTTAGGCCTGCTCCG	94	1942
1065550	456651	456670	CGTTTCCACAGCCAGGCTTA	83	1943
1065566	456921	456940	AGTCTTGGGTCACTAGGCAC	81	1944
1065582	457908	457927	CCAATATTTTGACTAGTTCG	23	1945
1065598	458568	458587	TTTAGTATGTCGAGAACTCA	31	1946
1065614	459652	459671	TGAAACCTGTATAGTTTACC	70	1947
1065630	460652	460671	CTAACCATAGACAGAGTGCA	33	1948
1065645	461463	461482	CATCATGATCTTGGTAAGGC	18	1949
1065661	461898	461917	GACCCCACAATTTGGTCCCA	62	1950
1065676	463668	463687	GACTATCTCAGCACTAGGGA	26	1951
1065691	464558	464577	GCCCTGTAGTATGTGGATAC	46	1952
1065706	465231	465250	CTCGGGTATATAAATTAATG	43	1953
1065722	465480	465499	GGATCTAGAATGATTGGTTG	75	1954
1065738	466218	466237	GGGCTGCTGTTTGAGTCCCC	65	1955
1065754	466397	466416	AGATACTCACTCGCTTTTCA	20	1956
1065770	467416	467435	ACGCTCCTTCATTTCATGCA	46	1957
1065786	468925	468944	GCTGTAAGTATAGATGCCTC	35	1958
1065802	472661	472680	ATTAGTTGACTCTATAAACG	70	1959
1065818	474805	474824	AAGTTTGGTATTGACACCTC	36	1960

1065834	475858	475877	CTTGATATAAGGGTAATACG	58	1961
1065850	476393	476412	GGCTCAGGCAAAGTAGCTTC	93	1962
1065866	479584	479603	GCCATCTTCAAGACTAAGGT	50	1963
1065882	480932	480951	CGAAAAATAGTATGCGAAGC	32	1964
1065898	482792	482811	GGAGACCCTAAAAAACCCGT	67	1965
1065914	483913	483932	CCTATAGGTGGCCTTCAGTC	30	1966
1065929	484322	484341	GGCAAGCCCAGACTCATGCT	86	1967
1065945	486491	486510	CGTCAACACTATAGATGAAT	40	1968
1065961	488332	488351	CCACTCATGTACATGAGATC	44	1969
1065977	489547	489566	GGCAAGCAACTATGGGTGGA	26	1970
1065993	493198	493217	GTTTACTTCGGGCCAGGTCC	97	1971
1066009	495221	495240	ACCCCTAGGAATAATGTTGC	36	1972
1066025	497750	497769	AGCGATACAAACCTACGCCA	71	1973
1066041	499146	499165	GGCAAGTTTTTATCGCTTAA	48	1974
1066057	500425	500444	AGTATTTTAGCCGGGATACG	53	1975
1066073	500846	500865	ACGGGTTCCTATTTGTCAGG	54	1976
1066089	501208	501227	GTGAGCTTTACTCTGCAATA	31	1977
1066105	501601	501620	GCCTTATTGGAGAGAGAACT	91	1978
1066121	502134	502153	TCAGTGCTACCCATTAGACC	35	1979
1066137	502512	502531	CATACATGGAGGAGTCCCTG	59	1980
1066153	502809	502828	TCCTAAGGATGTAGCCCATC	55	1981
1066169	503123	503142	CGCATCCAGTTAATCTCTGA	84	1982
1066185	503437	503456	GTCCCAGTTGGATTAAGGTG	64	1983
1066201	503970	503989	CTGTACAGGAGGGTGTCTCT	N.D.	1984
1066217	504426	504445	TAGTCTAAGGCAGTCAGGGT	28	1985
1066233	504757	504776	ATCTAGACTCTGCCTGGTTA	51	1986
1066249	505218	505237	GGACACTCTCGCTGAGGACA	21	1987
1066265	505800	505819	GGCACTATGACCACAGGGTA	35	1988
1066281	506127	506146	TCTGCTCTGTTAGCCGAGCA	77	1989
1066297	506641	506660	GCACAATGCTTGTATGCCCC	57	1990
1066313	507239	507258	GTGCCCTTACTGTTAAATCC	48	1991
1066329	507766	507785	TTTGCTCAGGATCGCTGGCC	93	1992
1066345	508230	508249	AGCCTCTGCCTAAAGGTAGT	64	1993
1066361	508780	508799	CGTGATTGCAAAGTCCAAGG	47	1994
1066377	509247	509266	CAGTAGTGGTATCAAATCTG	36	1995
1066393	510133	510152	TCCAGCACATAGACCATAGC	60	1996
1066409	510676	510695	GGTGGAAAGTCTAGTATGTC	73	1997
1066425	511077	511096	GACCCATGGAAAGACTCGGG	119	1998
1066441	511737	511756	GTTTCCCATAGGCCACGCTG	81	1999

Table 29

Reduction of UBE3A-ATS RNA by 7,000 nM 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages *in vitro* (37,000 cells/well)

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence (5' to 3')	UBE3A-ATS (%UTC)	SEQ ID NO
617557	483977	483996	ATCATGTGCATACCCAGGGT	35	172
749882	460115	460134	ACTTTATAGTGTGGATGGTA	26	586
749935	463695	463714	AGTGGTTGCTATCCTGCTAA	65	2000
750519	349103#	349122#	GTCATCACCTCTCTTCAGGA	16	181
1065263	430586	430605	ACGCAAGTCCTCCTCCGGGC	73	2001
1065279	433138	433157	TCAAGGGAACTAACTCCTCC	91	2002
1065295	441764	441783	GATTGATCATGTTATGCCCT	34	2003
1065311	442754	442773	GGTGGATTGGAGTTGCTACA	74	2004
1065327	443823	443842	TGGGACACATATGTTGCCGC	81	2005
1065343	445173	445192	CTGAAGCAAAGCTTATAGGC	91	2006
1065359	446483	446502	TGACACTGAGTAATCTGCGA	71	2007
1065375	446994	447013	TGTAAGATTCCCCCAAGGGT	103	2008
1065391	447907	447926	GGTGGGATTACATCTCTTAT	97	2009
1065407	448582	448601	CGTGATATTCATGTTGTCTG	89	2010
1065423	448947	448966	CGAAGCCAAAGGTACTTGAG	100	2011
1065439	449461	449480	GCTTGCACTCCATCATATAA	126	2012
1065455	449988	450007	AGGACCAGCCAGTCTAGTTT	47	2013
1065471	452256	452275	GGTCTCACGCTGTGTGAATC	90	2014
1065487	453229	453248	GGAGTCAAGTTGGTTAATAG	136	2015
1065503	454339	454358	GGGCGAAAGTATATCAGGCA	N.D.	2016
1065519	455012	455031	GGCTGTCAATGCTGATATAT	82	2017
1065535	455332	455351	GGAGTTCACCAGTTAGGCCT	88	2018
1065551	456669	456688	ACCCTCCCAACAAATAAGCG	160	2019
1065567	456925	456944	AGCAAGTCTTGGGTCACTAG	72	2020
1065583	457969	457988	GGCATCAATCAACAAGCACC	49	2021
1065599	458570	458589	GCTTTAGTATGTCGAGAACT	19	2022
1065615	460105	460124	GTGGATGGTATCCTGGTCAA	46	2023
1065631	460660	460679	GCATGATTCTAACCATAGAC	31	2024
1065646	461468	461487	GTACTCATCATGATCTTGGT	26	2025
1065662	462030	462049	GGAATAGGGCTCTGCTTATT	60	2026
1065692	464776	464795	CCTCGAGGATAGTTTCACTG	76	2027
1065707	465234	465253	CATCTCGGGTATATAAATTA	77	2028
1065723	465484	465503	TGTTGGATCTAGAATGATTG	71	2029
1065739	466222	466241	GTATGGGCTGCTGTTTGAGT	55	2030
1065755	466403	466422	CTGCAGAGATACTCACTCGC	55	2031
1065771	467421	467440	TTGATACGCTCCTTCATTTC	75	2032
1065787	468927	468946	ATGCTGTAAGTATAGATGCC	86	2033
1065803	472669	472688	CGTTGAATATTAGTTGACTC	74	2034
1065819	474875	474894	GGTGTTGTATGATAATGTGT	72	2035

1065835	475935	475954	CAATAGTAGTGATGACTTCC	41	2036
1065851	476439	476458	AGATGGAGCTTGAGCCATCC	76	2037
1065867	479607	479626	GCCCCACAGTAGAAATGTGG	87	2038
1065883	481338	481357	AGTCAACAAGACAACTCGAT	62	2039
1065899	482839	482858	CGTTATTCAGTCTCAGGGAG	28	2040
1065915	483919	483938	CTTTCACCTATAGGTGGCCT	67	2041
1065930	484442	484461	GAGTAATGGACTTCTGGTCT	133	2042
1065946	486772	486791	GTGTGAGGGAATCTAAGATC	54	2043
1065962	488566	488585	GGTGCCACACCATCAAAAGA	63	2044
1065978	489581	489600	GCTGCAGTGGTACCACAGAC	91	2045
1065994	493203	493222	AAGAAGTTTACTTCGGGCCA	59	2046
1066010	495383	495402	TCGGGAGTTGTTAGTCCAAG	62	2047
1066026	497873	497892	GCTCCCAAACAACTAATAGT	76	2048
1066042	499204	499223	TCAAAATCACGAAAGGCGGG	71	2049
1066058	500430	500449	TTAGAAGTATTTTAGCCGGG	44	2050
1066074	500857	500876	GGTAGGTAACTACGGGTTCC	59	2051
1066090	501222	501241	CACCCCTGTAAACAGTGAGC	96	2052
1066106	501609	501628	CTGCTCAAGCCTTATTGGAG	120	2053
1066122	502140	502159	GTGGAATCAGTGCTACCCAT	77	2054
1066138	502527	502546	AGCTGGGCACTCATACATAC	55	2055
1066154	502813	502832	AGCCTCCTAAGGATGTAGCC	108	2056
1066170	503131	503150	ATGGTCCTCGCATCCAGTTA	54	2057
1066186	503444	503463	CAGCACTGTCCCAGTTGGAT	61	2058
1066202	503986	504005	GTTGATTCACTGCACACTGT	80	2059
	508752	508771			
1066218	504433	504452	GGTATATTAGTCTAAGGCAG	43	2060
1066234	504789	504808	GCGAAGCCTTCTCAAAGACT	92	2061
1066250	505323	505342	GGGCCGCCTCTGTTATTGTG	88	2062
1066266	505808	505827	GAACTGTGGGCACTATGACC	86	2063
1066282	506165	506184	CCTTTGGAGCTTTGACTGGC	76	2064
1066298	506677	506696	CGATTTCCTGCCAGTGGCTG	79	2065
1066314	507244	507263	CTACTGTGCCCTTACTGTTA	83	2066
1066330	507795	507814	GAAGACTTAGGTCTCAAGCT	62	2067
1066346	508274	508293	GTAGTCATGTAGAACAGCAC	78	2068
1066362	508784	508803	CCACCGTGATTGCAAAGTCC	69	2069
1066378	509252	509271	GGGCACAGTAGTGGTATCAA	22	2070
1066394	510203	510222	AGAGCTGTCCTAAGGCAATT	54	2071
1066410	510711	510730	CTTGACATACAGGATAGGTG	52	2072
1066426	511088	511107	TTGGTAAATTAGACCCATGG	110	2073
1066442	511744	511763	GATGTATGTTTCCCATAGGC	56	2074

Table 30

Reduction of UBE3A-ATS RNA by 8,000 nM 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages *in vitro* (20,000 cells/well)

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence (5' to 3')	UBE3A-ATS (%UTC)	SEQ ID NO
617557	483977	483996	ATCATGTGCATACCCAGGGT	51	172
749882	460115	460134	ACTTTATAGTGTGGATGGTA	46	586
750519	349103#	349122#	GTCATCACCTCTCTTCAGGA	28	181
1165442	449002	449021	AGGTCTTATTTACCATTGGC	72	2377
1165447	449444	449463	TAATGATCATACTGGAGCCA	87	2378
1165449	452253	452272	CTCACGCTGTGTGAATCAAA	101	2379
1165455	452265	452284	GGAAGTCTAGGTCTCACGCT	88	2380
1165467	453362	453381	CTACATAGGCACTCTACTAG	96	2381
1165471	454154	454173	ACCCTTATGGAGACTTATAT	96	2382
1165477	454461	454480	GACTCCACACACCTACTAGA	97	2383
1165483	454578	454597	CAAGCAAAGACTACACCGTG	106	2384
1165487	454848	454867	TATCCAGGGTAGAAGACTAG	83	2385
1165493	454861	454880	GGTGTATATTCCCTATCCAG	89	2386
1165499	455020	455039	AGTGGGATGGCTGTCAATGC	82	2387
1165510	220439	220458	AGGGATCCCCAAATAGAGCC	96	2388
	456808	456827			
1165516	457018	457037	TCACAGTTGCTTGACCCTTA	79	2389
1165522	457572	457591	TATGAACCATGGAGTCTCTA	69	2390
1165528	458791	458810	TCCCTAATATAGGGCAGATG	88	2391
1165534	458942	458961	TATAGGACCTCAGGAGATTG	52	2392
1165539	458950	458969	TCAAGACCTATAGGACCTCA	37	2393
1165546	459550	459569	AAAGACTATCCTGGTATGAC	65	2394
1165557	460735	460754	GATTTGAGCCTGCTATGTCT	16*	2395
1165565	461525	461544	ACATTCAGCTAGACTAGTTG	58	2396
1165570	461901	461920	TGAGACCCCACAATTTGGTC	89	2397
1165572	464385	464404	TAGGTAGTTCACAACTCTTC	68	2398
1165582	464562	464581	ATATGCCCTGTAGTATGTGG	77	2399
1165587	465245	465264	ATTTTATTGGTCATCTCGGG	47	2400
1165592	465387	465406	TGTCAGACTTATTGAGGATG	67	2401
1165594	465891	465910	ACTCCCACAAGGTACTCTTG	84	2402
1165598	466249	466268	AACTGGTAGGATCTATGGCA	40	2403
1165603	467301	467320	TTCACAGAGTAGTCTATTGG	84	2404
1165609	468352	468371	TGTAGTATGCATTGACAAGC	58	2405
1165612	482161	482180	GAGTTACAAGTGTCATATAC	48	2406
1165618	483960	483979	GGTAGGATTCATGGTCCAAA	64	2407
1165625	485656	485675	CCTAGGACCAGTTGGTTCAC	99	2408
1165633	489492	489511	ACTGGGTTGAGACTATTCAG	68	2409

1165638	489521	489540	CAATGGACCACCTAAGACCT	104	2410
1165641	493854	493873	CTAATCTATGCTGGGCCCCA	89	2411
1165647	493864	493883	GAGATTAGGCCTAATCTATG	116	2412
1165653	496830	496849	ATTAGGTATGGAGGCCATGT	69	2413
1165664	499674	499693	AAGGTAGCCCCAATACAGAT	87	2414
1165668	500690	500709	GAGGTACTGTAAGCCCTTTG	115	2415
1165673	500906	500925	GTTTTGACCTAACTGGCCTT	86	2416
1165678	501567	501586	CTAAGGAGTGCTCTTTGTGG	59	2417
1165684	502371	502390	AGGTATTAAGGCCCTTGGCC	95	2418
1165690	502378	502397	GTATACAAGGTATTAAGGCC	69	2419
1165695	502449	502468	TAGGCAGCTCTTTGTAGGCC	82	2420
1165701	503155	503174	AGTTCTGTATACACCATCCC	51	2421
1165707	503361	503380	GGAGTGTTAGCCCAGGTGAT	95	2422
1165713	503367	503386	GTCATAGGAGTGTTAGCCCA	84	2423
1165719	503421	503440	GGTGATGACACCCCTACCAT	106	2424
1165725	503507	503526	GCCTTGGTTGTGGTGAAACC	64	2425
1165729	504076	504095	GTGAACTCCTGTGACTGATA	52	2426
1165736	504431	504450	TATATTAGTCTAAGGCAGTC	47	2427
1165747	505173	505192	GTGTACCGAGCTCAAGAACT	51	2428
1165753	505181	505200	CTGTCTCTGTGTACCGAGCT	64	2429
1165766	505320	505339	CCGCCTCTGTTATTGTGATA	78	2430
1165772	505327	505346	AATTGGGCCGCCTCTGTTAT	74	2431
1165778	505542	505561	AGTCAGGTACAGGTGTTGGA	56	2432
1165783	505745	505764	TGTAGGTTGACAGGACATGC	64	2433
1165789	505821	505840	GAGGGTGCTTAGTGAACTGT	87	2434
1165795	505830	505849	AAGACCTGTGAGGGTGCTTA	87	2435
1165800	506448	506467	AGTCTGTCTTTAGGGTCACC	57	2436
1165806	507907	507926	TAGCCATTCGATACCTGCTT	76	2437
1165812	507914	507933	TGCAGGATAGCCATTCGATA	75	2438
1165823	508791	508810	ATGAATGCCACCGTGATTGC	94	2439
1165828	510228	510247	AGTTGTGTCTGAGGGATATC	64	2440
1165839	448411	448430	AGGGTCTTAGTGCCAAATAT	102	2441
1165852	455763	455782	TACCAAAGTGGCTGCTCACC	76	2442
1165854	460426	460445	TAGCCCTTTCAGCACACTTC	44	2443
1165856	461342	461361	CTGGCAATATGTCAACCTTA	55	2444
1165864	464515	464534	AGTGCACAGATAATGACTAG	91	2445
1165880	484240	484259	GACTTGTCTTATGGCTGCCT	90	2446
1165884	486440	486459	CCTAATAGCACCAGAATAGT	104	2447
1165891	499666	499685	CCCAATACAGATTCAGTGGC	89	2448
1165901	504818	504837	TGAAGTAGTCCTGCCCTTTC	86	2449
1165902	505216	505235	ACACTCTCGCTGAGGACACA	74	2450
1165908	506966	506985	GGGCATTCAGTGCTCCCTCC	106	2451

Table 31

Reduction of UBE3A-ATS RNA by 8,000 nM 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages *in vitro* (20,000 cells/well)

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence (5' to 3')	UBE3A-ATS (%UTC)	SEQ ID NO
617557	483977	483996	ATCATGTGCATACCCAGGGT	53	172
749882	460115	460134	ACTTTATAGTGTGGATGGTA	50	586
750519	349103#	349122#	GTCATCACCTCTCTTCAGGA	31	181
1165439	448413	448432	CAAGGGTCTTAGTGCCAAAT	106	2452
1165444	449095	449114	TATGCTAGTCACTCATTGAG	113	2453
1165451	452258	452277	TAGGTCTCACGCTGTGTGAA	97	2454
1165457	452268	452287	GAGGGAAGTCTAGGTCTCAC	89	2455
1165468	453365	453384	TAACTACATAGGCACTCTAC	79	2456
1165473	454161	454180	AGATTTGACCCTTATGGAGA	115	2457
1165479	454465	454484	AGTGGACTCCACACACCTAC	108	2458
1165485	454843	454862	AGGGTAGAAGACTAGCATAC	96	22
1165489	454857	454876	TATATTCCCTATCCAGGGTA	92	2459
1165495	454865	454884	GACAGGTGTATATTCCCTAT	116	2460
1165505	456628	456647	TGTGCATGGTTATCTAATGC	74	2461
1165512	457013	457032	GTTGCTTGACCCTTAATTCA	108	2462
1165518	457022	457041	CATATCACAGTTGCTTGACC	132	2463
1165524	457984	458003	TTGATCTATTATGAGGGCAT	22	2464
1165530	458935	458954	CCTCAGGAGATTGTACAACA	47	2465
1165542	459545	459564	CTATCCTGGTATGACTGTCA	39	2466
1165548	460110	460129	ATAGTGTGGATGGTATCCTG	57	2467
1165553	460508	460527	TATAGGGTGGTTGGTTCAAA	29	2468
1165559	460844	460863	ACCACACATATAGGCTAGCC	39	2469
1165566	461527	461546	GAACATTCAGCTAGACTAGT	64	2470
1165574	464388	464407	ACTTAGGTAGTTCACAACTC	55	2471
1165579	464557	464576	CCCTGTAGTATGTGGATACT	97	2472
1165583	465239	465258	TTGGTCATCTCGGGTATATA	43	2473
1165589	465380	465399	CTTATTGAGGATGGTGTGTA	64	2474
1165605	467802	467821	TCCCTCTTAGTGATTGGTGG	80	2475
1165614	483844	483863	CTAGGCATTGAATGAGGGCC	93	2476
1165620	483962	483981	AGGGTAGGATTCATGGTCCA	95	2477
1165627	486353	486372	TTAATAGACTGCGATTATAC	100	2478
1165630	489097	489116	TCCCTAAGCTTAGATATACC	76	2479
1165634	489516	489535	GACCACCTAAGACCTCAAGG	73	2480
1165643	493860	493879	TTAGGCCTAATCTATGCTGG	84	2481
1165649	493866	493885	ATGAGATTAGGCCTAATCTA	108	2482
1165655	496832	496851	AGATTAGGTATGGAGGCCAT	85	2483
1165660	499668	499687	GCCCCAATACAGATTCAGTG	94	2484

1165675	500909	500928	GGTGTTTTGACCTAACTGGC	81	2485
1165680	501762	501781	GGCTAAGAGTCACCTGTATC	85	2486
1165686	502373	502392	CAAGGTATTAAGGCCCTTGG	92	2487
1165691	502438	502457	TTGTAGGCCCAAGGGAATTG	105	2488
1165696	502451	502470	GCTAGGCAGCTCTTTGTAGG	65	2489
1165703	503357	503376	TGTTAGCCCAGGTGATCAGC	69	2490
1165709	503363	503382	TAGGAGTGTTAGCCCAGGTG	56	2491
1165715	503370	503389	AGGGTCATAGGAGTGTTAGC	65	2492
1165721	503424	503443	TAAGGTGATGACACCCCTAC	109	2493
1165726	503871	503890	GGGTCAGTTGTGCAGTTGTT	46	2494
1165738	504434	504453	AGGTATATTAGTCTAAGGCA	49	2495
1165743	504977	504996	CTATTATCTTCTTAGGGTCG	57	2496
1165749	505175	505194	CTGTGTACCGAGCTCAAGAA	65	2497
1165755	505198	505217	CATCAGCTGTTAGCAGTCTG	82	2498
1165760	505219	505238	AGGACACTCTCGCTGAGGAC	64	2499
1165768	505322	505341	GGCCGCCTCTGTTATTGTGA	91	2500
1165774	505329	505348	GAAATTGGGCCGCCTCTGTT	91	2501
1165779	505651	505670	CTAGCTTCCACCTAAGAGCT	111	2502
1165785	505750	505769	AACTCTGTAGGTTGACAGGA	78	2503
1165791	505824	505843	TGTGAGGGTGCTTAGTGAAC	77	2504
1165796	505836	505855	CTGTCAAAGACCTGTGAGGG	78	2505
1165808	507910	507929	GGATAGCCATTCGATACCTG	101	2506
1165814	508119	508138	TTATTCTTACCGTCTTTAGG	70	2507
1165825	509129	509148	AGCTCATCACAACTGGGTGG	86	2508
1165842	449667	449686	AGAGATATGATTAGTACTGG	105	2509
1165850	455030	455049	GTGATATTGCAGTGGGATGG	89	2510
1165853	458945	458964	ACCTATAGGACCTCAGGAGA	70	2511
1165857	461416	461435	ACTGGGTTACTTTCCAATAG	61	2512
1165861	463093	463112	CAATTTACTTGATACAGGGC	43	2513
1165869	465393	465412	GTCAATTGTCAGACTTATTG	54	2514
1165873	466100	466119	GGGCCTGTATGTCTTGAGAA	88	2515
1165874	467294	467313	AGTAGTCTATTGGTGTTCCT	68	2516
1165876	468356	468375	ATACTGTAGTATGCATTGAC	79	2517
1165882	484300	484319	TTACTAGGGCCAGAGAATCC	94	2518
1165889	493623	493642	CAGATGACTAGCCTCCAAAC	102	2519
1165892	499910	499929	GCATAATAGGAGGTCCTTAA	46	2520
1165894	500764	500783	GTCAAATCAATTTGTGCCAC	72	2521
1165900	504422	504441	CTAAGGCAGTCAGGGTAATG	55	2522
1165905	506694	506713	TTAAGAAGCTTGCCTTTCGA	115	2523
1165909	507901	507920	TTCGATACCTGCTTTTGTGA	111	2524
1165914	511254	511273	CTGATGATTTGTTGATTACC	84	2525

Table 32

Reduction of UBE3A-ATS RNA by 8,000 nM 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages *in vitro* (20,000 cells/well)

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence (5' to 3')	UBE3A-ATS (%UTC)	SEQ ID NO
617557	483977	483996	ATCATGTGCATACCCAGGGT	49	172
749882	460115	460134	ACTTTATAGTGTGGATGGTA	33	586
750519	349103#	349122#	GTCATCACCTCTCTTCAGGA	22	181
1165440	448459	448478	ATAGTGCCAGTAGGACTTAC	98	2526
1165445	449097	449116	AGTATGCTAGTCACTCATTG	68	2527
1165452	452259	452278	CTAGGTCTCACGCTGTGTGA	84	2528
1165458	452271	452290	TATGAGGGAAGTCTAGGTCT	64	2529
1165474	454162	454181	AAGATTTGACCCTTATGGAG	96	2530
1165480	454466	454485	GAGTGGACTCCACACACCTA	80	2531
1165490	454858	454877	GTATATTCCCTATCCAGGGT	93	2532
1165496	454866	454885	TGACAGGTGTATATTCCCTA	55	2533
1165501	455031	455050	AGTGATATTGCAGTGGGATG	77	2534
1165506	220320	220339	CATCATCGATCCAAACAAGC	102	2535
	456689	456708			
1165513	457015	457034	CAGTTGCTTGACCCTTAATT	76	2536
1165519	457364	457383	ACATGGTGAGGGTCTCAATG	33	2537
1165525	457986	458005	ACTTGATCTATTATGAGGGC	35	2538
1165531	458936	458955	ACCTCAGGAGATTGTACAAC	42	2539
1165536	458947	458966	AGACCTATAGGACCTCAGGA	28	2540
1165543	459546	459565	ACTATCCTGGTATGACTGTC	40	2541
1165549	460112	460131	TTATAGTGTGGATGGTATCC	49	2542
1165554	460509	460528	TTATAGGGTGGTTGGTTCAA	24	2543
1165560	460845	460864	TACCACACATATAGGCTAGC	43	2544
1165567	461671	461690	CCTAAGGTGAAGTCTGTGTA	58	2545
1165575	464389	464408	CACTTAGGTAGTTCACAACT	59	2546
1165580	464559	464578	TGCCCTGTAGTATGTGGATA	69	2547
1165584	465241	465260	TATTGGTCATCTCGGGTATA	51	2548
1165595	466246	466265	TGGTAGGATCTATGGCAGTT	35	2549
1165600	467297	467316	CAGAGTAGTCTATTGGTGTT	83	2550
1165606	467803	467822	CTCCCTCTTAGTGATTGGTG	84	2551
1165610	468403	468422	CCTACCCTTGCATGCTATGT	88	2552
1165615	483850	483869	GCCTGACTAGGCATTGAATG	79	2553
1165622	484301	484320	GTTACTAGGGCCAGAGAATC	105	2554
1165628	486354	486373	GTTAATAGACTGCGATTATA	43	2555
1165631	489098	489117	CTCCCTAAGCTTAGATATAC	88	2556
1165635	489518	489537	TGGACCACCTAAGACCTCAA	73	139
1165644	493861	493880	ATTAGGCCTAATCTATGCTG	89	2557

1165650	493868	493887	AGATGAGATTAGGCCTAATC	136	2558
1165656	496834	496853	ACAGATTAGGTATGGAGGCC	57	2559
1165661	499670	499689	TAGCCCCAATACAGATTCAG	55	2560
1165666	499911	499930	TGCATAATAGGAGGTCCTTA	54	2561
1165670	500864	500883	TACTTTTGGTAGGTAACTAC	70	2562
1165676	500910	500929	AGGTGTTTTGACCTAACTGG	80	2563
1165681	501764	501783	TGGGCTAAGAGTCACCTGTA	109	2564
1165687	502374	502393	ACAAGGTATTAAGGCCCTTG	106	2565
1165692	502439	502458	TTTGTAGGCCCAAGGGAATT	119	2566
1165697	502740	502759	GCCCGATGACACCAGCCACT	61	2567
1165704	503358	503377	GTGTTAGCCCAGGTGATCAG	66	2568
1165710	503364	503383	ATAGGAGTGTTAGCCCAGGT	62	2569
1165716	503418	503437	GATGACACCCCTACCATGGC	63	2570
1165722	503425	503444	TTAAGGTGATGACACCCCTA	102	2571
1165727	503873	503892	AAGGGTCAGTTGTGCAGTTG	43	2572
1165733	504427	504446	TTAGTCTAAGGCAGTCAGGG	50	2573
1165739	504435	504454	TAGGTATATTAGTCTAAGGC	50	2574
1165744	505167	505186	CGAGCTCAAGAACTGTGACT	65	2575
1165750	505176	505195	TCTGTGTACCGAGCTCAAGA	41	2576
1165756	505199	505218	ACATCAGCTGTTAGCAGTCT	45	2577
1165761	505220	505239	GAGGACACTCTCGCTGAGGA	78	2578
1165769	505324	505343	TGGGCCGCCTCTGTTATTGT	79	2579
1165775	505331	505350	TAGAAATTGGGCCGCCTCTG	63	2580
1165780	505652	505671	CCTAGCTTCCACCTAAGAGC	78	2581
1165786	505751	505770	GAACTCTGTAGGTTGACAGG	43	2582
1165792	505826	505845	CCTGTGAGGGTGCTTAGTGA	76	2583
1165797	506166	506185	ACCTTTGGAGCTTTGACTGG	90	2584
1165804	507902	507921	ATTCGATACCTGCTTTTGTG	95	2585
1165809	507911	507930	AGGATAGCCATTCGATACCT	70	2586
1165837	511896	511915	AAGTGAACTACTTGGAGACC	38	2587
1165843	449698	449717	TGTATGGCTTATGCATGCTA	75	2588
1165847	453368	453387	TATTAACTACATAGGCACTC	58	2589
1165848	454844	454863	CAGGGTAGAAGACTAGCATA	109	2590
1165858	461430	461449	TTAGCACTTCTATAACTGGG	40	2591
1165862	463776	463795	ATAGATTGGGCTTTAGAGGT	45	2592
1165867	465383	465402	AGACTTATTGAGGATGGTGT	47	2593
1165870	465563	465582	TAGGACAAGTCTTATAGAGA	48	2594
1165878	483974	483993	ATGTGCATACCCAGGGTAGG	58	2595
1165890	493850	493869	TCTATGCTGGGCCCCAATTC	87	2596
1165906	506772	506791	AGGTTGTGGAGGTTGTTCCT	72	2597
1165911	508171	508190	ACCTGCAGTTATTTAGCCAT	68	2598
1165912	509171	509190	AACCTCCAAGTGCTTCAAGC	60	2599

Table 33

Reduction of UBE3A-ATS RNA by 8,000 nM 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages *in vitro* (20,000 cells/well)

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence (5' to 3')	UBE3A-ATS (%UTC)	SEQ ID NO
1065438	449442	449461	ATGATCATACTGGAGCCAGG	95	1936
1165509	220406	220425	CTTATTTGTCCTATTGGAGG	91	2600
	456775	456794			
1178377	220315	220334	TCGATCCAAACAAGCACCCT	98	2601
	456684	456703			
1178379	220318	220337	TCATCGATCCAAACAAGCAC	132	2602
	456687	456706			
1178384	456753	456772	CGCACATCTGGACCTCAGAT	98	2603
1178386	456755	456774	GCCGCACATCTGGACCTCAG	129	2604
1178388	456758	456777	AGGGCCGCACATCTGGACCT	115	2605
1178390	456760	456779	GGAGGGCCGCACATCTGGAC	70	2606
1178392	456762	456781	TTGGAGGGCCGCACATCTGG	106	2607
1178394	456764	456783	TATTGGAGGGCCGCACATCT	123	2608
1178396	456766	456785	CCTATTGGAGGGCCGCACAT	136	2609
1178398	456769	456788	TGTCCTATTGGAGGGCCGCA	100	2610
1178400	456771	456790	TTTGTCCTATTGGAGGGCCG	104	2611
1178404	220455	220474	TACTATGTTGTCACTGAGGG	83	2612
	456824	456843			
1178406	220457	220476	GGTACTATGTTGTCACTGAG	68	2613
	456826	456845			
1178408	456864	456883	TGCCCTCTTCGAAGAGATAG	87	2614
1178411	456914	456933	GGTCACTAGGCACACTAAAG	87	2615
1178413	456916	456935	TGGGTCACTAGGCACACTAA	87	2616
1178415	456923	456942	CAAGTCTTGGGTCACTAGGC	93	2617
1178417	456926	456945	AAGCAAGTCTTGGGTCACTA	72	2618
1178418	457232	457251	CTTAGCTACTCACCCCTGTT	111	2619
1178420	457237	457256	AATGGCTTAGCTACTCACCC	79	104
1178422	457240	457259	GATAATGGCTTAGCTACTCA	77	2620
1178423	457286	457305	CGACCTAAAGACCTAGCAAA	55	2621
1178425	457289	457308	AAACGACCTAAAGACCTAGC	50	2622
1178426	457294	457313	GTACAAAACGACCTAAAGAC	77	2623
1178428	457574	457593	ATTATGAACCATGGAGTCTC	47	2624
1179735	448291	448310	TCGCAATAAGATTCCATTGC	106	2625
1179742	448305	448324	GTGCAAAACAAGTTTCGCAA	119	2626
1179745	448453	448472	CCAGTAGGACTTACTAAATC	79	2627
1179747	448455	448474	TGCCAGTAGGACTTACTAAA	99	2628
1179749	448457	448476	AGTGCCAGTAGGACTTACTA	76	2629

1179751	448630	448649	GAGGATTGCATCACATGTGT	118	2630
1179753	448715	448734	TAGCGCATTGAGCAAAATTC	75	2631
1179755	448717	448736	TGTAGCGCATTGAGCAAAAT	75	2632
1179757	448719	448738	ACTGTAGCGCATTGAGCAAA	83	2633
1179759	448722	448741	ATAACTGTAGCGCATTGAGC	103	2634
1179761	448724	448743	CGATAACTGTAGCGCATTGA	68	2635
1179763	448727	448746	CCACGATAACTGTAGCGCAT	91	2636
1179765	448730	448749	AGACCACGATAACTGTAGCG	84	2637
1179767	448732	448751	TTAGACCACGATAACTGTAG	104	2638
1179769	448734	448753	ATTTAGACCACGATAACTGT	114	2639
1179770	448737	448756	TATATTTAGACCACGATAAC	106	2640
1179772	448740	448759	CTGTATATTTAGACCACGAT	78	2641
1179774	448828	448847	AGGACCCTTAAGTCATAAAG	75	2642
1179776	448834	448853	ATTGCAAGGACCCTTAAGTC	75	2643
1179778	448841	448860	TATCCCAATTGCAAGGACCC	131	2644
1179781	448948	448967	ACGAAGCCAAAGGTACTTGA	124	2645
1179783	449034	449053	GCCCTGACTGTCATTCATAT	86	2646
1179785	449037	449056	ACGGCCCTGACTGTCATTCA	98	2647
1179787	449039	449058	GAACGGCCCTGACTGTCATT	117	2648
1179789	449042	449061	AAGGAACGGCCCTGACTGTC	78	2649
1179791	449044	449063	TGAAGGAACGGCCCTGACTG	101	2650
1179793	449046	449065	CCTGAAGGAACGGCCCTGAC	108	2651
1179795	449049	449068	TGGCCTGAAGGAACGGCCCT	119	2652
1179797	449052	449071	ATGTGGCCTGAAGGAACGGC	76	2653
1179799	449058	449077	ATAATCATGTGGCCTGAAGG	104	2654
1179801	449060	449079	CGATAATCATGTGGCCTGAA	79	2655
1179803	449063	449082	TAACGATAATCATGTGGCCT	61	2656
1179805	449065	449084	CATAACGATAATCATGTGGC	81	2657
1179807	449101	449120	GGCAAGTATGCTAGTCACTC	73	2658
1179809	449103	449122	CTGGCAAGTATGCTAGTCAC	105	2659
1179811	449106	449125	ATCCTGGCAAGTATGCTAGT	83	2660
1179813	449108	449127	AGATCCTGGCAAGTATGCTA	103	2661
1179815	449110	449129	GTAGATCCTGGCAAGTATGC	68	2662
1179817	449115	449134	CTCTTGTAGATCCTGGCAAG	78	2663
1179818	449157	449176	CAACATTATATCGATGCAAT	89	2664
1179820	449160	449179	TGTCAACATTATATCGATGC	109	2665
1179822	449163	449182	ACTTGTCAACATTATATCGA	78	2666
1179825	448297	448316	CAAGTTTCGCAATAAGATTC	72	2667
1179833	456498	456517	TTAGATTAAAATCTGGCCGG	92	2668
1179834	456912	456931	TCACTAGGCACACTAAAGTG	107	2669
1179838	457298	457317	AGATGTACAAAACGACCTAA	99	2670
1179840	457386	457405	TAAGGATTCAATAGTGTAGG	34	2671
1179842	457503	457522	GGCACACCTGGATTTCACTA	12	2672

1179845	448416	448435	GAGCAAGGGTCTTAGTGCCA	108	2673
1179847	448625	448644	TTGCATCACATGTGTCAGTC	102	2674
1179849	448843	448862	TTTATCCCAATTGCAAGGAC	86	2675

Example 2: Effect of 5-10-5 MOE gapmer modified oligonucleotides on human UBE3A-ATS RNA *in vitro*, single dose

Modified oligonucleotides complementary to human UBE3A-ATS nucleic acid were tested for their effect on UBE3A-ATS RNA levels *in vitro*.

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

Each internucleoside linkage of Compound IDs 617456, 617457, 617460, 617461, and 617557 is a phosphorothioate internucleoside linkage. All other compounds have an internucleoside linkage motif of: soooosssssssssssooss, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage.

All cytosine residues are 5-methylcytosines.

"Start site" indicates the 5'-most nucleoside to which the modified oligonucleotide is complementary in target nucleic acid sequence. "Stop site" indicates the 3'-most nucleoside to which the modified oligonucleotide is complementary in the target nucleic acid sequence. Each modified oligonucleotide listed in the Tables below is 100% complementary to SEQ ID NO: 1. Start and stop sites for Compound 750519 are marked with a hashtag (#) in several tables below. The complete list of start sites for Compound 750519 are listed in Table 4b.

Human IPS cell derived ReproNeuro™ Neurons (ReproCELL) were cultured per manufacturer instructions at 40,000 cells per well and were treated with 8,000 nM of modified oligonucleotide by free uptake. After a treatment period of approximately 5 days, total RNA was isolated from the cells and UBE3A-ATS RNA levels were measured by quantitative real-time RTPCR. Human UBE3A-ATS primer probe set RTS4796 (described herein in Example 1) was used to measure RNA levels. UBE3A-ATS RNA levels were normalized to total RNA content, as measured by RIBOGREEN®. Reduction of UBE3A-ATS is presented in the tables below as percent UBE3A-ATS RNA amount relative to untreated control (UTC) cells. Each table represents results from an individual assay plate. The values marked with an asterisk (*) indicate that the modified oligonucleotide is complementary to the amplicon region of the primer probe set. Additional assays may be used to measure the potency and efficacy of the modified oligonucleotides complementary to the amplicon region.

Table 34

Reduction of UBE3A-ATS RNA by 8,000 nM 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages *in vitro*

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence (5' to 3')	UBE3A-ATS (%UTC)	SEQ ID NO
617557	483977	483996	ATCATGTGCATACCCAGGGT	38	172
749882	460115	460134	ACTTTATAGTGTGGATGGTA	30	586
750519	349103#	349122#	GTCATCACCTCTCTTCAGGA	23	181
1165438	448412	448431	AAGGGTCTTAGTGCCAAATA	75	2075
1165443	449094	449113	ATGCTAGTCACTCATTGAGA	65	2076
1165448	449641	449660	TGATCCATTAGATAGGCTAT	80	2077
1165450	452254	452273	TCTCACGCTGTGTGAATCAA	81	2078
1165456	452267	452286	AGGGAAGTCTAGGTCTCACG	54	2079
1165472	454155	454174	GACCCTTATGGAGACTTATA	77	2080
1165478	454464	454483	GTGGACTCCACACACCTACT	62	2081
1165484	454579	454598	GCAAGCAAAGACTACACCGT	48	2082
1165488	454856	454875	ATATTCCCTATCCAGGGTAG	91	2083
1165494	454862	454881	AGGTGTATATTCCCTATCCA	76	2084
1165500	455029	455048	TGATATTGCAGTGGGATGGC	59	2085
1165504	456625	456644	GCATGGTTATCTAATGCATC	60	2086
1165511	220440	220459	GAGGGATCCCCAAATAGAGC	51	2087
	456809	456828			
1165517	457019	457038	ATCACAGTTGCTTGACCCTT	63	2088
1165523	457983	458002	TGATCTATTATGAGGGCATC	25	2089
1165529	458792	458811	TTCCCTAATATAGGGCAGAT	49	2090
1165535	458943	458962	CTATAGGACCTCAGGAGATT	42	2091
1165540	458951	458970	CTCAAGACCTATAGGACCTC	50	2092
1165547	460109	460128	TAGTGTGGATGGTATCCTGG	55	2093
1165552	460506	460525	TAGGGTGGTTGGTTCAAAAT	24	2094
1165558	460842	460861	CACACATATAGGCTAGCCAA	44	2095
1165562	461414	461433	TGGGTTACTTTCCAATAGAG	27	2096
1165573	464387	464406	CTTAGGTAGTTCACAACTCT	37	2097
1165578	464556	464575	CCTGTAGTATGTGGATACTG	40	2098
1165588	465372	465391	GGATGGTGTGTATGTTATGA	32	2099
1165599	467293	467312	GTAGTCTATTGGTGTTCCTT	45	2100
1165604	467418	467437	ATACGCTCCTTCATTTCATG	49	2101
1165613	483363	483382	GAATTCAATGGACCCACATG	67	2102
1165619	483961	483980	GGGTAGGATTCATGGTCCAA	43	2103
1165626	486352	486371	TAATAGACTGCGATTATACA	64	2104
1165642	493857	493876	GGCCTAATCTATGCTGGGCC	63	2105
1165648	493865	493884	TGAGATTAGGCCTAATCTAT	79	2106
1165654	496831	496850	GATTAGGTATGGAGGCCATG	48	2107

1165659	499667	499686	CCCCAATACAGATTCAGTGG	75	2108
1165665	499676	499695	TCAAGGTAGCCCCAATACAG	44	2109
1165669	500693	500712	CAAGAGGTACTGTAAGCCCT	87	2110
1165674	500907	500926	TGTTTTGACCTAACTGGCCT	75	2111
1165679	501761	501780	GCTAAGAGTCACCTGTATCC	53	2112
1165685	502372	502391	AAGGTATTAAGGCCCTTGGC	54	2113
1165702	503347	503366	GGTGATCAGCTCAACACCCC	73	2114
1165708	503362	503381	AGGAGTGTTAGCCCAGGTGA	53	2115
1165714	503369	503388	GGGTCATAGGAGTGTTAGCC	77	2116
1165720	503423	503442	AAGGTGATGACACCCCTACC	67	2117
1165730	504128	504147	AGCTATTTCATTAAGTCACC	43	2118
1165737	504432	504451	GTATATTAGTCTAAGGCAGT	30	2119
1165742	504976	504995	TATTATCTTCTTAGGGTCGA	37	2120
1165748	505174	505193	TGTGTACCGAGCTCAAGAAC	55	2121
1165754	505184	505203	AGTCTGTCTCTGTGTACCGA	70	2122
1165759	505217	505236	GACACTCTCGCTGAGGACAC	58	2123
1165767	505321	505340	GCCGCCTCTGTTATTGTGAT	56	2124
1165773	505328	505347	AAATTGGGCCGCCTCTGTTA	41	2125
1165784	505746	505765	CTGTAGGTTGACAGGACATG	50	2126
1165790	505822	505841	TGAGGGTGCTTAGTGAACTG	78	2127
1165801	506449	506468	GAGTCTGTCTTTAGGGTCAC	42	2128
1165803	507899	507918	CGATACCTGCTTTTGTGACA	54	2129
1165807	507908	507927	ATAGCCATTCGATACCTGCT	56	2130
1165813	507916	507935	ACTGCAGGATAGCCATTCGA	72	2131
1165824	508792	508811	TATGAATGCCACCGTGATTG	79	2132
1165846	453364	453383	AACTACATAGGCACTCTACT	78	2133
1165859	461526	461545	AACATTCAGCTAGACTAGTT	43	2134
1165860	461902	461921	ATGAGACCCCACAATTTGGT	79	2135
1165866	464995	465014	ATAGAGGCCCTCTTGTTTCA	60	2136
1165868	465391	465410	CAATTGTCAGACTTATTGAG	66	2137
1165872	465893	465912	GAACTCCCACAAGGTACTCT	45	2138
1165875	468353	468372	CTGTAGTATGCATTGACAAG	53	2139
1165881	484299	484318	TACTAGGGCCAGAGAATCCA	55	2140
1165885	488335	488354	AAGCCACTCATGTACATGAG	55	2141
1165887	489494	489513	AAACTGGGTTGAGACTATTC	42	2142
1165888	489580	489599	CTGCAGTGGTACCACAGACC	40	2143
1165896	502392	502411	TGACTACACATCTTGTATAC	73	2144
1165897	502450	502469	CTAGGCAGCTCTTTGTAGGC	25	2145
1165898	503807	503826	CCCTATAGGTCAAAAATGCC	51	2146
1165903	505544	505563	TCAGTCAGGTACAGGTGTTG	58	2147
1165904	505834	505853	GTCAAAGACCTGTGAGGGTG	63	2148
1165913	510480	510499	GGTCTTTGCAGTTAAGTTAT	65	2149

Table 35

Reduction of UBE3A-ATS RNA by 8,000 nM 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages *in vitro*

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence (5' to 3')	UBE3A-ATS (%UTC)	SEQ ID NO
617557	483977	483996	ATCATGTGCATACCCAGGGT	52	172
749882	460115	460134	ACTTTATAGTGTGGATGGTA	38	586
750519	349103#	349122#	GTCATCACCTCTCTTCAGGA	26	181
1165437	448410	448429	GGGTCTTAGTGCCAAATATC	112	2150
1165454	452264	452283	GAAGTCTAGGTCTCACGCTG	84	2151
1165466	453361	453380	TACATAGGCACTCTACTAGC	96	2152
1165470	454153	454172	CCCTTATGGAGACTTATATA	81	2153
1165476	454164	454183	TGAAGATTTGACCCTTATGG	114	2154
1165482	454577	454596	AAGCAAAGACTACACCGTGA	80	2155
1165486	454847	454866	ATCCAGGGTAGAAGACTAGC	75	2156
1165492	454860	454879	GTGTATATTCCCTATCCAGG	83	2157
1165498	455016	455035	GGATGGCTGTCAATGCTGAT	84	2158
1165502	455214	455233	ACAAGTCTACTACCAATAAG	57	2159
1165508	220325	220344	ATTCTCATCATCGATCCAAA	58	2160
	456694	456713			
1165515	457017	457036	CACAGTTGCTTGACCCTTAA	58	2161
1165521	457382	457401	GATTCAATAGTGTAGGTGAC	29	2162
1165527	458789	458808	CCTAATATAGGGCAGATGAT	53	2163
1165533	458939	458958	AGGACCTCAGGAGATTGTAC	29	2164
1165538	458949	458968	CAAGACCTATAGGACCTCAG	29	2165
1165545	459548	459567	AGACTATCCTGGTATGACTG	22	2166
1165551	460353	460372	TGATTGACTACTTCAACCTG	64	2167
1165556	460512	460531	CGTTTATAGGGTGGTTGGTT	38	2168
1165564	461520	461539	CAGCTAGACTAGTTGAAATC	51	2169
1165569	461900	461919	GAGACCCCACAATTTGGTCC	94	2170
1165571	463886	463905	AGGCAGTTGTGATAGTCAAC	93	2171
1165577	464397	464416	CCATTCAGCACTTAGGTAGT	29	2172
1165581	464561	464580	TATGCCCTGTAGTATGTGGA	56	2173
1165586	465244	465263	TTTTATTGGTCATCTCGGGT	27	2174
1165591	465385	465404	TCAGACTTATTGAGGATGGT	47	2175
1165597	466248	466267	ACTGGTAGGATCTATGGCAG	43	2176
1165602	467299	467318	CACAGAGTAGTCTATTGGTG	62	2177
1165608	467805	467824	GTCTCCCTCTTAGTGATTGG	25	2178
1165611	474168	474187	AGTGGTTGCCTTAGTATTAC	20	2179
1165617	483858	483877	TGTAAATGGCCTGACTAGGC	75	2180
1165624	485655	485674	CTAGGACCAGTTGGTTCACT	72	2181
1165637	489520	489539	AATGGACCACCTAAGACCTC	85	2182

1165640	493853	493872	TAATCTATGCTGGGCCCCAA	76	2183
1165646	493863	493882	AGATTAGGCCTAATCTATGC	94	2184
1165652	496808	496827	GACCCTCATCACTTTTTGAC	66	2185
1165658	498508	498527	GCCCGGCAAGAGATTCACTT	79	2186
1165663	499673	499692	AGGTAGCCCCAATACAGATT	60	2187
1165667	500493	500512	AGGGCCATGTTAAAGGCCTC	82	2188
1165672	500901	500920	GACCTAACTGGCCTTTGGGT	64	2189
1165683	502143	502162	TATGTGGAATCAGTGCTACC	75	2190
1165689	502377	502396	TATACAAGGTATTAAGGCCC	55	2191
1165694	502446	502465	GCAGCTCTTTGTAGGCCCAA	25	2192
1165700	503099	503118	GACTAATAGGCCTTTCTACA	59	2193
1165706	503360	503379	GAGTGTTAGCCCAGGTGATC	57	2194
1165712	503366	503385	TCATAGGAGTGTTAGCCCAG	36	2195
1165718	503420	503439	GTGATGACACCCCTACCATG	96	2196
1165724	503427	503446	GATTAAGGTGATGACACCCC	27	2197
1165728	503943	503962	CACCAACCTTAAATAGTAGG	63	2198
1165735	504429	504448	TATTAGTCTAAGGCAGTCAG	78	2199
1165741	504653	504672	GGAGCCTTACGCTTGGCTGA	55	2200
1165746	505172	505191	TGTACCGAGCTCAAGAACTG	58	2201
1165752	505180	505199	TGTCTCTGTGTACCGAGCTC	59	2202
1165758	505215	505234	CACTCTCGCTGAGGACACAT	60	2203
1165765	505319	505338	CGCCTCTGTTATTGTGATAT	83	2204
1165771	505326	505345	ATTGGGCCGCCTCTGTTATT	54	2205
1165777	505333	505352	TGTAGAAATTGGGCCGCCTC	41	2206
1165782	505744	505763	GTAGGTTGACAGGACATGCT	75	2207
1165788	505819	505838	GGGTGCTTAGTGAACTGTGG	30	2208
1165794	505829	505848	AGACCTGTGAGGGTGCTTAG	84	2209
1165799	506279	506298	GTCTACCAGGGTGGTATTAT	70	2210
1165802	506782	506801	TATATACTCCAGGTTGTGGA	44	2211
1165805	507906	507925	AGCCATTCGATACCTGCTTT	50	2212
1165811	507913	507932	GCAGGATAGCCATTCGATAC	78	2213
1165822	508789	508808	GAATGCCACCGTGATTGCAA	51	2214
1165827	510129	510148	GCACATAGACCATAGCTGAA	32	2215
1165840	448466	448485	CAATAGAATAGTGCCAGTAG	74	2216
1165841	449441	449460	TGATCATACTGGAGCCAGGT	60	2217
1165845	452251	452270	CACGCTGTGTGAATCAAAAG	87	2218
1165855	460974	460993	GTGTTTATCCAAACCAAGGG	21	2219
1165871	465890	465909	CTCCCACAAGGTACTCTTGC	72	2220
1165879	484093	484112	GGATGTCAGTTCAGATGAAC	74	2221
1165883	486393	486412	CAACATAGATCCTCTGTTAG	74	2222
1165886	489101	489120	CTGCTCCCTAAGCTTAGATA	58	2223
1165895	501152	501171	AGTAAAGAGCCACCTAAGGG	100	2224

Table 36

Reduction of UBE3A-ATS RNA by 8,000 nM 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages *in vitro*

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence (5' to 3')	UBE3A-ATS (%UTC)	SEQ ID NO
617557	483977	483996	ATCATGTGCATACCCAGGGT	40	172
749882	460115	460134	ACTTTATAGTGTGGATGGTA	75	586
750519	349103#	349122#	GTCATCACCTCTCTTCAGGA	28	181
1165436	448409	448428	GGTCTTAGTGCCAAATATCC	46	2225
1165441	448460	448479	AATAGTGCCAGTAGGACTTA	71	2226
1165446	449099	449118	CAAGTATGCTAGTCACTCAT	40	2227
1165453	452260	452279	TCTAGGTCTCACGCTGTGTG	53	2228
1165460	453213	453232	ATAGTGTTCTTACATCCACC	59	2229
1165469	454152	454171	CCTTATGGAGACTTATATAC	103	2230
1165475	454163	454182	GAAGATTTGACCCTTATGGA	91	2231
1165481	454576	454595	AGCAAAGACTACACCGTGAC	69	2232
1165491	454859	454878	TGTATATTCCCTATCCAGGG	106	2233
1165497	455015	455034	GATGGCTGTCAATGCTGATA	53	2234
1165507	220321	220340	TCATCATCGATCCAAACAAG	58	2235
	456690	456709			
1165514	457016	457035	ACAGTTGCTTGACCCTTAAT	126	2236
1165520	457379	457398	TCAATAGTGTAGGTGACATG	63	2237
1165526	458398	458417	ATGTGGGCCTCTATTAAGAT	47	2238
1165532	458937	458956	GACCTCAGGAGATTGTACAA	45	2239
1165537	458948	458967	AAGACCTATAGGACCTCAGG	53	2240
1165544	459547	459566	GACTATCCTGGTATGACTGT	57	2241
1165550	460352	460371	GATTGACTACTTCAACCTGA	23	2242
1165555	460510	460529	TTTATAGGGTGGTTGGTTCA	30	2243
1165561	460850	460869	GGATTTACCACACATATAGG	39	2244
1165563	461451	461470	GGTAAGGCAGCTCCTGACAA	32	2245
1165568	461899	461918	AGACCCCACAATTTGGTCCC	51	2246
1165576	464390	464409	GCACTTAGGTAGTTCACAAC	41	2247
1165585	465243	465262	TTTATTGGTCATCTCGGGTA	44	2248
1165590	465384	465403	CAGACTTATTGAGGATGGTG	30	2249
1165593	465564	465583	TTAGGACAAGTCTTATAGAG	20	2250
1165596	466247	466266	CTGGTAGGATCTATGGCAGT	32	2251
1165601	467298	467317	ACAGAGTAGTCTATTGGTGT	67	2252
1165607	467804	467823	TCTCCCTCTTAGTGATTGGT	45	2253
1165616	483851	483870	GGCCTGACTAGGCATTGAAT	16	2254
1165621	483976	483995	TCATGTGCATACCCAGGGTA	76	2255
1165623	485654	485673	TAGGACCAGTTGGTTCACTG	66	2256
1165629	486356	486375	ATGTTAATAGACTGCGATTA	102	2257

1165632	489099	489118	GCTCCCTAAGCTTAGATATA	85	2258
1165636	489519	489538	ATGGACCACCTAAGACCTCA	79	2259
1165639	493852	493871	AATCTATGCTGGGCCCCAAT	52	2260
1165645	493862	493881	GATTAGGCCTAATCTATGCT	71	2261
1165651	496565	496584	TCCATCTACTATTAATGAGC	81	2262
1165657	497266	497285	GATTAGGCAGCTTCACTACT	52	2263
1165662	499671	499690	GTAGCCCCAATACAGATTCA	35	2264
1165671	500900	500919	ACCTAACTGGCCTTTGGGTC	111	2265
1165677	500913	500932	TCAAGGTGTTTTGACCTAAC	64	2266
1165682	501766	501785	GATGGGCTAAGAGTCACCTG	99	2267
1165688	502375	502394	TACAAGGTATTAAGGCCCTT	98	2268
1165693	502442	502461	CTCTTTGTAGGCCCAAGGGA	66	2269
1165698	502763	502782	AATAGGCACTTCGGGCAAAT	75	2270
1165705	503359	503378	AGTGTTAGCCCAGGTGATCA	71	2271
1165711	503365	503384	CATAGGAGTGTTAGCCCAGG	61	2272
1165717	503419	503438	TGATGACACCCCTACCATGG	96	2273
1165723	503426	503445	ATTAAGGTGATGACACCCCT	81	2274
1165734	504428	504447	ATTAGTCTAAGGCAGTCAGG	96	2275
1165740	504436	504455	GTAGGTATATTAGTCTAAGG	51	2276
1165745	505171	505190	GTACCGAGCTCAAGAACTGT	71	2277
1165751	505178	505197	TCTCTGTGTACCGAGCTCAA	58	2278
1165757	505214	505233	ACTCTCGCTGAGGACACATC	73	2279
1165762	505223	505242	AATGAGGACACTCTCGCTGA	76	2280
1165770	505325	505344	TTGGGCCGCCTCTGTTATTG	51	2281
1165776	505332	505351	GTAGAAATTGGGCCGCCTCT	35	2282
1165781	505743	505762	TAGGTTGACAGGACATGCTG	66	2283
1165787	505815	505834	GCTTAGTGAACTGTGGGCAC	72	2284
1165793	505827	505846	ACCTGTGAGGGTGCTTAGTG	62	2285
1165798	506277	506296	CTACCAGGGTGGTATTATAA	33	2286
1165810	507912	507931	CAGGATAGCCATTCGATACC	44	2287
1165821	508786	508805	TGCCACCGTGATTGCAAAGT	61	2288
1165826	510127	510146	ACATAGACCATAGCTGAACC	65	2289
1165844	449863	449882	GGCATCCTTAAATCCTGGTT	66	2290
1165849	454845	454864	CCAGGGTAGAAGACTAGCAT	74	2291
1165851	455058	455077	GAACCCTTTGGTCTAAGCAA	80	2292
1165863	463777	463796	TATAGATTGGGCTTTAGAGG	76	2293
1165865	464560	464579	ATGCCCTGTAGTATGTGGAT	74	2294
1165877	473792	473811	GTAATGCTGTTGTACACTAG	59	2295
1165893	499914	499933	TTTTGCATAATAGGAGGTCC	62	2296
1165899	503942	503961	ACCAACCTTAAATAGTAGGA	61	2297
1165907	506780	506799	TATACTCCAGGTTGTGGAGG	55	2298
1165910	507903	507922	CATTCGATACCTGCTTTTGT	71	2299

Table 37

Reduction of UBE3A-ATS RNA by 8,000 nM 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages *in vitro*

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence (5' to 3')	UBE3A-ATS (%UTC)	SEQ ID NO
1065438	449442	449461	ATGATCATACTGGAGCCAGG	65	1936
1178376	220314	220333	CGATCCAAACAAGCACCCTC	80	2300
	456683	456702			
1178378	220316	220335	ATCGATCCAAACAAGCACCC	69	2301
	456685	456704			
1178380	220319	220338	ATCATCGATCCAAACAAGCA	55	2302
	456688	456707			
1178385	456754	456773	CCGCACATCTGGACCTCAGA	97	2303
1178387	456756	456775	GGCCGCACATCTGGACCTCA	89	2304
1178389	456759	456778	GAGGGCCGCACATCTGGACC	94	2305
1178391	456761	456780	TGGAGGGCCGCACATCTGGA	83	2306
1178393	456763	456782	ATTGGAGGGCCGCACATCTG	93	2307
1178395	456765	456784	CTATTGGAGGGCCGCACATC	63	2308
1178397	456767	456786	TCCTATTGGAGGGCCGCACA	90	2309
1178399	456770	456789	TTGTCCTATTGGAGGGCCGC	64	2310
1178401	220403	220422	ATTTGTCCTATTGGAGGGCC	101	2311
	456772	456791			
1178403	220452	220471	TATGTTGTCACTGAGGGATC	78	2312
	456821	456840			
1178405	220456	220475	GTACTATGTTGTCACTGAGG	80	2313
	456825	456844			
1178407	456863	456882	GCCCTCTTCGAAGAGATAGA	90	2314
1178409	456865	456884	CTGCCCTCTTCGAAGAGATA	58	2315
1178410	456913	456932	GTCACTAGGCACACTAAAGT	62	2316
1178412	456915	456934	GGGTCACTAGGCACACTAAA	76	2317
1178414	456922	456941	AAGTCTTGGGTCACTAGGCA	63	2318
1178416	456924	456943	GCAAGTCTTGGGTCACTAGG	81	2319
1178419	457236	457255	ATGGCTTAGCTACTCACCCC	68	2320
1178421	457239	457258	ATAATGGCTTAGCTACTCAC	60	2321
1178424	457287	457306	ACGACCTAAAGACCTAGCAA	49	2322
1178427	457297	457316	GATGTACAAAACGACCTAAA	60	2323
1179741	448298	448317	ACAAGTTTCGCAATAAGATT	55	2324
1179743	448414	448433	GCAAGGGTCTTAGTGCCAAA	78	2325
1179744	448450	448469	GTAGGACTTACTAAATCATC	75	2326
1179746	448454	448473	GCCAGTAGGACTTACTAAAT	57	2327
1179748	448456	448475	GTGCCAGTAGGACTTACTAA	62	2328
1179750	448629	448648	AGGATTGCATCACATGTGTC	56	2329

1179752	448714	448733	AGCGCATTGAGCAAAATTCC	82	2330
1179754	448716	448735	GTAGCGCATTGAGCAAAATT	76	2331
1179756	448718	448737	CTGTAGCGCATTGAGCAAAA	83	2332
1179758	448720	448739	AACTGTAGCGCATTGAGCAA	52	2333
1179760	448723	448742	GATAACTGTAGCGCATTGAG	85	2334
1179762	448726	448745	CACGATAACTGTAGCGCATT	38	2335
1179764	448728	448747	ACCACGATAACTGTAGCGCA	67	2336
1179766	448731	448750	TAGACCACGATAACTGTAGC	80	2337
1179768	448733	448752	TTTAGACCACGATAACTGTA	54	2338
1179771	448738	448757	GTATATTTAGACCACGATAA	58	2339
1179773	448741	448760	TCTGTATATTTAGACCACGA	49	2340
1179775	448831	448850	GCAAGGACCCTTAAGTCATA	72	2341
1179777	448836	448855	CAATTGCAAGGACCCTTAAG	99	2342
1179779	448842	448861	TTATCCCAATTGCAAGGACC	49	2343
1179780	448920	448939	AGTCAGGCACCAGATTGCTC	112	2344
1179782	448949	448968	AACGAAGCCAAAGGTACTTG	80	2345
1179784	449036	449055	CGGCCCTGACTGTCATTCAT	71	2346
1179786	449038	449057	AACGGCCCTGACTGTCATTC	53	2347
1179788	449040	449059	GGAACGGCCCTGACTGTCAT	95	2348
1179790	449043	449062	GAAGGAACGGCCCTGACTGT	70	2349
1179792	449045	449064	CTGAAGGAACGGCCCTGACT	105	2350
1179794	449047	449066	GCCTGAAGGAACGGCCCTGA	111	2351
1179796	449051	449070	TGTGGCCTGAAGGAACGGCC	100	2352
1179798	449054	449073	TCATGTGGCCTGAAGGAACG	68	2353
1179800	449059	449078	GATAATCATGTGGCCTGAAG	49	2354
1179802	449062	449081	AACGATAATCATGTGGCCTG	86	2355
1179804	449064	449083	ATAACGATAATCATGTGGCC	52	2356
1179806	449096	449115	GTATGCTAGTCACTCATTGA	91	2357
1179808	449102	449121	TGGCAAGTATGCTAGTCACT	12	2358
1179810	449104	449123	CCTGGCAAGTATGCTAGTCA	76	2359
1179812	449107	449126	GATCCTGGCAAGTATGCTAG	103	2360
1179814	449109	449128	TAGATCCTGGCAAGTATGCT	71	2361
1179816	449111	449130	TGTAGATCCTGGCAAGTATG	79	2362
1179819	449158	449177	TCAACATTATATCGATGCAA	66	2363
1179821	449162	449181	CTTGTCAACATTATATCGAT	61	2364
1179823	449164	449183	AACTTGTCAACATTATATCG	79	2365
1179824	448294	448313	GTTTCGCAATAAGATTCCAT	98	2366
1179835	457231	457250	TTAGCTACTCACCCCTGTTC	74	2367
1179836	457241	457260	AGATAATGGCTTAGCTACTC	63	2368
1179837	457290	457309	AAAACGACCTAAAGACCTAG	92	2369
1179839	457384	457403	AGGATTCAATAGTGTAGGTG	25	2370
1179841	457502	457521	GCACACCTGGATTTCACTAC	33	2371
1179843	457505	457524	TTGGCACACCTGGATTTCAC	28	2372

1179844	457674	457693	ATAACTTACCTTGTTGCAAC	65	2373
1179846	448600	448619	TTGAGAAGAAAACCCTATCG	82	2374
1179848	448736	448755	ATATTTAGACCACGATAACT	83	2375
1179850	449117	449136	CCCTCTTGTAGATCCTGGCA	51	2376

Example 3: Effect of 5-10-5 MOE gapmer modified oligonucleotides on human UBE3A-ATS RNA *in vitro*, single dose

Modified oligonucleotides complementary to human UBE3A-ATS nucleic acid were tested for their effect on UBE3A-ATS RNA levels *in vitro*, essentially as described in Example 1, except that human UBE3A-ATS primer probe set LTS01075 (forward sequence GCCCGAAGTGCCTATTCCTT, designated herein as SEQ ID NO: 5; reverse sequence TGGTCAGGAGAACATAGGCATAAA, designated herein as SEQ ID NO: 6; probe sequence ACTCCCAGGGTTGATGGGCTACATCC, designated herein as SEQ ID NO: 7) was used to measure RNA levels.

The modified oligonucleotides in the tables below are 5-10-5 gapmers. The gapmers are 20 nucleosides in length, wherein the central gap segment consists of ten 2'-β-D-deoxynucleosides and the 3' and 5' wing segements each consists of five 2'-MOE nucleosides. The sugar motif for the gapmer is (from 5' to 3'): eeeeddddddddddeeeee; wherein 'd' represents a 2'-β-D-deoxyribosyl sugar moiety, and 'e' represents a 2'-MOE sugar moiety. . Each internucleoside linkage of Compound IDs 617456, 617457, 617460, 617461, and 617557 is a phosphorothioate internucleoside linkage. All other compounds have an internucleoside linkage motif of: soooosssssssssssooss, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage.

All cytosine residues are 5-methylcytosines.

"Start site" indicates the 5'-most nucleoside to which the modified oligonucleotide is complementary in the target nucleic acid. "Stop site" indicates the 3'-most nucleoside to which the modified oligonucleotide is complementary in the target nucleic acid. Each modified oligonucleotide listed in the Tables below is 100% complementary to SEQ ID NO: 1.

Reduction of UBE3A-ATS RNA is presented in the tables below as percent UBE3A-ATS RNA amount relative to untreated control (UTC) cells. The values marked with an asterisk (*) indicate that the modified oligonucleotide is complementary to the amplicon region of the primer probe set. Additional assays may be used to measure the potency and efficacy of the modified oligonucleotides complementary to the amplicon region.

Table 38

Reduction of UBE3A-ATS RNA by 7,000 nM 5-10-5 MOE gapmers with PS internucleoside linkages *in vitro* (35,000 cells/well)

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence (5' to 3')	UBE3A-ATS (%UTC)	SEQ ID NO
617456	463905	463924	CAACTGTTACCAAGACTTCA	25	32
617457	465003	465022	ATCTGCGAATAGAGGCCCTC	14	33
617460	466539	466558	TAGGTTGCATAAAGCCAGGC	22	36

617461	466981	467000	CACACATCTTGTTCCCTCAA	15	37
617557	483977	483996	ATCATGTGCATACCCAGGGT	17	172
699779	463905	463924	CAACTGTTACCAAGACTTCA	42	32
749897	461087	461106	AATAATATTACTGCCAAATG	85	2676
749898	461222	461241	TGAATCAATTTTCAATATTT	104	2677
749899	461325	461344	TTATAAACTTCAGCAGAGTC	41	2678
749900	461397	461416	GAGTTGTTATTTGCATTAAG	44	2679
749901	461431	461450	ATTAGCACTTCTATAACTGG	49	2680
749902	461442	461461	GCTCCTGACAAATTAGCACT	91	1329
749903	461455	461474	TCTTGGTAAGGCAGCTCCTG	64	2681
749904	461467	461486	TACTCATCATGATCTTGGTA	54	2682
749905	461516	461535	TAGACTAGTTGAAATCGGAA	46	2683
749906	461556	461575	AATTCTAAAAGTCCTCTCTT	69	2684
749907	461590	461609	TGTGAGATAATTCAGGAGGT	11	2685
749908	461810	461829	ATTCACTTTATAAACACTGA	68	2686
749909	461895	461914	CCCACAATTTGGTCCCATTG	39	2687
749910	462029	462048	GAATAGGGCTCTGCTTATTT	57	2688
749911	462064	462083	TTTTATGGCCCTCCCATCAG	81	2689
749912	462098	462117	CATGAATTTAATTCTTTAAA	80	2690
749913	462126	462145	CATTGTGGAATTAAATTAAC	54	2691
749914	462141	462160	TTTCTAATTCAATATCATTG	59	2692
749915	462149	462168	TCCTCTTATTTCTAATTCAA	54	2693
749916	462159	462178	CAAGAGATATTCCTCTTATT	41	2694
749917	462212	462231	CAATAAATAGGTCAGAAATG	84	2695
749918	462406	462425	CTAAGTTTCTTAAGGTAAAA	65	2696
749919	462607	462626	CATTTTCAAATATTGGTATT	77	2697
749920	462625	462644	TAATGATTTGCCCTCCTACA	51	2698
749921	462626	462645	GTAATGATTTGCCCTCCTAC	26	1702
749922	462674	462693	CCTTTTAAATAATTTTTCCT	66	2699
749923	462992	463011	AAAATGTTGGCATACATTTT	70	2700
749924	462993	463012	AAAAATGTTGGCATACATTT	69	2701
749925	463248	463267	CCTGGGTATTGCTGTCCAAA	36	2702
749926	463307	463326	TATGTTCCTAAGGAATAATG	113	2703
749927	463318	463337	TTCTTTGCATTTATGTTCCT	40	2704
749928	463319	463338	TTTCTTTGCATTTATGTTCC	36	2705
749929	463453	463472	TTACTCTGACTTTCCAGAAG	70	2706
749930	463474	463493	GGAGTAGATTTTTGGAGTTT	43	2707
749931	463512	463531	TCAACTATTTCTATCAAGGC	22	2708
749932	463519	463538	ATTAATTTCAACTATTTCTA	87	2709
749933	463601	463620	TCTTACTGATTCAGCCATTT	27	2710
749934	463663	463682	TCTCAGCACTAGGGAGAAAA	56	2711
749935	463695	463714	AGTGGTTGCTATCCTGCTAA	71	2000
749936	463788	463807	AATATAAATCCTATAGATTG	71	2712

749937	463805	463824	CTGAGTCAGTCCAAATGAAT	40	2713
749938	463840	463859	TACCTTGAAATTGAGATTTC	50	2714
749939	463853	463872	TCTTTTTGACCAATACCTTG	34	2715
749940	463871	463890	TCAACAATTGCCATGGATTC	78	2716
749941	463895	463914	CAAGACTTCAGGCAGTTGTG	54	2717
749942	463898	463917	TACCAAGACTTCAGGCAGTT	51	2718
749943	463900	463919	GTTACCAAGACTTCAGGCAG	35	2719
749944	463903	463922	ACTGTTACCAAGACTTCAGG	37	2720
749945	463907	463926	CCCAACTGTTACCAAGACTT	27	2721
749946	463910	463929	TATCCCAACTGTTACCAAGA	37	2722
749947	463912	463931	TTTATCCCAACTGTTACCAA	29	2723
749948	463915	463934	TTGTTTATCCCAACTGTTAC	42	2724
749949	463926	463945	TGATCAGCTTCTTGTTTATC	29	2725
749950	464355	464374	CCAGAGCATAAAAGGAAAGC	87	2726
749951	464377	464396	TCACAACTCTTCCTTAGCTT	28	2727
749952	464525	464544	CAGTTAGGTTAGTGCACAGA	44	2728
749953	464530	464549	CTGCTCAGTTAGGTTAGTGC	31	2729
749954	464542	464561	ATACTGAAGTCTCTGCTCAG	53	2730
749955	464738	464757	TGTGCCATATTTTTCTATTT	41	2731
749956	464993	465012	AGAGGCCCTCTTGTTTCAAT	36	2732
749957	464996	465015	AATAGAGGCCCTCTTGTTTC	42	2733
749958	464998	465017	CGAATAGAGGCCCTCTTGTT	59	2734
749959	465001	465020	CTGCGAATAGAGGCCCTCTT	35	2735
749960	465003	465022	ATCTGCGAATAGAGGCCCTC	30	33
749961	465005	465024	AAATCTGCGAATAGAGGCCC	33	2736
749962	465008	465027	CTCAAATCTGCGAATAGAGG	34	2737
749963	465010	465029	TGCTCAAATCTGCGAATAGA	67	2738
749964	465013	465032	GCCTGCTCAAATCTGCGAAT	24	2739
749965	465050	465069	AGTTGACATATCTTCAAGTT	69	2740
749966	465057	465076	TAATCTCAGTTGACATATCT	55	2741
749967	465059	465078	GATAATCTCAGTTGACATAT	42	2742

Example 4: Effect of modified oligonucleotides on human UBE3A-ATS RNA *in vitro*, multiple doses

Modified oligonucleotides selected from the examples above were tested at various doses in human IPS derived iCell GABANeurons (Cellular Dynamics). Cells were plated at a density of 35,000-60,000 cells per well, maintained per manufacturer instructions, and treated with modified oligonucleotides by free uptake at various concentrations as specified in the tables below. After a treatment period of approximately 6 days, total RNA was isolated from the cells and UBE3A-ATS RNA levels were measured by quantitative real-time PCR. Human UBE3A-ATS primer probe set RTS4796, described hereinabove, was used to measure RNA levels. UBE3A-ATS RNA levels were normalized according to total RNA content, as measured by RIBOGREEN®. Reduction of UBE3A-ATS RNA is presented in the tables below as percent UBE3A-ATS RNA amount relative to untreated control (UTC) cells.

Where possible, the half maximal inhibitory concentration (IC_{50}) of each modified oligonucleotide was calculated using a linear regression on a log/linear plot of the data in excel. In some cases, an IC_{50} could not be reliably calculated and the data point is marked as "N.C.". Values marked with "N.D." indicate that a value was not determined in this experiment.

Table 39

Dose-dependent percent reduction of human UBE3A-ATS RNA *in vitro* (60,000 cells/well)

Compound Number	UBE3A-ATS expression (% UTC)			
	740.7 nM	2,222 nM	6,666 nM	20,000 nM
617456	43	35	16	11
617457	38	32	27	18
617460	28	29	24	15
617461	40	19	11	12
617557	23	18	20	16

Table 40

Dose-dependent percent reduction of human UBE3A-ATS RNA *in vitro* (60,000 cells/well)

Compound Number	UBE3A-ATS expression (% UTC)			
	740.7 nM	2,222 nM	6,666 nM	20,000 nM
617456	48	38	17	15
617457	35	27	18	18
617460	29	31	24	18
617461	38	24	13	12
617557	23	17	14	13

Table 41

Dose-dependent percent reduction of human UBE3A-ATS RNA *in vitro* (60,000 cells/well)

Compound Number	UBE3A-ATS expression (% UTC)				IC_{50} (μM)
	740.7 nM	2,222 nM	6,666 nM	20,000 nM	
617456	41	26	15	20	N.C.
617557	69	43	24	30	1.9
749969	46	15	12	5	N.C.
749991	43	27	19	13	N.C.
750028	54	31	24	15	N.C.
750030	57	37	23	14	1.0
750032	40	18	14	7	N.C.
750326	76	60	38	25	3.8
750329	60	57	33	16	2.1
750344	63	77	49	29	5.6
750350	67	71	59	35	8.6

750359	110	56	38	41	6.7
750360	69	47	39	38	3.3
750365	58	60	38	22	2.4
750366	87	58	44	24	4.6
750386	76	57	42	40	5.3
750517	30	25	12	8	N.C.
750519	45	23	10	8	N.C.
750542	96	71	55	41	9.9
750549	92	54	40	24	4.3

Table 42

Dose-dependent percent reduction of human UBE3A-ATS RNA *in vitro* (60,000 cells/well)

Compound Number	UBE3A-ATS expression (% UTC)				IC_{50} (μM)
	740.7 nM	2,222 nM	6,666 nM	20,000 nM	
617557	85	57	37	25	4.1
749861	47	31	25	14	N.C.
749863	83	52	34	23	3.5
749869	46	30	18	11	N.C.
749882	84	60	40	27	4.5
749885	61	53	31	20	2.0
749893	63	36	25	13	1.3
749894	28	21	10	11	N.C.
750040	78	59	46	32	5.1
750051	47	18	21	23	N.C.
750092	80	54	40	28	3.9
750100	82	67	59	51	N.C.
750270	43	34	25	21	N.C.
750292	58	37	28	26	1.0
750312	57	54	41	30	2.3
750325	101	94	68	46	18.4
750413	98	60	35	28	4.9
750416	94	48	38	15	3.7
750430	85	47	33	24	3.3
750431	136	125	90	62	N.C.

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Table 43

Dose-dependent percent reduction of human UBE3A-ATS RNA *in vitro* (35,000 cells/well)

Compound Number	UBE3A-ATS expression (% UTC)				IC_{50} (μM)
	740.7 nM	2,222 nM	6,666 nM	20,000 nM	
617459	118	69	33	20	5.4
617470	84	51	28	13	2.9
617473	44	33	30	20	N.C.

617536	100	54	57	24	5.9
617547	122	52	29	18	4.6
617593	81	75	32	21	4.2
749794	89	102	66	52	N.C.
750418	135	132	105	51	N.C.
750439	98	60	44	26	5.4
750452	113	94	78	51	N.C.

Table 44

Dose-dependent percent reduction of human UBE3A-ATS RNA *in vitro* (35,000 cells/well)

Compound Number	UBE3A-ATS expression (% UTC)				IC_{50} (µM)
	740.7 nM	2,222 nM	6,666 nM	20,000 nM	
617557	129	53	32	28	5.5
749796	84	31	29	17	2.3
749816	94	56	46	22	4.8
749907	65	57	21	16	2.1
749921	50	47	25	18	1.0
749931	246	39	32	12	6.3
749933	51	41	26	11	0.9
749937	74	46	27	16	2.3
749944	116	N/A	74	40	15.3
749956	136	74	18	27	5.7
749964	75	80	35	17	4.2
750131	73	50	36	25	2.9
750139	35	29	21	15	N.C.
750140	27	27	13	11	N.C.
750141	52	61	25	24	1.6
750196	107	95	129	47	N.C.
750210	53	38	26	23	0.8
750214	34	70	47	41	N.C.
750228	109	105	95	70	N.C.
750242	77	70	36	15	3.8

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Table 45

Dose-dependent percent reduction of human UBE3A-ATS RNA *in vitro* (35,000 cells/well)

Compound Number	UBE3A-ATS expression (% UTC)				IC_{50} (µM)
	740.7 nM	2,222 nM	6,666 nM	20,000 nM	
617557	80	59	31	13	3.1
750519	87	67	41	27	5.2
1065438	120	90	88	95	N.C.
1065582	65	61	41	29	3.4
1065597	142	135	111	103	N.C.
1065599	63	47	47	26	2.5

1065613	96	70	65	39	11.5
1065631	60	61	48	26	3.4
1065644	64	65	42	27	3.8
1065645	68	50	36	19	2.4
1065646	52	55	34	16	1.5
1065676	50	38	33	23	N.C.
1065690	56	53	38	24	1.9
1065754	74	56	57	27	5.1
1065817	94	76	42	38	7.6
1065899	59	56	46	30	3.0
1066072	133	108	86	63	N.C.
1066249	73	60	70	48	N.C.
1066378	116	114	87	52	N.C.

Table 46

Dose-dependent percent reduction of human UBE3A-ATS RNA by modified oligonucleotides *in vitro* (42,000 cells/well)

Compound Number	UBE3A-ATS expression (% UTC)				IC_{50} (μM)
	740.7 nM	2,222 nM	6,666 nM	20,000 nM	
617557	83	54	31	13	3.1
750519	63	48	43	26	2.4
1065578	77	36	36	24	2.4
1065579	55	58	30	66	N.C.
1065595	75	60	32	19	3.1
1065642	52	58	40	27	2.0
1065672	85	67	42	18	4.5
1065674	64	69	40	22	3.5
1065719	76	62	46	38	6.1
1065750	38	28	25	28	N.C.
1065766	78	52	32	37	3.7
1065768	86	66	43	30	5.5
1065799	66	52	41	34	3.2
1065863	54	60	46	27	2.6
1065894	82	100	52	52	N.C.
1066037	66	70	56	62	N.C.
1066119	82	116	101	72	N.C.
1066375	116	98	68	77	N.C.
1066423	39	70	63	46	N.C.

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Table 47

Dose-dependent percent reduction of human UBE3A-ATS RNA *in vitro* (42,000 cells/well)

Compound Number	UBE3A-ATS expression (% UTC)				IC_{50} (μM)
	740.7 nM	2,222 nM	6,666 nM	20,000 nM	
617557	65	52	23	8	1.9
1065324	86	90	67	43	18.4
1065369	107	91	108	83	N.C.
1065465	97	96	97	100	N.C.
1065513	156	104	66	70	N.C.
1065558	116	125	92	112	N.C.
1065592	85	84	50	23	6.5
1065624	87	71	39	20	4.7
1065667	64	59	35	21	2.7
1065747	91	65	55	N/A	N.C.
1065955	84	55	43	23	4.1
1066002	94	75	68	50	N.C.
1066003	90	73	49	43	9.5
1066034	137	120	101	67	N.C.
1066201	98	110	84	79	N.C.
1066273	101	95	108	104	N.C.
1066359	111	96	101	81	N.C.
1066420	70	43	27	33	2.2

Table 48

Dose-dependent percent reduction of human UBE3A-ATS RNA *in vitro* (42,000 cells/well)

Compound Number	UBE3A-ATS expression (% UTC)				IC_{50} (μM)
	740.7 nM	2,222 nM	6,666 nM	20,000 nM	
617557	70	46	23	10	1.9
1065654	96	87	54	43	11.9
1065680	78	63	41	28	4.5
1065686	63	64	62	24	5.1
1065735	102	66	41	41	7.4
1065785	81	74	52	50	14.7
1065829	64	59	45	31	3.7
1065858	69	49	28	23	2.2
1065859	52	36	28	20	N.C.
1065901	89	69	73	55	N.C.
1065914	108	111	82	74	N.C.
1065977	106	87	101	76	N.C.
1066009	88	71	130	84	N.C.
1066046	84	59	43	36	5.5
1066089	46	71	58	41	N.C.
1066217	67	64	46	41	6.5

1066221	59	49	39	31	2.0
1066311	93	75	73	49	N.C.
1066377	94	73	51	35	7.9
1066396	100	75	82	54	N.C.

Table 49

Dose-dependent percent reduction of human UBE3A-ATS RNA *in vitro* (42,000 cells/well)

Compound Number	UBE3A-ATS expression (% UTC)				IC_{50} (μM)
	740.7 nM	2,222 nM	6,666 nM	20,000 nM	
617557	66	47	21	6	1.7
750519	75	58	36	25	3.5
1065272	90	63	38	33	5.4
1065576	21	28	19	13	N.C.
1065590	74	49	31	27	2.8
1065591	83	60	29	13	3.2
1065607	68	47	28	17	2.1
1065608	72	38	18	13	1.7
1065623	46	28	21	13	N.C.
1065669	89	75	57	28	7.6
1065685	64	34	19	20	1.2
1065795	100	86	56	38	10.8
1065810	62	46	23	22	1.6
1065812	77	67	36	24	4.1
1065826	108	93	54	43	12.1
1065937	86	61	60	37	8.7
1065953	77	46	34	29	3.0
1065954	78	62	45	38	6.1
1066097	133	121	119	125	N.C.

Table 50

Dose-dependent percent reduction of human UBE3A-ATS RNA *in vitro* (42,000 cells/well)

Compound Number	UBE3A-ATS expression (% UTC)				IC_{50} (μM)
	740.7 nM	2,222 nM	6,666 nM	20,000 nM	
617557	39	43	25	13	N.C.
750519	44	36	34	17	N.C.
1065605	50	48	29	19	N.C.
1065619	95	73	47	5	4.6
1065621	5	63	44	21	4.6
1065635	48	29	19	4	N.C.
1065651	13	8	29	10	N.C.
1065696	77	71	61	7	4.7
1065712	58	40	34	20	1.3
1065713	4	4	7	6	N.C.
1065728	73	54	42	25	3.5

1065823	7	9	10	N/A	N.C.
1065840	73	61	41	32	4.4
1065856	78	49	37	24	3.2
1065857	10	61	49	28	5.1
1065889	58	81	61	62	N.C.
1065903	85	65	60	6	4.6
1065920	53	42	40	26	1.0
1066350	89	101	78	21	11.3

Table 51

Dose-dependent percent reduction of human UBE3A-ATS RNA *in vitro* (42,000 cells/well)

Compound Number	UBE3A-ATS expression (% UTC)				IC_{50} (µM)
	740.7 nM	2,222 nM	6,666 nM	20,000 nM	
617557	14	16	3	0	N.C.
750519	31	27	22	12	N.C.
1065296	78	56	45	7	3.2
1065330	13	5	4	3	N.C.
1065586	5	44	22	11	N.C.
1065600	79	55	36	4	2.9
1065616	84	75	65	5	5.4
1065708	9	8	6	N/A	N.C.
1065709	6	4	4	4	N.C.
1065710	52	33	16	9	N.C.
1065821	110	58	29	16	4.3
1065868	73	42	28	6	2.0
1065902	8	60	35	24	3.6
1065932	51	42	35	17	0.9
1065947	65	48	38	10	2.1
1066076	81	76	41	22	5.0
1066092	80	49	40	27	3.6
1066253	0	71	31	21	4.5
1066429	28	17	6	6	N.C.

Table 52

Dose-dependent percent reduction of human UBE3A-ATS RNA *in vitro* (42,000 cells/well)

Compound Number	UBE3A-ATS expression (% UTC)				IC_{50} (µM)
	740.7 nM	2,222 nM	6,666 nM	20,000 nM	
617557	37	17	29	12	N.C.
750519	50	40	40	20	N.C.
1065295	78	73	74	49	N.C.
1065473	31	29	16	11	N.C.
1065503	105	107	107	77	N.C.
1065561	66	44	21	13	1.7
1065593	59	45	30	6	1.5

1065609	59	50	34	6	1.7
1065625	70	56	41	22	3.2
1065641	43	31	18	7	N.C.
1065671	55	49	30	8	1.4
1065678	75	78	54	33	8.0
1065765	64	46	28	12	1.8
1065791	7	58	44	30	4.1
1065806	24	72	82	74	N.C.
1065813	12	11	11	7	N.C.
1065924	107	94	79	41	18.4
1066011	94	85	83	50	N.C.
1066220	24	83	75	62	N.C.

Table 53

Dose-dependent percent reduction of human UBE3A-ATS RNA *in vitro* (40,000 cells/well)

Compound Number	UBE3A-ATS expression (% UTC)				IC_{50} (µM)
	740.7 nM	2,222 nM	6,666 nM	20,000 nM	
750519	83	53	21	14	2.8
1165521	55	38	32	27	0.9
1165524	42	33	26	14	N.C.
1165536	47	39	32	21	N.C.
1165545	62	49	32	33	2.0
1165552	53	35	24	16	0.8
1165553	55	34	24	18	0.8
1165554	63	55	29	19	2.1
1165555	53	43	21	22	0.9
1165562	72	69	35	23	3.8
1165577	65	59	33	28	2.8
1165588	78	57	33	38	4.3
1165590	44	41	30	21	N.C.
1165593	85	92	83	50	N.C.
1165611	47	39	25	21	N.C.
1165724	80	71	57	54	N.C.
1165788	66	71	42	25	4.2
1165798	73	81	86	52	N.C.
1179842	78	37	27	20	2.2

Example 5: Effect of modified oligonucleotides on human UBE3A-ATS RNA *in vitro*, multiple doses

Modified oligonucleotides selected from the examples above were tested at various doses in human IPS derived ReproNeuro™ Neurons (ReproCELL). Cells were plated at a density of 20,000 cells per well, maintained per manufacturer instructions, and treated with modified oligonucleotides by free uptake at various concentrations as specified in the tables below. After a treatment period of approximately 5 days, total RNA was isolated from the cells and UBE3A-ATS RNA levels were measured by quantitative real-time PCR. Human UBE3A-ATS primer probe set RTS4796, described hereinabove, was used to measure RNA levels. UBE3A-ATS RNA levels were normalized

according to total RNA content, as measured by RIBOGREEN®. Reduction of UBE3A-ATS RNA is presented in the tables below as percent UBE3A-ATS RNA amount relative to untreated control (UTC) cells.

The half maximal inhibitory concentration (IC_{50}) of each modified oligonucleotide was calculated using a linear regression on a log/linear plot of the data in excel. In cases where IC_{50} could not be calculated, IC_{50}s are marked as N.C. (Not Calculated).

Table 54

Dose-dependent percent reduction of human UBE3A-ATS RNA *in vitro*

Compound Number	UBE3A-ATS expression (% UTC)				IC_{50} (μM)
	740.7 nM	2,222 nM	6,666 nM	20,000 nM	
750519	73	54	19	11	2.3
1165523	75	60	43	33	4.7
1165533	60	50	18	33	1.5
1165538	64	47	34	26	2.1
1165550	65	62	47	32	4.5
1165563	69	51	41	29	3.1
1165586	62	50	35	32	2.3
1165596	88	72	69	43	16.4
1165608	88	89	62	54	N.C.
1165616	89	88	80	74	N.C.
1165694	71	57	55	50	15.0
1165737	71	55	53	46	9.1
1165827	72	59	65	42	13.6
1165855	60	60	37	19	2.5
1165897	78	76	54	50	N.C.
1179808	101	100	85	75	N.C.
1179839	58	41	26	23	1.2
1179841	68	45	38	26	2.4
1179843	52	57	36	21	1.7

Example 6: Effect of modified oligonucleotides on human UBE3A-ATS RNA and UBE3A RNA *in vitro*, multiple doses

Modified oligonucleotides selected from the examples above were tested at various doses in 10-week differentiated human neuronal cells derived from Angelman Syndrome patient derived IPS cells (Protocols and cells described in Chamberlain SJ., et al., *Induced pluripotent stem cell models of the genomic imprinting disorders Angelman and Prader–Willi syndromes*. PNAS, 2010. 41: 17668-17673). At the end of the 10-week differentiation period, cells were treated with modified oligonucleotides by free uptake at various concentrations as specified in the tables below. After a treatment period of approximately 6 days, total RNA was isolated from the cells. Both UBE3A-ATS RNA and UBE3A RNA levels were measured by quantitative real-time PCR. Human UBE3A-ATS primer probe set RTS4796 was used to measure UBE3A-ATS RNA levels as described above. Human UBE3A primer probe set RTS35984 (forward sequence CACCCTGATGTCACCGAATG, designated herein as SEQ ID NO: 8; reverse sequence GCGTTCTATTAGATGCTTTGCAG, designated herein as SEQ ID NO: 9; probe sequence

ACTGAGGTTCTCCTGATCTTTTACAAGCTG, designated herein as SEQ ID NO: 10) was used to measure UBE3A RNA levels. RNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Reduction of UBE3A-ATS RNA or induction of UBE3A RNA is presented in the tables below as percent UBE3A-ATS RNA amount or percent UBE3A RNA relative to untreated control (UTC) cells. Values marked with "N.D." indicate that a value was not determined in this experiment.

Several modified oligonucleotides were found to reduce UBE3A-ATS RNA accompanied by concurrent increase in UBE3A RNA in Angelman's patient IPS cell derived neurons.

Table 55

Reduction of UBE3A-ATS RNA and increase of UBE3A RNA in Angelman Syndrome IPS cell derived neurons

Compound ID	UBE3A-ATS RNA (% UTC) (RTS4796)			UBE3A RNA (% UTC) (RTS35984)		
	741nM	2222nM	6667nM	741nM	2222nM	6667nM
617557	17	16	N.D.	142	151	N.D.
750140	7	N.D.	N.D.	226	N.D.	N.D.
750139	35	10	3	104	196	194
750131	29	25	N.D.	49	53	N.D.
750141	22	N.D.	N.D.	89	N.D.	N.D.
750242	42	N.D.	N.D.	45	N.D.	N.D.
750210	49	14	6	122	101	166
750214	53	56	13	87	154	85
749907	16	13	7	133	298	205
749931	35	17	11	152	271	260
749964	27	15	6	144	160	202
749921	25	12	N.D.	73	98	N.D.
749933	42	10	13	116	92	210
749956	51	33	N.D.	94	103	N.D.
749937	52	27	7	104	131	137
749796	73	67	N.D.	81	79	N.D.
749816	75	N.D.	19	63	N.D.	27
749969	33	14	10	171	249	305
749991	32	15	15	193	165	276

Table 56

Reduction of UBE3A-ATS RNA and increase of UBE3A RNA in Angelman Syndrome IPS cell derived neurons

Compound ID	UBE3A-ATS RNA (% UTC) (RTS4796)			UBE3A RNA (% UTC) (RTS35984)		
	741nM	2222nM	6667nM	741nM	2222nM	6667nM
617557	54	51	39	144	365	252
750140	22	37	N.D.	345	328	N.D.

750517	34	30	19	269	328	418
750549	60	72	72	337	225	309
750542	64	70	22	98	113	234
617456	58	35	26	142	176	253
750519	33	26	18	374	440	447
750360	93	113	59	151	221	204
750359	32	31	27	267	134	229
750386	35	40	17	182	282	320
750366	77	45	37	87	122	185
750344	51	50	30	91	139	150
750326	67	49	31	106	108	166
750350	68	66	102	111	132	138
750365	74	63	37	122	160	183
750329	88	82	N.D.	154	148	N.D.
750028	81	N.D.	14	324	N.D.	448
750030	87	30	22	221	307	373
750032	47	17	13	202	323	254

Table 57

Reduction of UBE3A-ATS RNA and increase of UBE3A RNA in Angelman Syndrome IPS cell derived neurons

Compound ID	UBE3A-ATS RNA (% UTC) (RTS4796)			UBE3A RNA (% UTC) (RTS35984)		
	741nM	2222nM	6667nM	741nM	2222nM	6667nM
617557	28	54	N.D.	318	411	N.D.
750140	19	20	10	619	542	132
750040	38	49	25	171	192	318
750051	21	21	13	106	544	416
750092	40	32	12	175	507	118
749894	12	19	6	143	2085	605
749869	10	11	13	376	802	1504
749882	34	31	19	502	907	926
749863	45	42	22	326	2584	927
749893	34	10	7	215	428	1023
749885	22	12	10	105	233	614
749861	19	11	8	209	236	466
750292	28	15	13	123	318	645
750270	18	14	10	267	578	584
750312	39	19	12	87	289	420
750413	46	49	20	123	375	143
750416	49	N.D.	N.D.	119	N.D.	N.D.
750430	33	21	12	329	359	241
750439	40	31	19	188	197	183

Table 58

Reduction of UBE3A-ATS RNA and increase of UBE3A RNA in Angelman Syndrome IPS cell derived neurons

Compound ID	UBE3A-ATS RNA (% UTC) (RTS4796)			UBE3A RNA (% UTC) (RTS35984)		
	741nM	2222nM	6667nM	741nM	2222nM	6667nM
617557	60	39	N.D.	266	161	N.D.
617557	65	23	8	229	204	122
750140	18	29	N.D.	312	222	N.D.
617470	36	34	23	141	191	317
617473	29	37	20	91	162	87
617459	38	18	8	80	155	191
617547	31	19	28	52	145	226
617536	83	28	109	165	108	265
617593	67	142	107	100	73	83
750544	98	107	51	221	258	307
750554	65	72	88	57	80	55
750540	46	26	29	202	344	458
750567	62	49	31	86	108	227
749984	47	42	N.D.	68	99	277
750009	31	39	22	65	92	217
749865	44	N.D.	12	201	N.D.	249
749860	36	22	9	285	265	263
750006	32	17	66	241	329	513
582468	102	79	33	120	33	62
141923	150	169	100	135	126	53

Table 59

Reduction of UBE3A-ATS RNA and increase of UBE3A RNA in Angelman Syndrome IPS cell derived neurons

Compound ID	UBE3A-ATS RNA (% UTC) (RTS4796)				UBE3A RNA (% UTC) (RTS35984)			
	741nM	2222nM	6667nM	20000nM	741nM	2222nM	6667nM	20000nM
749894	20	13	11	10	301	200	159	546
749969	47	44	45	51	125	88	85	205
750032	16	17	12	17	215	190	182	236
750140	26	33	13	22	252	429	160	222
1065690	18	7	11	9	313	295	203	254
1065868	32	17	9	9	249	303	211	143
1065579	20	19	25	7	155	134	133	231
1065858	22	24	25	17	190	239	229	249
1065859	55	57	36	29	117	141	199	193
1065812	25	29	9	10	133	120	185	163

749860	35	21	14	11	129	250	196	278
1065593	18	10	7	9	228	181	211	261
1065953	15	11	12	10	148	269	243	221
1065856	15	18	11	9	292	286	103	234
1065937	21	26	12	10	93	205	225	208
1065728	35	24	20	12	132	143	144	198
750139	38	28	13	14	176	229	248	315
617557	55	23	30	33	166	206	193	226
750519	15	15	5	3	173	101	220	324

Table 60

Reduction of UBE3A-ATS RNA and increase of UBE3A RNA in Angelman Syndrome IPS cell derived neurons

Compound ID	UBE3A-ATS RNA (% UTC) (RTS4796)				UBE3A RNA (% UTC) (RTS35984)			
	741nM	2222nM	6667nM	20000nM	741nM	2222nM	6667nM	20000nM
1066092	138	160	98	55	247	253	254	111
1065902	92	85	55	42	168	231	203	304
1065840	57	54	37	22	209	176	141	307
1066253	77	37	52	36	182	167	184	236
1065785	93	35	41	54	155	198	225	240
1065821	40	19	20	20	220	288	215	276
750006	78	33	33	56	132	119	168	185
750028	36	17	16	19	173	235	189	216
617557	37	26	13	23	194	166	214	241

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Table 61

Reduction of UBE3A-ATS RNA and increase of UBE3A RNA in Angelman Syndrome IPS cell derived neurons

Compound ID	UBE3A-ATS RNA (% UTC) (RTS4796)				UBE3A RNA (% UTC) (RTS35984)			
	741nM	2222nM	6667nM	20000nM	741nM	2222nM	6667nM	20000nM
750519	41	26	11	8	138	158	148	158
1065671	106	81	108	61	213	189	387	235
617557	69	52	37	35	129	132	210	195
1065686	101	101	81	88	145	105	118	164
750359	121	70	79	48	108	119	134	131
1065817	75	78	40	N.D.	119	174	131	N.D.
750386	100	65	58	50	106	155	190	128
749894	58	40	19	20	176	187	159	244
1065591	68	51	52	34	138	132	227	155
750140	178	165	133	129	129	117	98	142

750032	95	56	40	31	109	144	126	172
1065599	73	45	42	33	135	131	188	210
1065690	66	48	35	29	182	175	211	185
1065868	132	125	107	90	93	125	113	99
1065645	83	47	50	25	169	144	287	158
1065858	78	46	22	18	175	192	162	227
1065856	76	66	49	35	138	195	167	165
1065667	137	127	137	94	115	116	163	134
1066092	133	126	87	75	100	113	104	106

Example 7: Design and synthesis of modified oligonucleotides complementary to a human UBE3A-ATS nucleic acid

Modified oligonucleotides were synthesized as indicated in the tables below.

The compounds in Table 62 are 4-10-6 MOE gapmers. The gapmers are 20 nucleosides in length, wherein the central gap segment consists of ten 2'-β-D-deoxynucleosides, the 5' wing segment consists of four 2'-MOE nucleosides, and the 3' wing segment consists of six 2'-MOE nucleosides. The sugar motif of the gapmers is (from 5' to 3'): eeeeddddddddddeeeeee; wherein 'd' represents a 2'-β-D-deoxyriboxyl sugar moiety, and 'e' represents a 2'-MOE sugar moiety. The gapmers have an internucleoside linkage motif of (from 5' to 3'): sooossssssssssoooss; wherein "s" represents a phosphorothioate internucleoside linkage and "o" represents a phosphodiester internucleoside linkage. All cytosine residues are 5-methylcytosines.

Table 62

4-10-6 MOE gapmers with a mixed PO/PS internucleoside linkages complementary to human UBE3A-ATS

Compound ID	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQUENCE	SEQ ID NO
1263473	460996	461015	TTTTTCCATTTTTCTCTTAG	2745
1263474	460997	461016	GTTTTTCCATTTTTCTCTTA	2746
1263475	460999	461018	GTGTTTTTCCATTTTTCTCT	598
1263476	461000	461019	TGTGTTTTTCCATTTTTCTC	2747
1263477	461001	461020	GTGTGTTTTTCCATTTTTCT	2748
1263478	461002	461021	TGTGTGTTTTTCCATTTTTC	2749
1263479	465235	465254	TCATCTCGGGTATATAAATT	2750
1263480	465236	465255	GTCATCTCGGGTATATAAAT	1132
1263481	465237	465256	GGTCATCTCGGGTATATAAA	1207
1263482	465238	465257	TGGTCATCTCGGGTATATAA	318
1263483	465239	465258	TTGGTCATCTCGGGTATATA	2473
1263484	465240	465259	ATTGGTCATCTCGGGTATAT	1655
1263485	465241	465260	TATTGGTCATCTCGGGTATA	2548
1263486	468985	469004	TCACCATTTTGACCTTCTTA	2751

1263487	468986	469005	TTCACCATTTTGACCTTCTT	2752
1263488	468987	469006	CTTCACCATTTTGACCTTCT	2753
1263489	468988	469007	GCTTCACCATTTTGACCTTC	377
1263490	468989	469008	TGCTTCACCATTTTGACCTT	2754
1263491	468990	469009	CTGCTTCACCATTTTGACCT	2755
1263492	468991	469010	ACTGCTTCACCATTTTGACC	2756
1263494	464526	464545	TCAGTTAGGTTAGTGCACAG	2757
1263495	464527	464546	CTCAGTTAGGTTAGTGCACA	2758
1263496	464528	464547	GCTCAGTTAGGTTAGTGCAC	1504
1263497	464529	464548	TGCTCAGTTAGGTTAGTGCA	2759
1263498	464530	464549	CTGCTCAGTTAGGTTAGTGC	2729
1263499	464531	464550	TCTGCTCAGTTAGGTTAGTG	2760
1263500	479994	480013	GAGCTATCTGTACAAAATGG	2761
1263501	479995	480014	TGAGCTATCTGTACAAAATG	2743
1263502	479996	480015	GTGAGCTATCTGTACAAAAT	2744
1263503	479997	480016	CGTGAGCTATCTGTACAAAA	1142
1263532	483970	483989	GCATACCCAGGGTAGGATTC	765
1263534	483971	483990	TGCATACCCAGGGTAGGATT	1445
1263536	483972	483991	GTGCATACCCAGGGTAGGAT	766
1263539	483973	483992	TGTGCATACCCAGGGTAGGA	2762
1263541	483974	483993	ATGTGCATACCCAGGGTAGG	2595
1273009	457735	457754	GCCAGGTGTCTTATATCTAT	2852
1273010	474393	474412	GGTCAACCAATTTGCTATTC	1809
1273011	474394	474413	AGGTCAACCAATTTGCTATT	2853
1273012	474396	474415	TTAGGTCAACCAATTTGCTA	2854
1273013	457736	457755	AGCCAGGTGTCTTATATCTA	2855
1273014	478535	478554	AACGCAATGTATCAGGCAAC	2856
1273015	478536	478555	AAACGCAATGTATCAGGCAA	2857
1273016	478730	478749	GATCACATTACCCATCCGTT	2858
1273017	478731	478750	TGATCACATTACCCATCCGT	2859
1273018	478732	478751	CTGATCACATTACCCATCCG	2860
1273019	474395	474414	TAGGTCAACCAATTTGCTAT	2861
1273020	478733	478752	GCTGATCACATTACCCATCC	1291
1273021	478734	478753	TGCTGATCACATTACCCATC	2862
1273022	478735	478754	TTGCTGATCACATTACCCAT	2863

The compounds in Table 63 are 5-10-5 MOE gapmers. The gapmers are 20 nucleosides in length, wherein the central gap segment consists of ten 2'-β-D-deoxyribonucleosides and the 5' and 3' wing segments each consist of five 2'-MOE nucleosides. The sugar motif for the gapmers is (from 5' to 3'): eeeeeddddddddddeeeee; wherein 'd' represents a 2'-β-D-deoxyribosyl sugar moiety, and 'e' represents a 2'-MOE sugar moiety The gapmers have an internucleoside

linkage motif of (from 5' to 3'): soooossssssssssooss, wherein "s" represents a phosphorothioate internucleoside linkage and "o" represents a phosphodiester internucleoside linkage. All cytosine residues are 5-methylcytosines.

Table 63

5-10-5 MOE gapmers with a mixed PO/PS internucleoside linkages complementary to human UBE3A-ATS

Compound ID	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQUENCE	SEQ ID NO
1263451	460996	461015	TTTTTCCATTTTTCTCTTAG	2745
1263452	460997	461016	GTTTTTCCATTTTTCTCTTA	2746
1263453	461000	461019	TGTGTTTTTCCATTTTTCTC	2747
1263454	461001	461020	GTGTGTTTTTCCATTTTTCT	2748
1263455	461002	461021	TGTGTGTTTTTCCATTTTTC	2749
1263456	465235	465254	TCATCTCGGGTATATAAATT	2750
1263460	468985	469004	TCACCATTTTGACCTTCTTA	2751
1263461	468986	469005	TTCACCATTTTGACCTTCTT	2752
1263462	468987	469006	CTTCACCATTTTGACCTTCT	2753
1263463	468989	469008	TGCTTCACCATTTTGACCTT	2754
1263464	468990	469009	CTGCTTCACCATTTTGACCT	2755
1263465	468991	469010	ACTGCTTCACCATTTTGACC	2756
1263466	464526	464545	TCAGTTAGGTTAGTGCACAG	2757
1263467	464527	464546	CTCAGTTAGGTTAGTGCACA	2758
1263468	464529	464548	TGCTCAGTTAGGTTAGTGCA	2759
1263469	464531	464550	TCTGCTCAGTTAGGTTAGTG	2760
1263470	479994	480013	GAGCTATCTGTACAAAATGG	2761
1263471	479995	480014	TGAGCTATCTGTACAAAATG	2743
1263472	479996	480015	GTGAGCTATCTGTACAAAAT	2744
1263538	483973	483992	TGTGCATACCCAGGGTAGGA	2762
1272943	467048	467067	TTTCATCAGTTAGTCAGGTT	2786
1272944	465605	465624	CCTTTCTATTTCAGACCGAA	2787
1272945	465607	465626	TGCCTTTCTATTTCAGACCG	2788
1272946	465608	465627	GTGCCTTTCTATTTCAGACC	2789
1272947	465609	465628	AGTGCCTTTCTATTTCAGAC	2790
1272948	468919	468938	AGTATAGATGCCTCTCCTCT	2791
1272949	468920	468939	AAGTATAGATGCCTCTCCTC	2792
1272950	468921	468940	TAAGTATAGATGCCTCTCCT	2793
1272951	474796	474815	ATTGACACCTCCAACTGTAA	2794
1272952	474798	474817	GTATTGACACCTCCAACTGT	2795
1272953	474800	474819	TGGTATTGACACCTCCAACT	2796
1272954	474801	474820	TTGGTATTGACACCTCCAAC	2797
1272955	474802	474821	TTTGGTATTGACACCTCCAA	2798

1272956	476012	476031	GTTTTCGCCCGTTACCTCAA	2799
1272957	476013	476032	AGTTTTCGCCCGTTACCTCA	2800
1272958	476014	476033	CAGTTTTCGCCCGTTACCTC	2801
1272959	476017	476036	CTCCAGTTTTCGCCCGTTAC	2802
1272960	467052	467071	ACACTTTCATCAGTTAGTCA	2803
1272961	476018	476037	TCTCCAGTTTTCGCCCGTTA	2804
1272962	478437	478456	GCTATAGGTGTCACATATTC	2805
1272963	478442	478461	TTGTAGCTATAGGTGTCACA	2806
1272964	478443	478462	TTTGTAGCTATAGGTGTCAC	2807
1272965	483106	483125	GCAATGGACTTAGTACACAA	2808
1272966	483107	483126	GGCAATGGACTTAGTACACA	2809
1272967	483110	483129	TTAGGCAATGGACTTAGTAC	2810
1272968	483111	483130	CTTAGGCAATGGACTTAGTA	2811
1272969	485766	485785	CAGATTCCTAAATACGCACA	2812
1272970	485767	485786	TCAGATTCCTAAATACGCAC	2813
1272971	485768	485787	GTCAGATTCCTAAATACGCA	2814
1272972	485771	485790	GTGGTCAGATTCCTAAATAC	2815
1272973	487601	487620	AGTGTCATATGTAGCAATTA	2816
1272974	487603	487622	TTAGTGTCATATGTAGCAAT	2817
1272975	501337	501356	TATGTAGCTCAGCTCAATGT	2818
1272976	501339	501358	CTTATGTAGCTCAGCTCAAT	2819
1272977	501342	501361	CTGCTTATGTAGCTCAGCTC	2820
1272978	468734	468753	AAAATCCATTTGTCCAGTCT	2821
1272979	505552	505571	TTTGCTTTTCAGTCAGGTAC	2822
1272980	468735	468754	TAAAATCCATTTGTCCAGTC	2823
1272981	468736	468755	CTAAAATCCATTTGTCCAGT	2824
1272982	506110	506129	GCATTGGCTTCATATTTCTC	2825
1272983	506112	506131	GAGCATTGGCTTCATATTTC	2826
1272984	508942	508961	CATTATTCTCTAGTGCCTAT	2827
1272985	508943	508962	TCATTATTCTCTAGTGCCTA	2828
1272986	508947	508966	GTCTTCATTATTCTCTAGTG	2829
1272987	508948	508967	AGTCTTCATTATTCTCTAGT	2830
1272988	458439	458458	AACTTCATCAATATTTCCCC	2831
1272989	458397	458416	TGTGGGCCTCTATTAAGATC	2832
1272990	458399	458418	CATGTGGGCCTCTATTAAGA	2833
1272991	458401	458420	TGCATGTGGGCCTCTATTAA	2834
1272992	458453	458472	TTTATACTTTACCCAACTTC	2835
1272993	458454	458473	CTTTATACTTTACCCAACTT	2836
1272994	458455	458474	GCTTTATACTTTACCCAACT	2837
1272995	458440	458459	CAACTTCATCAATATTTCCC	2838

1272996	458457	458476	TGGCTTTATACTTTACCCAA	2839
1272997	458458	458477	TTGGCTTTATACTTTACCCA	2840
1272998	458459	458478	TTTGGCTTTATACTTTACCC	2841
1272999	458569	458588	CTTTAGTATGTCGAGAACTC	2842
1273000	458441	458460	CCAACTTCATCAATATTTCC	2843
1273001	461466	461485	ACTCATCATGATCTTGGTAA	2844
1273002	463053	463072	TCACTGAGTTTTTGTAGTTC	2845
1273003	463191	463210	TCTGGAATCTTGTAGAGGAT	2846
1273004	463192	463211	TTCTGGAATCTTGTAGAGGA	2847
1273005	467047	467066	TTCATCAGTTAGTCAGGTTA	2848
1273006	464395	464414	ATTCAGCACTTAGGTAGTTC	2849
1273007	464399	464418	TCCCATTCAGCACTTAGGTA	2850
1273008	464400	464419	TTCCCATTCAGCACTTAGGT	2851
1273061	468982	469001	CCATTTTGACCTTCTTAGCC	2872
1273062	468983	469002	ACCATTTTGACCTTCTTAGC	2873
1273063	465232	465251	TCTCGGGTATATAAATTAAT	2874
1273064	465233	465252	ATCTCGGGTATATAAATTAA	2875
1273065	468992	469011	AACTGCTTCACCATTTTGAC	2876
1273066	468993	469012	TAACTGCTTCACCATTTTGA	2877
1273067	468994	469013	TTAACTGCTTCACCATTTTG	2878
1273068	464522	464541	TTAGGTTAGTGCACAGATAA	2879
1273069	464523	464542	GTTAGGTTAGTGCACAGATA	2880
1273070	464534	464553	GTCTCTGCTCAGTTAGGTTA	2881
1273071	479991	480010	CTATCTGTACAAAATGGAAC	2882
1273072	479992	480011	GCTATCTGTACAAAATGGAA	2883
1273073	479993	480012	AGCTATCTGTACAAAATGGA	2884
1273084	457732	457751	AGGTGTCTTATATCTATGAT	2885
1273085	457742	457761	GAAACCAGCCAGGTGTCTTA	2886
1273086	474391	474410	TCAACCAATTTGCTATTCAT	2887
1273087	474392	474411	GTCAACCAATTTGCTATTCA	2888
1273088	457733	457752	CAGGTGTCTTATATCTATGA	2889
1273089	474394	474413	AGGTCAACCAATTTGCTATT	2853
1273090	474395	474414	TAGGTCAACCAATTTGCTAT	2861
1273091	474396	474415	TTAGGTCAACCAATTTGCTA	2854
1273092	474397	474416	TTTAGGTCAACCAATTTGCT	2890
1273093	474398	474417	GTTTAGGTCAACCAATTTGC	2891
1273094	474399	474418	GGTTTAGGTCAACCAATTTG	2892
1273095	478527	478546	GTATCAGGCAACAGAATCTC	2893
1273096	478528	478547	TGTATCAGGCAACAGAATCT	2894
1273097	478529	478548	ATGTATCAGGCAACAGAATC	2895

1273098	457734	457753	CCAGGTGTCTTATATCTATG	2896
1273099	478535	478554	AACGCAATGTATCAGGCAAC	2856
1273101	478537	478556	AAAACGCAATGTATCAGGCA	2897
1273102	478538	478557	TAAAACGCAATGTATCAGGC	2898
1273103	457735	457754	GCCAGGTGTCTTATATCTAT	2852
1273104	478727	478746	CACATTACCCATCCGTTCTT	2899
1273105	478728	478747	TCACATTACCCATCCGTTCT	2900
1273106	478729	478748	ATCACATTACCCATCCGTTC	2901
1273107	478730	478749	GATCACATTACCCATCCGTT	2858
1273108	478731	478750	TGATCACATTACCCATCCGT	2859
1273109	478732	478751	CTGATCACATTACCCATCCG	2860
1273110	478734	478753	TGCTGATCACATTACCCATC	2862
1273111	478735	478754	TTGCTGATCACATTACCCAT	2863
1273112	457736	457755	AGCCAGGTGTCTTATATCTA	2855
1273113	478737	478756	TCTTGCTGATCACATTACCC	2902
1273114	478738	478757	TTCTTGCTGATCACATTACC	2903
1273115	457737	457756	CAGCCAGGTGTCTTATATCT	2904

The compounds in Table 64 are 6-10-4 MOE gapmers. The gapmers are 20 nucleosides in length, wherein the central gap segment consists of ten 2'-β-D-deoxynucleosides, the 5' wing segment consists of six 2'-MOE nucleosides, and the 3' wing segment consists of four 2'-MOE nucleosides. The sugar motif of the gapmers is (from 5' to 3'): eeeeeddddddddddeeee; wherein 'd' represents a 2'-β-D-deoxyriboxyl sugar moiety, and 'e' represents a 2'-MOE sugar moiety. The gapmers have an internucleoside linkage motif of (from 5' to 3'): sooooossssssssssoss, wherein "s" represents a phosphorothioate internucleoside linkage and "o" represents a phosphodiester internucleoside linkage. All cytosine residues are 5-methylcytosines.

Table 64

6-10-4 MOE gapmers with a mixed PO/PS internucleoside linkages complementary to human UBE3A-ATS

Compound ID	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQUENCE	SEQ ID NO
1263457	479995	480014	TGAGCTATCTGTACAAAATG	2743
1263458	479996	480015	GTGAGCTATCTGTACAAAAT	2744
1263459	479997	480016	CGTGAGCTATCTGTACAAAA	1142
1263504	460996	461015	TTTTTCCATTTTTCTCTTAG	2745
1263505	460997	461016	GTTTTTCCATTTTTCTCTTA	2746
1263506	460999	461018	GTGTTTTTCCATTTTTCTCT	598
1263507	461000	461019	TGTGTTTTTCCATTTTTCTC	2747
1263508	461001	461020	GTGTGTTTTTCCATTTTTCT	2748
1263509	461002	461021	TGTGTGTTTTTCCATTTTTC	2749

1263510	465235	465254	TCATCTCGGGTATATAAATT	2750
1263511	465236	465255	GTCATCTCGGGTATATAAAT	1132
1263512	465237	465256	GGTCATCTCGGGTATATAAA	1207
1263513	465238	465257	TGGTCATCTCGGGTATATAA	318
1263514	465239	465258	TTGGTCATCTCGGGTATATA	2473
1263515	465240	465259	ATTGGTCATCTCGGGTATAT	1655
1263516	465241	465260	TATTGGTCATCTCGGGTATA	2548
1263517	468985	469004	TCACCATTTTGACCTTCTTA	2751
1263518	468986	469005	TTCACCATTTTGACCTTCTT	2752
1263519	468987	469006	CTTCACCATTTTGACCTTCT	2753
1263520	468988	469007	GCTTCACCATTTTGACCTTC	377
1263521	468989	469008	TGCTTCACCATTTTGACCTT	2754
1263522	468990	469009	CTGCTTCACCATTTTGACCT	2755
1263523	468991	469010	ACTGCTTCACCATTTTGACC	2756
1263524	464525	464544	CAGTTAGGTTAGTGCACAGA	2728
1263525	464526	464545	TCAGTTAGGTTAGTGCACAG	2757
1263526	464527	464546	CTCAGTTAGGTTAGTGCACA	2758
1263527	464528	464547	GCTCAGTTAGGTTAGTGCAC	1504
1263528	464529	464548	TGCTCAGTTAGGTTAGTGCA	2759
1263529	464530	464549	CTGCTCAGTTAGGTTAGTGC	2729
1263530	464531	464550	TCTGCTCAGTTAGGTTAGTG	2760
1263531	479994	480013	GAGCTATCTGTACAAAATGG	2761
1263533	483970	483989	GCATACCCAGGGTAGGATTC	765
1263535	483971	483990	TGCATACCCAGGGTAGGATT	1445
1263537	483972	483991	GTGCATACCCAGGGTAGGAT	766
1263540	483973	483992	TGTGCATACCCAGGGTAGGA	2762
1263542	483974	483993	ATGTGCATACCCAGGGTAGG	2595
1273023	457735	457754	GCCAGGTGTCTTATATCTAT	2852
1273024	457736	457755	AGCCAGGTGTCTTATATCTA	2855
1273025	474393	474412	GGTCAACCAATTTGCTATTC	1809
1273026	474394	474413	AGGTCAACCAATTTGCTATT	2853
1273027	474395	474414	TAGGTCAACCAATTTGCTAT	2861
1273028	474396	474415	TTAGGTCAACCAATTTGCTA	2854
1273029	478535	478554	AACGCAATGTATCAGGCAAC	2856
1273030	478536	478555	AAACGCAATGTATCAGGCAA	2857
1273031	478730	478749	GATCACATTACCCATCCGTT	2858
1273032	478731	478750	TGATCACATTACCCATCCGT	2859
1273033	478732	478751	CTGATCACATTACCCATCCG	2860
1273034	478733	478752	GCTGATCACATTACCCATCC	1291
1273035	478734	478753	TGCTGATCACATTACCCATC	2862

1273036	478735	478754	TTGCTGATCACATTACCCAT	2863

The compounds in Table 65 are 4-8-6 MOE gapmers. The gapmers are 18 nucleosides in length, wherein the central gap segment consists of eight 2'-β-D-deoxynucleosides, the 5' segment consists of four 2'-MOE nucleosides, and the 3' wing segment consists of six 2'-MOE nucleosides. The sugar motif of the gapmers is (from 5' to 3'): eeeedddddddeeeeee; wherein 'd' represents a 2'-β-D-deoxyriboxyl sugar moiety, and 'e' represents a 2'-MOE sugar moiety. The gapmers have an internucleoside linkage motif of (from 5' to 3'): soosssssssssoooss; wherein "s" represents a phosphorothioate internucleoside linkage and "o" represents a phosphodiester internucleoside linkage. All cytosine residues are 5-methylcytosines.

Table 65

4-8-6 MOE gapmers with a mixed PO/PS internucleoside linkages complementary to human UBE3A-ATS

Compound ID	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQUENCE	SEQ ID NO
1263403	465237	465254	TCATCTCGGGTATATAAA	2768
1263404	465238	465255	GTCATCTCGGGTATATAA	2769
1263405	465239	465256	GGTCATCTCGGGTATATA	2770
1263406	465240	465257	TGGTCATCTCGGGTATAT	2771
1263407	465241	465258	TTGGTCATCTCGGGTATA	2772
1263408	468987	469004	TCACCATTTTGACCTTCT	2773
1263409	468988	469005	TTCACCATTTTGACCTTC	2774
1263410	468989	469006	CTTCACCATTTTGACCTT	2775
1263411	468991	469008	TGCTTCACCATTTTGACC	2776
1263412	464527	464544	CAGTTAGGTTAGTGCACA	2777
1263413	464528	464545	TCAGTTAGGTTAGTGCAC	2778
1263414	464529	464546	CTCAGTTAGGTTAGTGCA	2779
1263415	464530	464547	GCTCAGTTAGGTTAGTGC	2780
1263416	464531	464548	TGCTCAGTTAGGTTAGTG	2781
1263417	479996	480013	GAGCTATCTGTACAAAAT	2782
1263418	479997	480014	TGAGCTATCTGTACAAAA	2783
1263419	479998	480015	GTGAGCTATCTGTACAAA	2784
1263420	479999	480016	CGTGAGCTATCTGTACAA	2785
1263543	483971	483988	CATACCCAGGGTAGGATT	2763
1263546	483972	483989	GCATACCCAGGGTAGGAT	2764
1263549	483973	483990	TGCATACCCAGGGTAGGA	2765
1263552	483974	483991	GTGCATACCCAGGGTAGG	2766
1263557	483975	483992	TGTGCATACCCAGGGTAG	2767
1273037	457737	457754	GCCAGGTGTCTTATATCT	2864

1273038	478535	478552	CGCAATGTATCAGGCAAC	2865
1273039	478536	478553	ACGCAATGTATCAGGCAA	2866
1273040	478732	478749	GATCACATTACCCATCCG	2867
1273041	478733	478750	TGATCACATTACCCATCC	2868
1273042	478735	478752	GCTGATCACATTACCCAT	2869
1273043	457738	457755	AGCCAGGTGTCTTATATC	2870
1273060	474393	474410	TCAACCAATTTGCTATTC	2871

The compounds in Table 66 are 5-8-5 MOE gapmers. The gapmers are 18 nucleosides in length, wherein the central gap segment consists of eight 2'-β-D-deoxynucleosides and the 5' and 3' wing segments each consists of five 2'-MOE nucleosides. The sugar motif of the gapmers is (from 5' to 3'): eeeeeddddddddeeeee; wherein 'd' represents a 2'-β-D-deoxyriboxyl sugar moiety, and 'e' represents a 2'-MOE sugar moiety. The gapmers have an internucleoside linkage motif of (from 5' to 3'): sooosssssssssooss; wherein "s" represents a phosphorothioate internucleoside linkage and "o" represents a phosphodiester internucleoside linkage. All cytosine residues are 5-methylcytosines.

Table 66

5-8-5 MOE gapmers with a mixed PO/PS internucleoside linkages complementary to human UBE3A-ATS

Compound ID	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQUENCE	SEQ ID NO
1263421	465237	465254	TCATCTCGGGTATATAAA	2768
1263422	465238	465255	GTCATCTCGGGTATATAA	2769
1263423	465239	465256	GGTCATCTCGGGTATATA	2770
1263424	465240	465257	TGGTCATCTCGGGTATAT	2771
1263425	465241	465258	TTGGTCATCTCGGGTATA	2772
1263426	468987	469004	TCACCATTTTGACCTTCT	2773
1263427	464527	464544	CAGTTAGGTTAGTGCACA	2777
1263428	464528	464545	TCAGTTAGGTTAGTGCAC	2778
1263429	464529	464546	CTCAGTTAGGTTAGTGCA	2779
1263430	464530	464547	GCTCAGTTAGGTTAGTGC	2780
1263431	464531	464548	TGCTCAGTTAGGTTAGTG	2781
1263432	479996	480013	GAGCTATCTGTACAAAAT	2782
1263433	479997	480014	TGAGCTATCTGTACAAAA	2783
1263434	479998	480015	GTGAGCTATCTGTACAAA	2784
1263435	479999	480016	CGTGAGCTATCTGTACAA	2785
1263544	483971	483988	CATACCCAGGGTAGGATT	2763
1263547	483972	483989	GCATACCCAGGGTAGGAT	2764
1263550	483973	483990	TGCATACCCAGGGTAGGA	2765
1263553	483974	483991	GTGCATACCCAGGGTAGG	2766

1263554	483975	483992	TGTGCATACCCAGGGTAG	2767
1273052	457737	457754	GCCAGGTGTCTTATATCT	2864
1273053	457738	457755	AGCCAGGTGTCTTATATC	2870
1273054	474393	474410	TCAACCAATTTGCTATTC	2871
1273055	478535	478552	CGCAATGTATCAGGCAAC	2865
1273056	478536	478553	ACGCAATGTATCAGGCAA	2866
1273057	478732	478749	GATCACATTACCCATCCG	2867
1273058	478733	478750	TGATCACATTACCCATCC	2868
1273059	478735	478752	GCTGATCACATTACCCAT	2869

The compounds in Table 67 are 6-8-4 MOE gapmers. The gapmers are 18 nucleosides in length, wherein the central gap segment consists of eight 2'-β-D-deoxynucleosides, the 5' wing segment consists of six 2'-MOE nucleosides, and the 3' wing segment consists of four 2'-MOE nucleosides. The sugar motif of the gapmers is (from 5' to 3'): eeeeeddddddddeeee; wherein 'd' represents a 2'-β-D-deoxyriboxyl sugar moiety, and 'e' represents a 2'-MOE sugar moiety. The gapmers have an internucleoside linkage motif of (from 5' to 3'): soooosssssssssoss; wherein "s" represents a phosphorothioate internucleoside linkage and "o" represents a phosphodiester internucleoside linkage. All cytosine residues are 5-methylcytosines.

Table 67

6-8-4 MOE gapmers with a mixed PO/PS internucleoside linkages complementary to human UBE3A-ATS

Compound ID	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQUENCE	SEQ ID NO
1263436	465237	465254	TCATCTCGGGTATATAAA	2768
1263437	465238	465255	GTCATCTCGGGTATATAA	2769
1263438	465239	465256	GGTCATCTCGGGTATATA	2770
1263439	465240	465257	TGGTCATCTCGGGTATAT	2771
1263440	465241	465258	TTGGTCATCTCGGGTATA	2772
1263441	468987	469004	TCACCATTTTGACCTTCT	2773
1263442	464527	464544	CAGTTAGGTTAGTGCACA	2777
1263443	464528	464545	TCAGTTAGGTTAGTGCAC	2778
1263444	464529	464546	CTCAGTTAGGTTAGTGCA	2779
1263445	464530	464547	GCTCAGTTAGGTTAGTGC	2780
1263446	464531	464548	TGCTCAGTTAGGTTAGTG	2781
1263447	479996	480013	GAGCTATCTGTACAAAAT	2782
1263448	479997	480014	TGAGCTATCTGTACAAAA	2783
1263449	479998	480015	GTGAGCTATCTGTACAAA	2784
1263450	479999	480016	CGTGAGCTATCTGTACAA	2785
1263545	483971	483988	CATACCCAGGGTAGGATT	2763
1263548	483972	483989	GCATACCCAGGGTAGGAT	2764

1263551	483973	483990	TGCATACCCAGGGTAGGA	2765
1263555	483974	483991	GTGCATACCCAGGGTAGG	2766
1263556	483975	483992	TGTGCATACCCAGGGTAG	2767
1273044	457737	457754	GCCAGGTGTCTTATATCT	2864
1273045	457738	457755	AGCCAGGTGTCTTATATC	2870
1273046	474393	474410	TCAACCAATTTGCTATTC	2871
1273047	478535	478552	CGCAATGTATCAGGCAAC	2865
1273048	478536	478553	ACGCAATGTATCAGGCAA	2866
1273049	478732	478749	GATCACATTACCCATCCG	2867
1273050	478733	478750	TGATCACATTACCCATCC	2868
1273051	478735	478752	GCTGATCACATTACCCAT	2869

Example 8: Effect of modified oligonucleotides on human UBE3A-ATS RNA *in vitro*, multiple doses

Modified oligonucleotides selected from the examples above were tested at various doses in human IPS derived iCell GABANeurons (Cellular Dynamics), as described in Example 4. Reduction of UBE3A-ATS RNA is presented in the tables below as percent UBE3A-ATS RNA amount relative to untreated control (UTC) cells. Where possible, the half maximal inhibitory concentration (IC_{50}) of each modified oligonucleotide was calculated using a linear regression on a log/linear plot of the data in excel. In some cases, an IC_{50} could not be reliably calculated and the data point is marked as "N.C.". Values marked with "N.D." indicate that a value was not determined in this experiment.

Table 68

Dose-dependent percent reduction of human UBE3A-ATS RNA *in vitro* (40,000 cells/well)

Compound Number	UBE3A-ATS expression (% UTC)					IC_{50} (µM)
	250 nM	740.7 nM	2,222 nM	6,666 nM	20,000 nM	
750519	69	53	23	N.D.	N.D.	0.7
617557	66	54	34	25	N.D.	0.9
749860	62	48	39	20	13	0.7
1065593	44	32	21	11	9	N.C.
1263517	55	47	35	17	18	0.4
1263519	52	39	25	17	16	0.2
1263533	51	34	29	28	23	0.1
1263540	39	29	29	29	24	N.C.
1272994	51	39	28	14	10	0.2
1272996	62	45	38	20	13	0.6
1272997	73	53	39	24	18	1.1
1272998	67	53	30	19	13	0.8
1273030	68	54	33	30	22	1.0
1273033	51	50	31	32	20	0.4
1273049	57	41	32	24	21	0.3

Table 69

Dose-dependent percent reduction of human UBE3A-ATS RNA *in vitro* (40,000 cells/well)

Compound Number	UBE3A-ATS expression (% UTC)					IC_{50} (μM)
	250 nM	740.7 nM	2,222 nM	6,666 nM	20,000 nM	
750519	79	66	29	15	N.D.	1.1
1263426	64	48	34	29	25	0.7
1273042	92	72	58	43	40	5.5
1273051	70	47	34	29	22	0.9
1273055	71	58	47	40	27	1.9
1273057	73	71	50	37	39	3.4
1273058	80	69	58	48	34	4.8
1273087	55	34	26	14	20	0.2
1273107	63	59	36	26	26	1.0
1273113	75	68	58	47	28	3.6

Table 70

Dose-dependent percent reduction of human UBE3A-ATS RNA *in vitro* (40,000 cells/well)

Compound Number	UBE3A-ATS expression (% UTC)					IC_{50} (μM)
	250 nM	740.7 nM	2,222 nM	6,666 nM	20,000 nM	
750519	56	38	22	10	25	0.2
749860	68	47	37	19	16	0.8
1065645	66	45	31	19	12	0.6
1263461	70	66	55	32	27	2.3
1263486	74	48	44	25	21	1.2

Table 71

Dose-dependent percent reduction of human UBE3A-ATS RNA *in vitro* (40,000 cells/well)

Compound Number	UBE3A-ATS expression (% UTC)					IC_{50} (μM)
	250 nM	740.7 nM	2,222 nM	6,666 nM	20,000 nM	
750519	63	39	19	9	4	0.4
1263517	56	40	27	17	11	0.3
1263518	72	65	42	28	20	1.6
1263532	57	44	38	33	64	0.5
1263533	41	56	37	ND	26	NC

Table 72

Dose-dependent percent reduction of human UBE3A-ATS RNA *in vitro* (40,000 cells/well)

Compound Number	UBE3A-ATS expression (% UTC)					IC_{50} (μM)
	250 nM	740.7 nM	2,222 nM	6,666 nM	20,000 nM	
617557	59	56	37	23	23	0.8

1263537	70	86	82	77	59	N.C.
1272944	51	39	23	13	8	0.2
1273033	55	40	32	21	15	0.3
1273039	68	58	37	28	20	1.1

Table 73

Dose-dependent percent reduction of human UBE3A-ATS RNA *in vitro* (40,000 cells/well)

Compound Number	UBE3A-ATS expression (% UTC)					IC_{50} (µM)
	250 nM	740.7 nM	2,222 nM	6,666 nM	20,000 nM	
617557	70	57	38	N.D.	N.D.	1.0
1273050	81	75	76	62	41	16.5
1273055	59	48	40	26	18	0.6
1273062	54	37	28	18	13	0.2
1273090	76	64	71	56	55	N.C.
1273091	75	79	56	44	32	4.3

Example 9: Effect of modified oligonucleotides on human UBE3A-ATS RNA and UBE3A RNA *in vitro*, multiple doses

Modified oligonucleotides selected from the examples above were tested at various doses in 10-week differentiated human neuronal cells derived from Angelman Syndrome patient derived IPS cells as described in Example 6 above. Reduction of UBE3A-ATS RNA or induction of UBE3A RNA is presented in the tables below as percent UBE3A-ATS RNA amount or percent UBE3A RNA relative to untreated control (UTC) cells. Values marked with "N.D." indicate that a value was not determined in this experiment.

Several modified oligonucleotides were found to reduce UBE3A-ATS RNA accompanied by concurrent increase in UBE3A RNA in Angelman's patient IPS cell derived neurons.

Table 74

Reduction of UBE3A-ATS RNA and increase of UBE3A RNA in Angelman Syndrome IPS cell derived neurons

Compound ID	UBE3A-ATS RNA (% UTC) (RTS4796)					UBE3A RNA (% UTC) (RTS35984)				
	250nM	741nM	2222nM	6667nM	20000nM	250nM	741nM	2222nM	6667nM	20000nM
750519	51	20	11	7	5	297	224	235	250	205
749860	47	21	18	15	8	148	119	245	307	324
1065645	41	15	13	11	13	213	185	298	315	353
1263461	49	42	34	25	16	141	185	248	235	221
1263486	64	47	33	29	16	136	174	215	323	264

Table 75

Reduction of UBE3A-ATS RNA and increase of UBE3A RNA in Angelman Syndrome IPS cell derived neurons

Compound ID	UBE3A-ATS RNA (% UTC) (RTS4796)					UBE3A RNA (% UTC) (RTS35984)				
	250nM	741nM	2222nM	6667nM	20000nM	250nM	741nM	2222nM	6667nM	20000nM
750519	46	22	13	7	7	259	274	520	482	272
1263517	37	29	16	12	12	230	261	462	521	283
1263518	66	39	29	21	18	187	183	269	496	277
1263532	39	26	21	17	24	192	162	393	390	357
1263533	34	25	24	18	29	296	367	389	371	548

Table 76

Reduction of UBE3A-ATS RNA and increase of UBE3A RNA in Angelman Syndrome IPS cell derived neurons

Compound ID	UBE3A-ATS RNA (% UTC) (RTS4796)					UBE3A RNA (% UTC) (RTS35984)				
	250nM	741nM	2222nM	6667nM	20000nM	250nM	741nM	2222nM	6667nM	20000nM
617557	68	44	28	24	20	120	210	319	453	396
1263537	29	26	21	26	16	139	203	414	440	480
1272944	35	25	13	11	7	148	235	469	702	677
1273033	38	21	21	16	18	119	244	487	422	514
1273039	64	41	29	20	17	183	237	395	376	418

Table 77

Reduction of UBE3A-ATS RNA and increase of UBE3A RNA in Angelman Syndrome IPS cell derived neurons

Compound ID	UBE3A-ATS RNA (% UTC) (RTS4796)					UBE3A RNA (% UTC) (RTS35984)				
	250nM	741nM	2222nM	6667nM	20000nM	250nM	741nM	2222nM	6667nM	20000nM
617557	63	50	33	28	27	126	230	347	335	368
1273050	64	48	59	41	28	165	152	240	457	483
1273055	44	31	38	22	17	541	664	1014	1094	887
1273062	34	54	51	47	27	253	296	421	705	997
1273090	70	54	30	39	23	155	165	259	487	692
1273091	91	86	54	37	31	96	121	135	156	284

Example 10: Tolerability of modified oligonucleotides complementary to human UBE3A-ATS in wild-type mice. 3 hour study

Modified oligonucleotides described above were tested in wild-type female C57/Bl6 mice to assess the tolerability of the oligonucleotides. Wild-type female C57/Bl6 mice each received a single ICV dose of 700 µg of modified oligonucleotide listed in the table below. Each treatment group consisted of 4 mice. A group of 4 mice received PBS as a negative control for each experiment (identified in separate tables below). At 3 hours post-injection, mice were evaluated according to seven 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 (the functional observational battery score or FOB). After all 7 criteria were evaluated, the scores were summed for each mouse and averaged within each treatment group. The results are presented in the tables below.

Table 78

Tolerability scores in mice at 700 µg dose

Compound Number	3 hr FOB
PBS	0.0
749860	0.0
749865	4.0
749984	4.8
750006	3.5
750009	3.8
750540	3.5
750544	2.8
750567	5.0

Table 79

Tolerability scores in mice at 700 µg dose

Compound Number	3 hr FOB
PBS	0
1065272	5.0
1065295	2.0
1065296	5.5
1065324	2.8
1065330	6.8
1065369	6.8
1065438	5.8
1065465	5.0
1065513	5.8

1065576	7.0
1065578	3.2
1065579	3.8
1065582	4.2
1065586	3.0
1065590	6.0
1065591	4.0
1065593	1.0
1065595	4.8
1065597	4.5
1065599	6.0
1065600	4.2
1065605	3.8
1065607	5.2
1065608	3.0

Table 80

Tolerability scores in mice at 700 µg dose

Compound Number	3 hr FOB
PBS	0.0
1065609	0.0
1065613	0.0
1065616	5.5
1065619	5.0
1065621	2.0
1065623	3.5
1065624	3.5
1065631	1.0
1065635	1.0
1065641	1.5
1065642	4.0
1065644	6.8
1065645	3.0
1065646	2.0
1065651	4.0
1065654	7.0
1065667	4.0
1065669	1.0
1065671	4.0
1065672	6.8
1065674	4.0
1065676	2.0
1065678	5.0

1065680	1.0

Table 81

Tolerability scores in mice at 700 µg dose

Compound Number	3 hr FOB
PBS	0
1065685	5.0
1065686	4.8
1065690	3.8
1065696	6.2
1065708	5.5
1065709	4.2
1065710	2.8
1065712	6.8
1065713	5.0
1065719	4.0
1065728	1.0
1065735	3.5
1065750	6.2
1065754	3.2
1065765	4.2
1065766	5.2
1065768	5.5
1065785	3.8
1065795	1.0
1065799	1.0
1065810	2.2
1065812	3.8
1065813	5.0
1065817	5.0

Table 82

Tolerability scores in mice at 700 µg dose

Compound Number	3 hr FOB
PBS	0.0
1065821	6.5
1065823	4.0
1065826	3.0
1065829	4.8
1065840	4.5

1065856	6.2
1065857	6.0
1065858	4.0
1065859	0.0
1065863	4.8
1065868	3.2
1065889	1.0
1065894	3.8
1065899	4.5
1065901	4.0
1065902	4.0
1065903	5.5
1065914	5.0
1065920	2.0
1065932	4.5
1065937	1.0
1065947	1.2
1065953	6.5
1065954	5.5

Table 83

Tolerability scores in mice at 700 µg dose

Compound Number	3 hr FOB
PBS	0.0
1065955	5.0
1065977	6.2
1066009	2.0
1066037	4.2
1066046	1.0
1066072	4.0
1066076	5.0
1066089	1.0
1066092	1.0
1066097	1.2
1066119	11.0
1066217	6.0
1066221	3.8
1066249	4.5
1066253	6.0
1066311	2.0
1066350	4.0
1066375	1.0

1066377	6.2
1066378	5.2
1066396	6.0
1066420	4.0
1066423	2.8
1066429	5.8

Table 84

Tolerability scores in mice at 700 µg dose

Compound Number	3 hr FOB
PBS	0.0
749931	0.0
749933	4.0
749937	0.5
749944	3.8
749956	1.8
749964	2.0
749969	5.2
749991	2.2
750028	4.2
750030	3.2
750032	2.2
750040	4.2
750051	2.5
750092	0.8
750100	2.5
750131	0.5
750139	3.0
750140	1.2
750196	4.0
750210	3.5
750214	3.25
750228	0.0
750270	1.0
750292	0.0
750312	4.8
750325	1.0
750326	0.0
750329	5.5
750344	6.2
750350	2.8

750359	0.0
750360	3.2
750365	5.2
750366	0.0
750386	0.0
750413	0.0
750416	7.0
750418	1.8
750430	6.2
750431	5.0
750439	5.5
750452	2.5
750517	3.0
750519	1.0
750542	3.5
750549	0.0

Table 85

Tolerability scores in mice at 700 µg dose

Compound Number	3 hr FOB
PBS	0.0
617456	4.8
617459	7.0
617470	6.5
617473	6.8
617536	6.5
617547	6.8
617557	5.2
617593	6.5
749794	5.0
749796	4.5
749816	5.8
749861	3.0
749863	5.5
749869	3.8
749882	6.8
749885	0.5
749893	1.2
749894	0.0
749907	5.0
749921	6.0

Table 86

Tolerability scores in mice at 700 µg dose

Compound Number	3 hr FOB
PBS	0.0
1065473	3.2
1065561	6.0
1065592	4.0
1065625	7.0
1065791	1.0
1065924	1.0
1066003	4.0

Table 87

Tolerability scores in mice at 700 µg dose

Compound ID	3 hr FOB
PBS	0.0
1263471	6.2
1263472	3.2
1263473	1.0
1263474	0.0
1263475	0.0
1263476	1.0
1263477	0.0
1263478	1.0
1263479	4.0
1263480	4.0
1263481	5.5
1263482	4.0
1263483	4.0
1263484	4.0
1263485	4.0
1263486	2.0
1263487	1.0
1263488	1.0
1263489	0.0
1263490	0.0
1263491	0.0

1263492	1.0
1263494	4.0
1263495	4.0
1263496	4.0
1263497	4.0
1263498	4.0
1263499	4.0
1263500	4.7
1263501	5.5
1263502	4.0
1263503	4.0
1263504	1.0
1263505	0.0
1263506	0.0
1263507	0.0
1263508	0.0
1263509	0.0
1263510	2.0

Table 88

Tolerability scores in mice at 700 µg dose

Compound ID	3 hr FOB
PBS	0.0
1165878	4.0
1263511	4.0
1263512	6.0
1263513	6.0
1263514	6.5
1263515	4.0
1263516	4.0
1263517	1.0
1263518	0.0
1263519	1.0
1263520	1.0
1263521	0.0
1263522	0.0
1263523	1.0
1263524	5.2

1263525	4.8
1263526	4.0
1263527	4.0
1263528	4.0
1263529	3.0
1263530	4.0
1263531	5.2
1263532	1.0
1263533	1.0
1263534	1.0
1263535	4.0
1263536	2.0
1263537	1.0
1263538	3.0
1263539	1.0
1263540	0.0

Table 89

Tolerability scores in mice at 700 µg dose

Compound ID	3 hr FOB
PBS	0.0
1263541	1.8
1263542	3.5
1263543	1.0
1263544	1.0
1263545	2.0
1263546	0.0
1263547	1.0
1263548	1.0
1263549	0.0
1263550	1.0
1263551	2.0
1263552	1.0
1263553	5.5
1263554	1.0
1263555	4.0
1263556	1.0
1263557	1.0

Table 90

Tolerability scores in mice at 700 µg dose

Compound ID	3 hr FOB
PBS	0.0
1263403	5.3
1263404	4.3
1263405	6.3
1263406	4.7
1263407	2.3
1263408	0.3
1263409	0.0
1263410	0.0
1263411	0.0
1263412	2.0
1263413	2.3
1263414	5.3
1263415	4.0
1263416	7.0
1263417	3.3
1263418	3.0
1263419	1.7
1263420	1.0
1263421	3.0
1263422	4.3
1263423	6.0
1263424	6.3
1263425	5.0

Table 91

Tolerability scores in mice at 700 µg dose

Compound ID	3 hr FOB
PBS	0.0
749952	6.0
749953	3.3
1165583	5.7

1165584	3.3
1263426	2.0
1263427	4.0
1263428	4.3
1263429	1.3
1263430	2.3
1263431	6.3
1263432	6.0
1263433	4.7
1263434	1.0
1263435	1.3
1263436	2.3
1263437	4.7
1263438	6.0
1263439	4.7
1263440	6.7
1263441	0.3
1263442	3.7
1263443	3.0
1263444	6.3
1263445	5.0
1263446	5.7
1263447	4.7
1263448	5.0
1263449	4.7
1263450	2.0
1263451	1.3
1263452	0
1263453	0

Table 92

Tolerability scores in mice at 700 µg dose

Compound ID	3 hr FOB
PBS	0
1065786	2.0
1165526	0.7
1165577	3.7
1263454	0.0

1263455	0.0
1263456	3.3
1263457	5.3
1263458	1.3
1263459	1.0
1263460	1.0
1263461	1.0
1263462	1.0
1263463	1.0
1263464	1.3
1263465	1.7
1263466	5.0
1263467	6.0
1263468	4.3
1263469	7.0
1263470	6.7
1272943	2.0
1272944	2.3
1272945	2.7
1272946	0.0
1272947	0.0
1272948	3.3
1272949	4.0
1272950	3.7
1272951	0.7
1272952	2.0
1272953	0.3
1272954	1.0

Table 93

Tolerability scores in mice at 700 µg dose

Compound ID	**3 hr FOB**
PBS	0.0
1272955	3.7
1272956	5.3

1272957	4.0
1272958	5.0
1272959	3.3
1272960	1.0
1272961	4.7
1272962	2.0
1272963	4.0
1272964	2.3
1272965	1.0
1272966	2.3
1272967	1.0
1272968	1.0
1272969	0.0
1272970	0.0
1272971	0.0
1272972	0.0
1272973	4.0
1272974	1.0
1272975	1.0
1272976	2.0
1272977	1.0
1272978	2.3
1272979	1.0

Table 94

Tolerability scores in mice at 700 µg dose

Compound ID	3 hr FOB
PBS	0.0
1272980	3.3
1272981	3.3
1272982	1.0
1272983	1.0
1272984	4.0
1272985	1.0
1272986	4.7
1272987	1.0
1272988	1.0
1272989	1.0

1272990	4.0
1272991	4.0
1272992	0.0
1272993	0.0
1272994	1.0
1272995	1.0
1272996	0.7
1272997	1.0
1272998	0.0
1272999	5.0
1273000	0.0
1273001	3.0
1273002	3.7
1273003	2.7
1273004	3.0
1273005	4.0
1273006	3.3
1273007	3.0
1273008	3.3
1273009	1.0
1273010	4.7
1273011	1.0

Table 95

Tolerability scores in mice at 700 µg dose

Compound ID	**3 hr FOB**
PBS	0.0
699781	0.0
1065707	2.0
1065711	4.0
1065921	5.7
1165585	3.7
1165621	1.0
1273012	0.0
1273013	4.0
1273014	2.0
1273015	2.0
1273016	0.0

1273017	1.0
1273018	0.0
1273019	0.0
1273020	0.0
1273021	0.0
1273022	0.0
1273023	0.0
1273024	0.0
1273025	5.0
1273026	5.3
1273027	5.0
1273028	0.0
1273029	4.7
1273030	3.0
1273031	0.0
1273032	0.0
1273033	0.0

Table 96

Tolerability scores in mice at 700 µg dose

Compound ID	**3 hr FOB**
PBS	0.0
1273034	0.0
1273035	1.0
1273036	1.0
1273037	1.0
1273038	1.0
1273039	1.0
1273040	0.0
1273041	0.0
1273042	0.0
1273043	6.0
1273044	0.0
1273045	0.0
1273046	3.0
1273047	3.0

1273048	0.0
1273049	0.0
1273050	0.0
1273051	0.0
1273052	0.0
1273053	6.0
1273054	3.0
1273055	2.0
1273056	2.3
1273057	2.0
1273058	1.0
1273059	1.0
1273060	0.7
1273061	1.0
1273062	0.0
1273063	0.0
1273064	0.0
1273065	0.0
1273066	0.0
1273067	1.0
1273068	6.0
1273069	6.0
1273070	1.0
1273071	0.0
1273072	0.0
1273073	4.0
1273084	0.0
1273085	3.0
1273086	2.0
1273087	1.0
1273088	0.0
1273089	5.3
1273090	0.0
1273091	0.0
1273092	0.0
1273093	1.0

1273094	6.0
1273095	4.3
1273096	4.7
1273097	5.0
1273098	1.0
1273099	1.0
1273101	0.7
1273102	1.0
1273103	0.0
1273104	0.0
1273105	0.0
1273106	0.0
1273107	0.0
1273108	0.0
1273109	1.0
1273110	0.0
1273111	0.0
1273112	2.3
1273113	0.0
1273114	0.0
1273115	2.3

Table 97

Tolerability scores in mice at 700 µg dose

Compound ID	3 hr FOB
PBS	0.0
1165523	2.0
1165533	2.3
1165538	3.0
1165550	1.3
1165563	1.3
1165586	2.3
1165596	2.3
1165608	4.0
1165616	3.0
1165694	3.3

1165737	3.7
1165827	3.3
1165855	3.0
1165897	0.3
1179808	2.3
1179839	6.7
1179841	2.0
1179843	2.0
1273100	7.0

Table 98

Tolerability scores in mice at 700 µg dose

Compound Number	3 hr FOB
PBS	0.0
1165521	3.3
1165524	4.7
1165536	4.0
1165545	6.0
1165552	5.7
1165553	6.0
1165554	7.0
1165555	6.0
1165562	5.7
1165588	4.7
1165590	5.7
1165611	6.0

Example 11: Tolerability of modified oligonucleotides complementary to human UBE3A-ATS in rats, 3 hour study

Modified oligonucleotides described above were tested in rats to assess the tolerability of the oligonucleotides. Sprague Dawley rats each received a single intrathecal (IT) dose of 3 mg of oligonucleotide listed in the table below. Each treatment group consisted of 4 rats. A group of four rats received PBS as a negative control. At 3 hours post-injection, movement in 7 different parts of the body were evaluated for each rat. The 7 body parts are (1) the rat's tail; (2) the rat's posterior posture; (3) the rat's hind limbs; (4) the rat's hind paws; (5) the rat's forepaws; (6) the rat's anterior posture; (7) the rat's head. For each of the 7 different body parts, each rat was given a sub-score of 0 if the body part was moving or 1 if the body part was paralyzed (the functional observational battery score or FOB). After each of the 7 body parts were evaluated, the sub-scores were summed for each rat and then averaged for each group. For example, if a rat's tail, head, and all other evaluated body parts were moving 3 hours after the 3 mg IT dose, it would get

a summed score of 0. If another rat was not moving its tail 3 hours after the 3 mg IT dose but all other evaluated body parts were moving, it would receive a score of 1. Results are presented as the average score for each treatment group.

Table 99

Tolerability scores in rats at 3 mg dose

Compound No.	FOB 3hr
PBS	0.0
749860	0.0
749861	4.0
749869	4.8
749885	0.8
749893	0.5
749931	0.5
750006	4.5

Table 100

Tolerability scores in rats at 3 mg dose

Compound No.	FOB 3hr
PBS	0.0
750030	4.0
750051	4.0
750092	2.5
750100	4.0
750139	5.3
750140	3.5
750270	3.0
750292	0.0
750325	1.8
750386	0.8

Table 101

Tolerability scores in rats at 3 mg dose

Compound No.	FOB 3hr
PBS	0.0
1065578	4.0
1065586	3.0
1065609	2.0
1065613	3.8
1065635	1.8
1065641	3.3
1065645	3.0

1065646	2.5

Table 102

Tolerability scores in rats at 3 mg dose

Compound No.	FOB 3hr
PBS	0.0
750413	0.3
1065669	2.8
1065680	4.0
1065710	5.5
1065754	5.3
1065785	6.0
1065795	3.3
1065799	2.0
1065812	4.0
1065826	2.0

Table 103

Tolerability scores in rats at 3 mg dose

Compound No.	FOB 3hr
PBS	0.0
1065920	3.5
1065937	3.8
1066092	3.3
1066221	4.0
1066350	2.3

Table 104

Tolerability scores in rats at 3 mg dose

Compound No.	FOB 3hr
PBS	0.3
1263408	2.0
1263409	2.5
1263410	2.5
1263411	1.3
1263412	3.0
1263419	1.8
1263420	1.8
1263429	2.5
1263434	2.0

Table 105

Tolerability scores in rats at 3 mg dose

Compound No.	FOB 3hr
PBS	0.3
1263435	3.0
1263441	2.3*
1263450	2.0
1263451	4.0
1263452	2.0
1263453	1.8
1263454	1.5
1263455	3.3
1263458	0.3

*One of the four rats in this group died during surgery, and so is excluded from this value.

Table 106

Tolerability scores in rats at 3 mg dose

Compound No.	FOB 3hr
PBS	0.5
1263476	0.3
1263478	1.0
1263488	3.0
1263489	2.3
1263507	2.0
1263517	1.3
1263518	1.8
1263519	1.0
1263521	2.0
1263533	1.3

Table 107

Tolerability scores in rats at 3 mg dose

Compound No.	FOB 3hr
PBS	0.0
1165563	3.0
1179841	3.0
1179843	3.3
1263407	3.8
1263413	4.0
1263430	4.3
1263436	2.8

1263540	2.5
1272944	2.0
1272994	1.0
1272996	1.0

Table 108

Tolerability scores in rats at 3 mg dose

Compound No.	FOB 3hr
PBS	0.0
1272998	0.3
1273034	0.0
1273035	0.8
1273036	0.0
1273049	0.3
1273051	0.0.
1273055	2.0
1273056	3.7
1273057	1.0
1273058	0.8
1273062	2.5
1273065	2.3
1273087	2.0
1273099	2.5
1273102	4.5
1273106	2.0
1273107	2.0
1273108	2.0
1273113	1.0
1273115	3.3
1165523	5.0
1165550	3.0

Table 109

Tolerability scores in rats at 3 mg dose

Compound No.	FOB 3hr
PBS	0.0
1263426	2.3
1263462	2.8
1272974	3.8
1272997	0.8
1273020	0.5
1273033	1.8
1273038	3.0

1273039	3.3
1273042	2.0
1273048	3.0
1273104	3.0
1273105	3.0
1273109	3.8
1273110	1.0
1273111	2.7
1065593	1.5
1263547	4.0
1165586	0.0
1263537	1.5

Table 110

Tolerability scores in rats at 3 mg dose

Compound No.	FOB 3hr
PBS	0.0
749953	4.5
1065711	3.5
1263417	6.3
1263418	3.3
1263421	5.8
1263443	5.0
1263456	5.0
1263529	2.5
1263538	4.7
1273030	0.0
1273047	4.0
1273085	4.0

Table 111

Tolerability scores in rats at 3 mg dose

Compound No.	FOB 3hr
PBS	0.0
749991	1.3
1263460	3.0
1263461	2.0
1263486	3.0
1263532	1.5
1263551	4.0
1273050	1.0
1273090	1.0
1273091	2.0

1273101	3.5
1263522	1.7

Example 12: Tolerability of modified oligonucleotides complementary to human UBE3A-ATS in wild-type mice, two week study

Modified oligonucleotides described above were tested in wild-type female C57/Bl6 mice to assess the tolerability of the oligonucleotides. Wild-type female C57/Bl6 mice each received a single ICV dose of 700 µg of modified oligonucleotide listed in the table below. Each treatment group consisted of 4 mice. A group of 4 mice received PBS as a negative control for each experiment (identified in separate tables below). At 2 weeks post-injection, mice were evaluated according to seven 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 (the functional observational battery score or FOB). After all 7 criteria were evaluated, the scores were summed for each mouse and averaged within each treatment group. The results are presented in the table below.

Table 112

Tolerability scores in mice at 700 µg dose

Compound Number	2-week FOB
PBS	0.0
1065645	0.0
1263517	0.0
1263518	0.0
1263533	0.0
1273039	0.0
1273062	0.0

Example 13: Activity of modified oligonucleotides complementary to human UBE3A-ATS in transgenic mice

Modified oligonucleotides described above were tested in a UBE3A-ATS BAC transgenic mouse model. The transgenic mouse model was developed at the University of Michigan Bacterial Artificial Chromosome Recombineering Core and contains region 25163935-25348867 from human chromosome 15 (GRCh38/hg38 assembly) (from BAC clone RP11-664B13). UBE3A-ATS expression is driven by the ENO2 promoter and terminated with the BGH poly(A) signal. The gene fragment was introduced into fertilized eggs from C57BL/6 mice by pronuclear injection to produce line RP11-748 that is used in the experiments described below.

Treatment

The UBE3A-ATS transgenic mice were divided into groups of 2-4 mice each. Each mouse received a single ICV bolus of 350 µg of modified oligonucleotide. A group of 4 mice received PBS as a negative control.

RNA analysis

After two weeks, mice were sacrificed and RNA was extracted from cortical brain tissue, hippocampal brain tissue, and spinal cord for real-time PCR analysis of measurement of RNA expression of UBE3A-ATS using primer probe set RTS4796 (described herein above) and/or primer probe set RTS40595 (forward sequence TCCTTCCCTACCTTAGTCTTGA, designated herein as SEQ ID NO: 14; reverse sequence CCCTCTTGAACCAGGAAACA, designated herein as SEQ ID NO: 15; probe sequence AGATGGCAGCCCACATTTCTACTGT, designated herein as SEQ ID NO: 16). Primer probe set RTS4796 is less reliable when the oligonucleotide binds at a site far from the primer probe binding site. Results are presented as percent change of RNA, relative to PBS control, normalized to mouse GAPDH. Mouse GAPDH was amplified using primer probe set RTS108 (forward sequence GGCAAATTCAACGGCACAGT, designated herein as SEQ ID NO: 11; reverse sequence GGGTCTCGCTCCTGGAAGAT, designated herein as SEQ ID NO: 12; probe sequence AAGGCCGAGAATGGGAAGCTTGTCATC, designated herein as SEQ ID NO: 13). In some cases, RTPCR value is not defined for a certain sample, and is labeled N.D. (Not Defined).

As shown in the table below, treatment with modified oligonucleotides resulted in reduction of UBE3A-ATS RNA in comparison to the PBS control.

Table 113

Reduction of human UBE3A-ATS RNA in transgenic mice

Compound ID	UBE3A-ATS RNA (%control) RTS4796			UBE3A-ATS RNA (%control) RTS40595		
	SPINAL CORD	HIPPOCAMPUS	CORTEX	SPINAL CORD	HIPPOCAMPUS	CORTEX
PBS	100	100	100	100	100	100
749860	14	N.D.	26	12	24	23
749861	27	N.D.	51	26	48	49
749863	39	N.D.	57	36	45	54
749865	61	N.D.	92	66	97	85
749869	31	37	51	29	38	47
749882	31	28	35	30	30	32
749885	59	65	85	61	68	83
749893	28	35	44	27	35	40
749894	5	7	9	3	6	7
749907	53	48	70	51	47	63
749931	35	24	33	15	22	28
749969	17	14	14	11	13	10
749991	27	26	38	22	24	31
750006	24	21	24	19	19	18
750028	26	22	34	17	19	26
750030	40	30	44	32	26	34
750032	17	9	12	10	6	6
750040	55	42	65	50	44	59
750051	35	27	35	27	26	29

750092	55	43	63	47	40	53
750139	24	22	30	17	20	23
750140	22	16	22	15	13	15
750214	48	46	60	45	41	55
750292	27	35	40	21	31	34
750312	59	48	47	53	43	42
750359	30	23	25	25	19	20
750360	44	40	54	39	37	47
750365	58	69	88	56	65	82
750386	34	24	27	26	19	19
750413	45	37	38	36	34	30
750430	48	42	41	41	42	33
750439	53	46	52	34	44	46
1065296	34	34	39	31	34	34
1065578	35	42	49	34	42	42
1065579	19	18	19	17	18	14
1065586	45	55	74	43	55	68
1065590	43	53	67	42	51	63
1065591	21	24	29	19	21	25
1065595	25	34	49	13	30	41
1065599	19	22	27	18	22	24
1065600	31	35	42	32	35	39
1065605	44	64	67	44	62	63
1065607	28	36	39	29	33	34
1065608	18	42	53	18	38	49
1065623	16	28	34	15	29	30
1065635	32	39	41	30	38	36
1065641	32	55	50	30	49	44
1065642	43	58	65	42	52	59
1065645	18	30	24	15	24	18
1065646	39	60	50	39	54	45
1065651	29	47	38	28	43	34
1065667	23	30	26	19	24	22
1065671	21	29	30	18	25	26
1065685	71	76	82	40	68	71
1065690	12	16	20	9	12	15
1065708	28	38	33	24	31	27
1065710	29	34	32	27	29	26
1065713	31	34	40	29	29	34
1065765	25	27	33	21	22	28
1065813	38	49	67	34	41	62
1065823	37	33	36	30	24	28
1065858	23	25	21	15	14	13
1065859	29	20	22	19	11	13
1065863	52	45	39	39	34	29

1065868	22	19	19	14	13	12
1065920	47	60	56	45	51	44
1065932	28	33	35	23	25	26
1065947	34	35	40	28	25	30
1066221	44	74	76	43	69	69
1066420	55	74	71	52	71	61
1066423	43	42	39	37	35	32
1066429	75	74	83	70	65	72

Table 114

Reduction of human UBE3A-ATS RNA in transgenic mice

Compound ID	UBE3A-ATS RNA (%control) RTS4796			UBE3A-ATS RNA (%control) RTS40595		
	SPINAL CORD	HIPPOCAMPUS	CORTEX	SPINAL CORD	HIPPOCAMPUS	CORTEX
PBS	100	100	100	100	100	100
1065272	40	29	39	37	31	39
1065582	45	28	52	43	31	51
1065616	38	25	45	36	25	42
1065619	33	23	54	31	27	55
1065621	42	33	57	43	41	54
1065624	20	40	62	20	42	61
1065631	24	32	71	24	34	65
1065669	38	33	89	34	30	72
1065674	37	36	111	35	34	101
1065678	33	36	105	32	35	96
1065680	43	61	134	40	59	121
1065686	21	25	63	19	22	55
1065696	44	36	117	40	32	108
1065719	63	36	122	56	32	109
1065728	20	11	53	14	9	42
1065754	47	25	112	41	24	105
1065766	29	41	110	24	41	98
1065768	40	41	99	32	38	84
1065799	44	43	104	38	40	99
1065812	19	15	35	12	12	26
1065817	29	23	60	22	20	52
1065821	23	19	42	16	17	34
1065829	36	19	80	27	18	58
1065840	27	15	61	21	14	45
1065856	22	19	44	14	13	30
1065857	35	28	58	26	21	38
1065899	37	30	77	30	24	58
1065902	21	17	55	17	14	41
1065937	22	12	91	17	11	65
1065953	19	13	58	13	10	41

1065955	34	19	69	26	16	53
1066046	58	35	122	50	32	106
1066076	46	27	76	41	25	N.D.
1066092	27	15	56	21	13	47
1066217	37	26	68	32	26	62
1066253	27	15	50	22	14	39
1066377	50	30	79	40	28	73

Table 115

Reduction of human UBE3A-ATS RNA in transgenic mice

Compound ID	UBE3A-ATS RNA (%control) RTS4796		
	SPINAL CORD	HIPPOCAMPUS	CORTEX
PBS	100	100	100
1263473	43	71	66
1263474	8	15	10
1263475	6	10	8
1263476	6	12	14
1263477	4	10	11
1263478	13	18	17
1263486	27	27	32
1263487	31	43	43
1263488	23	24	14
1263489	16	17	16
1263490	24	28	23
1263491	22	25	21
1263492	29	50	58
1263504	9	11	12
1263505	6	11	7
1263506	5	10	6
1263507	5	14	6
1263508	7	15	9
1263509	6	17	7
1263510	37	70	72
1263517	13	22	17
1263518	19	36	30
1263519	20	25	15
1263520	15	19	11
1263521	20	44	20
1263522	22	29	35
1263523	21	30	32
1263532	29	49	40
1263533	18	24	17
1263534	27	52	37
1263536	30	45	36

1263537	29	43	34
1263539	51	59	88
1263540	22*	21*	29*
1263541	52	66	80
1263543	49	362	84
1263544	53	100	104
1263545	36	54	57
1263546	45	45	88
1263547	26	28	30
1263548	36	45	47
1263549	66	87	84
1263550	47	75	76
1263551	30	45	39
1263552	66	65	93
1263554	72	75	88
1263556	60	59	83
1263557	86	91	109
1263408	45	70	46
1263409	29	44	33
1263410	29	64	42
1263411	42	72	58
1263419	47	126	65
1263420	73	130	72
1263429	27	33	36
1263434	44	50	42
1263435	47	42	61
1263441	22	17	29
1263451	21	16	28
1263452	14	8	15
1263453	13	9	9

* Only 1 animal in group

Table 116

Reduction of human UBE3A-ATS RNA in transgenic mice

Compound ID	UBE3A-ATS RNA (%control)		
	SPINAL CORD	HIPPOCAMPUS	CORTEX
PBS	100	100	100
1263454	6	8	13
1263455	5	19	35
1263458	39	62	88
1263459	28	45	52
1263460	11	28	34
1263461	24	30	35
1263462	25	24	25

1263463	36	40	66
1263464	25	22	38
1263465	32	35	39
1065786	121	75	32
1165526	116	78	46
1272943	41	73	32
1272946	37	69	33
1272947	55	94	54
1272951	70	89	75
1272952	125	85	109
1272953	86	78	51
1272954	110	89	70
1272955	137	136	70
1272960	59	77	40
1272962	45	52	26
1272964	74	58	62
1272965	43	39	25
1272966	52	68	67
1272967	65	69	62
1272968	76	62	66
1272969	83	60	147
1272970	143	57	60
1272971	81	58	48
1272972	74	69	38
1272974	40	29	18
1272975	124	86	96
1272976	93	62	50
1272977	58	59	47
1272978	39	46	40
1272979	61	69	46
1272982	60	58	42
1272983	84	83	70
1272985	72	56	38
1272987	181	37	28
1272988	66	34	31
1272989	87	60	68
1272992	77	45	42
1272993	57	36	60
1272994	16	12	10
1272995	182	35	93
1272996	26	9	18
1272997	24	12	27
1272998	26	14	17
1273000	104	45	56
1273003	93	28	60

1273009	39	8	19
1273011	145	78	80
1273012	110	36	71
1273014	46	19	37
1273015	79	35	68
1273016	58	34	37
1273017	46	39	56
1273018	41	24	60
1273019	98	39	80
1273020	44	10	19
1273021	59	27	47
1273022	73	23	45
1273023	54	23	31
1273024	29	21	25
1273028	46	50	28
1273031	45	17	28
1273032	40	21	35
1273033	36	12	26
699781	66	25	37
1065707	78	44	70
1165621	107	41	71

Table 117

Reduction of human UBE3A-ATS RNA in transgenic mice

Compound ID	UBE3A-ATS RNA (%control)	
	SPINAL CORD	HIPPOCAMPUS
PBS	100	100
1273034	25	23
1273035	16	20
1273036	24	26
1273061	33	22
1273062	28	10
1273063	32	29
1273064	38	25
1273065	27	16
1273066	34	36
1273067	44	42
1273070	25	23
1273071	57	71
1273072	38	48
1273037	12	25
1273038	16	29
1273039	15	29
1273040	39	33

1273041	48	29
1273042	51	17
1273044	45	27
1273045	48	24
1273048	30	18
1273049	19	15
1273050	30	31
1273051	17	21
1273052	14	15
1273055	14	20
1273056	16	22
1273057	16	18
1273058	20	22
1273059	16	17
1273060	36	35
1273084	41	35
1273087	12	14
1273088	33	28
1273090	24	41
1273091	26	31
1273092	37	38
1273093	28	23
1273098	17	23
1273099	14	10
1273101	29	32
1273102	20	18
1273103	12	5
1273104	57	16
1273105	34	9
1273106	30	11
1273107	24	8
1273108	31	13
1273109	30	13
1273110	37	8
1273111	46	12
1273113	25	10
1273114	46	26
1273115	15	7
1165523	38	17
1165533	31	19
1165538	64	25
1165550	47	11
1165563	30	12
1165586	35	19
1165596	69	49

1165616	109	25
1165855	49	16
1165897	39	28
1179808	83	36
1179841	22	9
1179843	22	11

Example 14: Activity of modified oligonucleotides complementary to human UBE3A-ATS in transgenic mice, multiple doses

Modified oligonucleotides described above were tested in the UBE3A-ATS BAC transgenic mouse model RP11-748 line.

Treatment

The UBE3A-ATS transgenic mice were divided into groups of 3 mice each. Each mouse received a single ICV bolus of 10, 30, 100, 300, or 700 µg of modified oligonucleotide. and sacrificed two weeks later. A group of 8 mice received PBS as a negative control.

RNA analysis

After two weeks, mice were sacrificed, and RNA was extracted from cortical brain tissue, hippocampal brain tissue, and spinal cords for real-time PCR analysis of measurement of RNA expression of UBE3A-ATS using primer probe set RTS40595 (forward sequence TCCTTCCCTACCTTAGTCTTGA, designated herein as SEQ ID NO: 14; reverse sequence CCCTCTTGAACCAGGAAACA, designated herein as SEQ ID NO: 15; probe sequence AGATGGCAGCCCACATTTCTACTGT, designated herein as SEQ ID NO: 16). Results are presented as percent change of RNA, relative to PBS control, normalized to mouse GAPDH (measured by primer-probe set RTS108).

As shown in the table below, treatment with modified oligonucleotides resulted in dose-dependent reduction of UBE3A-ATS RNA in comparison to the PBS control.

Table 118

Dose-dependent percent reduction of human UBE3A-ATS RNA in transgenic mice

Compound ID	Dose (µg)	Cortex		Hippocampus		Spinal Cord	
		UBE3A-ATS RNA (%control)	ED50 (µg)	UBE3A-ATS RNA (%control)	ED50 (µg)	UBE3A-ATS RNA (%control)	ED50 (µg)
PBS	0	100	-	100	-	100	-
749860	10	98.16531	138	81.99485	109	59.65406	17
	30	84.95562		91.16468		45.18495	
	100	67.32992		52.07824		25.79271	
	300	26.23195		33.3197		10.36557	
	700	11.97921		16.72183		9.517061	
1065645	10	90.14288	74	88.23692	71	37.14751	6
	30	72.43123		66.81222		16.11173	
	100	49.12943		51.83015		10.87515	

	300	16.34235		25.55912		7.843655	
1263461	10	88.27412	94	86.23292	126	60.06681	14
	30	81.19946		84.36883		33.7366	
	100	55.94376		68.69458		21.85816	
	300	16.25568		23.08811		28.43356	
	700	11.55421		20.98394		18.26012	
1263486	10	84.88829	91	88.16814	110	80.05438	49
	30	73.65319		88.23227		67.24883	
	100	53.51549		46.18175		35.76668	
	300	29.17494		39.41106		25.80888	
	700	13.16333		21.58236		14.67831	
1263517	10	61.99356	27	78.62965	38	28.43223	5
	30	57.35782		64.77742		4.093424	
	100	28.22543		31.27599		3.855931	
	300	13.48909		11.49965		2.253222	
	700	6.218008		9.114471		0.845911	
1263518	10	83.49507	47	74.9207	36	7.813722	N.C.
	30	63.00462		58.90944		6.925703	
	100	36.83505		35.79351		9.984906	
	300	10.60636		16.33499		22.15675	
1263532	10	87.76102	437	104.2908	508	85.92361	126
	30	93.21178		107.4279		86.97925	
	100	82.08274		79.80543		56.10128	
	300	63.11973		71.02516		37.9068	
1263533	10	85.64712	62	91.08657	93	79.33594	35
	30	74.82061		92.99996		56.07265	
	100	37.83251		50.48182		32.95345	
	300	17.85169		15.11169		16.13775	
	700	13.22447		16.26845		14.77717	
1263537	10	99.27557	167	101.6452	149	58.69295	32
	30	61.11154		67.12889		57.56289	
	100	70.65222		60.23925		35.5374	
	300	35.35647		38.67746		31.30235	
	700	37.55784		42.24916		26.47357	
1272944	10	85.26636	171	98.97738	241	86.06921	66
	30	83.3624		91.08809		60.22092	
	100	64.40395		69.68625		45.39798	
	300	47.00232		54.90247		34.02307	
	700	18.19851		26.34956		26.27892	
1273033	10	92.81903	159	104.9703	202	71.92708	27
	30	86.45458		92.23621		47.44761	
	100	71.94214		74.17289		34.27954	
	300	28.94805		34.12991		17.19729	
	700	19.14991		35.15452		16.60517	
1273039	10	84.62214	63	93.89685	77	52.24285	33

	30	70.19074		70.45983		45.93645	
	100	40.06878		45.44749		30.60229	
	300	22.18407		28.77613		27.68067	
	700	16.46246		23.35814		20.2156	
	10	60.65157		76.1426		108.4293	
	30	46.72804		76.65907		59.53868	
1273050	100	42.13233	34	63.21802	178	30.24442	45
	300	35.42049		42.84989		16.76795	
	700	27.88596		44.42969		16.65603	
	10	54.09476		101.4753		95.64317	
	30	75.60993		80.40454		46.396	
1273055	100	62.55598	104	61.10855	139	43.64926	46
	300	37.44794		36.83808		26.42752	
	700	18.68964		24.28962		17.02671	
	10	83.90397		91.25815		96.79799	
	30	71.94265		68.4521		78.51707	
1273062	100	41.74674	65	43.10219	65	45.07505	85
	300	23.62598		26.78065		25.9929	
	700	8.048482		17.65158		20.9903	
	10	51.37967		83.05922		94.48769	
	30	53.46583		70.46917		79.90936	
1273090	100	41.09529	25	69.46586	143	53.85753	120
	300	25.47022		49.33954		51.06804	
	10	48.66948		86.34518		126.1334	
	30	49.31716		78.33165		118.9585	
1273091	100	48.19272	28	67.14459	195	75.20145	240
	300	31.19941		48.97407		42.91308	
	700	28.63277		34.46767		43.51426	

Example 15: Tolerability of modified oligonucleotides complementary to human UBE3A-ATS in wild-type mice. 3 hour and 2 week study

Modified oligonucleotides closely matched to LNA/DNA oligonucleotides described in WO2017/081223 were tested in female wild-type C57/B16 mice to assess the tolerability of the oligonucleotides. See, Certain Comparator Compouonds, hereinabove. Wild-type female C57/Bl6 mice each received a single ICV dose of 700 μg of modified oligonucleotide listed in the table below. Each treatment group consisted of 4 mice. A group of 4 mice received PBS as a negative control for the experiment. At 3 hours post-injection and 2 weeks post-injection, mice were evaluated according to seven 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 (the functional observational battery score or FOB). After all 7 criteria were evaluated, the

scores were summed for each mouse and averaged within each treatment group. The results are presented in the table below.

Table 119

Tolerability scores in mice at 700 µg dose

Compound ID	3 hr FOB	2 week FOB	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Chemistry Notation (5' to 3')	SEQ ID NO
PBS	0.0	0.0				
1219022	7.0	n.d.	468275	468294	$A_{ls}A_{ls}A_{ds}T_{ds}T_{ls}A_{ds}T_{ls}T_{ds}T_{ds}A_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ls}T_{ls}{}^{m}C_{ls}A_{l}$	2905
1219023	1.0	3.5	462549	462566	$T_{ls}T_{ls}T_{ls}A_{ds}T_{ds}{}^{m}C_{ls}A_{ds}A_{ds}T_{ds}A_{ds}T_{ds}{}^{m}C_{ds}T_{ds}T_{ds}{}^{m}C_{ds}T_{ls}{}^{m}C_{ls}A_{l}$	2906
1219024	5.3	6.5	471876	471894	$G_{ls}{}^{m}C_{ds}A_{ls}{}^{m}C_{ds}A_{ls}T_{ds}T_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}T_{ds}A_{ds}T_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ls}T_{l}$	2907
1219025	4.0	6.0	461987	462003	$T_{ls}T_{ls}A_{ds}T_{ls}A_{ls}G_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}T_{ds}T_{ds}{}^{m}C_{ds}T_{ds}A_{ds}T_{ds}{}^{m}C_{ls}T_{l}$	2908
1219026	1.0	6.0	487371	487387	$^{m}C_{ls}T_{ds}{}^{m}C_{ls}A_{ls}A_{ls}A_{ds}G_{ds}A_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}T_{ds}{}^{m}C_{ls}T_{ls}{}^{m}C_{ls}A_{l}$	2909
1219027	1.0	0.0	487430	487449	$T_{ls}T_{ds}A_{ls}{}^{m}C_{ds}A_{ls}{}^{m}C_{ds}T_{ls}T_{ds}A_{ds}A_{ds}T_{ds}T_{ds}A_{ds}T_{ds}A_{ds}{}^{m}C_{ds}T_{ls}T_{ds}{}^{m}C_{ls}{}^{m}C_{l}$	2910
1219028	6.0	6.0	496570	496587	$G_{ls}T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}T_{ds}{}^{m}C_{ds}T_{ds}A_{ds}{}^{m}C_{ds}T_{ls}A_{ls}T_{ds}T_{ls}A_{ls}A_{l}$	2911
1219029	6.3	6.0	503154	503170	$^{m}C_{ls}T_{ls}G_{ds}T_{ds}A_{ls}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}{}^{m}C_{ls}A_{l}$	2912
1219030	5.0	5.0	487478	487494	$A_{ls}G_{ds}T_{ds}T_{ls}{}^{m}C_{ls}T_{ds}A_{ds}{}^{m}C_{ds}T_{ds}A_{ds}T_{ds}A_{ds}{}^{m}C_{ds}T_{ls}T_{ls}T_{ls}{}^{m}C_{l}$	2913
1219031	5.3	6.0	464879	464898	$T_{ls}A_{ls}T_{ds}A_{ds}{}^{m}C_{ls}{}^{m}C_{ds}T_{ls}T_{ds}T_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}A_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}{}^{m}C_{ds}T_{ls}T_{l}$	2914

A subscript "l" indicates a 4'-2' LNA modified sugar moiety, a subscript "d" indicates a 2'-β-D-deoxyribosyl sugar moiety, a subscript "s" indicates a phosphorothioate internucleoside linkage, and a superscript "m" before a C indicates 5-methyl cytosine.

n.d. means no data; not tested.

Example 16: Tolerability of modified oligonucleotides complementary to human UBE3A-ATS in rats, 8 week study

Modified oligonucleotides described above were tested in rats to assess the tolerability of the oligonucleotides. Groups of male, 6-8 week old Sprague Dawley rats each received a single intrathecal (IT) dose of 3 mg of oligonucleotide as listed in the table below. Each treatment group consisted of 4 rats, approximately matched for starting weights. A group of four rats received PBS as a negative control. The rats were weighed before dosing, and were weighed again at 8 weeks post-dose. Rats are expected to gain weight over the course of the study due to growth; too little weight gain is a sign of compound toxicity. Absolute values of body weight change were normalized to the body weight change observed in PBS-treated groups to allow comparison between two studies with different average starting weights for the rats, with the body weight change of the PBS group set to 100%. Statistical significance (p-value) of the change in body weight compared to the PBS-treated group was calculated by a two-tailed Welch's T-test in Excel (two sample, unequal variance). A p-value of <0.05 indicates that there is less than a 5% chance that the observed differences are due to random sampling errors.

Table 120

Body Weight Change in Rats at 8 weeks post-dose

Compound ID	B.W. change as % PBS	p-value
PBS	100	n/a
1219027	87	0.03
1065645	101	0.83
1263517	100	0.91
1263518	103	0.50
1263533	100	0.99
1273039	105	0.26
1273062	100	0.98

CLAIMS:

1. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides wherein the nucleobase sequence of the modified oligonucleotide is at least 90% complementary to an equal length portion of a UBE3A-ATS RNA, and wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage.
2. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 12, 13, 14, 15, 16, 17, 18, 19, or 20 contiguous nucleobases of any of SEQ ID NOs: 17-2762, 2786-2863, 2872-2904.
3. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 12, 13, 14, 15, 16, 17, or 18 contiguous nucleobases of any of SEQ ID NOs: 2763-2785 or 2864-2871.
4. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or at least 20 contiguous nucleobases complementary to:

   an equal length portion of nucleobases 461,413-461,487 of SEQ ID NO: 1;

   an equal length portion of nucleobases 468,968-469,013 of SEQ ID NO: 1; or

   an equal length portion of nucleobases 483,965-484,003 of SEQ ID NO: 1
5. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, or at least 18 contiguous nucleobases of a sequence selected from:

   SEQ ID Nos:1053, 1329, 1501, 1576, 1873, 1949, 2025, 2096, 2245, 2512,2591,2680-2682, and 2844;

   SEQ ID Nos: 376, 377, 2751-2756, 2773-2776, 2872, 2873, 2876-2878; or

   SEQ ID Nos: 172, 764-770, 995, 1445, 1668, 1743, 2255, 2595, 2762-2767.
6. The oligomeric compound of any of claims 1-5, wherein the modified oligonucleotide has a nucleobase sequence that is at least 80%, 85%, 90%, 95%, or 100% complementary to the nucleobase sequence of SEQ ID NO: 1, SEQ ID NO: 2915 or SEQ ID NO: 2916 when measured across the entire nucleobase sequence of the modified oligonucleotide.
7. The oligomeric compound of any of claims 1-6, wherein the modified oligonucleotide comprises at least one modified nucleoside.
8. The oligomeric compound of claim 7, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a modified sugar moiety.
9. The oligomeric compound of claim 8, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a bicyclic sugar moiety.
10. The oligomeric compound of claim 9, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a bicyclic sugar moiety having a 2'-4' bridge, wherein the 2'-4' bridge is selected from –O-CH_2-; and –O-$CH(CH_3)$-.
11. The oligomeric compound of any of claims 7-10, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a non-bicyclic modified sugar moiety.

12. The oligomeric compound of claim 11, wherein the non-bicyclic modified sugar moiety is a 2'-MOE modified sugar moiety or 2'-OMe modified sugar moiety.
13. The oligomeric compound of any of claims 7-8, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a sugar surrogate.
14. The oligomeric compound of claim 13, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a sugar surrogate selected from morpholino and PNA.
15. The oligomeric compound of any of claims 1-8 or 11-14, wherein the modified oligonucleotide does not comprise a bicyclic sugar moiety.
16. The oligomeric compound of any of claims 1-15, wherein the modified oligonucleotide is a gapmer.
17. The oligomeric compound of any of claims 1-16, wherein the modified oligonucleotide has a sugar motif comprising:

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

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

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

    each of the 5'-region nucleosides and each of the 3'-region nucleosides comprises a modified sugar moiety and each of the central region nucleosides comprises a 2'-β-D-deoxyribosyl sugar moiety.
18. The oligomeric compound of claim 17, wherein the modified oligonucleotide has

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

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

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

    each of the 5'-region nucleosides and each of the 3'-region nucleosides comprises a 2'-MOE modified sugar moiety, and each of the central region nucleosides comprises a 2'-β-D-deoxyribosyl sugar moiety.
19. The oligomeric compound of claim 17, wherein the modified oligonucleotide has

    a 5'-region consisting of 4 linked 5'-region nucleosides;

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

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

    each of the 5'-region nucleosides and each of the 3'-region nucleosides a 2'-MOE modified sugar moiety, and each of the central region nucleosides comprises a 2'-β-D-deoxyribosyl sugar moiety.
20. The oligomeric compound of claim 17, wherein the modified oligonucleotide has

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

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

    a 3'-region consisting of 4 linked 3'-region nucleosides; wherein

    each of the 5'-region nucleosides and each of the 3'-region nucleosides a 2'-MOE modified sugar moiety, and each of the central region nucleosides comprises a 2'-β-D-deoxyribosyl sugar moiety.
21. The oligomeric compound of claim 17, wherein the modified oligonucleotide has

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

    a central region consisting of 8 linked central region nucleosides; and

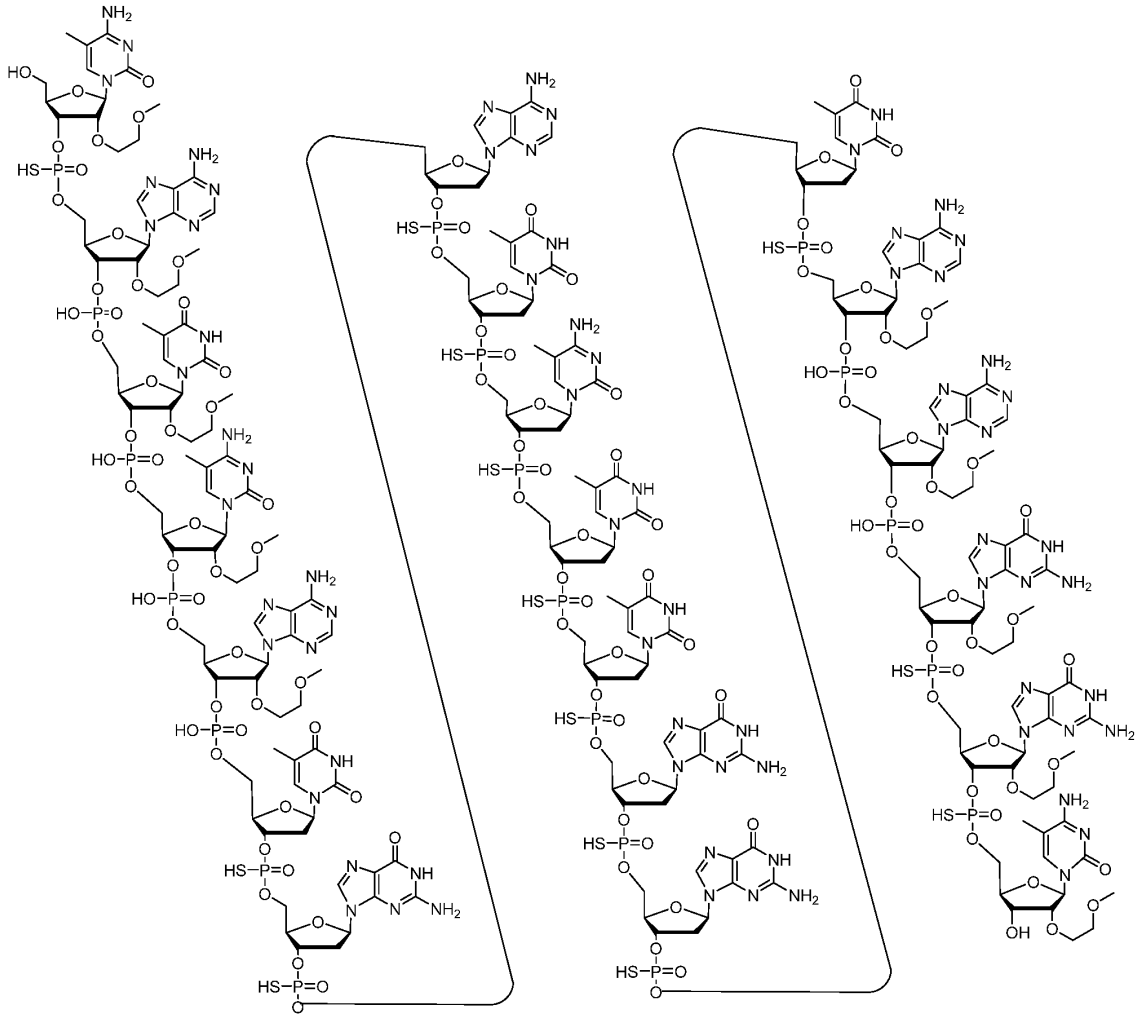
    a 3'-region consisting of 5 linked 3'-region nucleosides; wherein

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

22. The oligomeric compound of claim 17, wherein the modified oligonucleotide has
a 5'-region consisting of 4 linked 5'-region nucleosides;
a central region consisting of 8 linked central region nucleosides; and
a 3'-region consisting of 6 linked 3'-region nucleosides; wherein
each of the 5'-region nucleosides and each of the 3'-region nucleosides a 2'-MOE modified sugar moiety, and each of the central region nucleosides comprises a 2'-β-D-deoxyribosyl sugar moiety.
23. The oligomeric compound of claim 17, wherein the modified oligonucleotide has
a 5'-region consisting of 4 linked 5'-region nucleosides;
a central region consisting of 8 linked central region nucleosides; and
a 3'-region consisting of 6 linked 3'-region nucleosides; wherein
each of the 5'-region nucleosides and each of the 3'-region nucleosides a 2'-MOE modified sugar moiety, and each of the central region nucleosides comprises a 2'-β-D-deoxyribosyl sugar moiety.
24. The oligomeric compound of any of claims 1-23, wherein the modified oligonucleotide comprises at least one modified internucleoside linkage.
25. The oligomeric compound of claim 24, wherein each internucleoside linkage of the modified oligonucleotide is a modified internucleoside linkage.
26. The oligomeric compound of claim 24 or 25 wherein the modified internucleoside linkage is a phosphorothioate internucleoside linkage.
27. The oligomeric compound of claim 24 or 26 wherein the modified oligonucleotide comprises at least one phosphodiester internucleoside linkage.
28. The oligomeric compound of any of claims 24, 26, or 27, wherein each internucleoside linkage is independently selected from a phosphodiester internucleoside linkage or a phosphorothioate internucleoside linkage.
29. The oligomeric compound of claims 1-24 or 27-28, wherein the modified oligonucleotide has an internucleoside linkage motif selected from among: soooosssssssssssooss, sooooossssssssssoss, soooossssssssssoss, sooossssssssssooss, soooossssssssssooooss, or soossssssssssoooss; wherein,
s = a phosphorothioate internucleoside linkage and o = a phosphodiester internucleoside linkage.
30. The oligomeric compound of any of claims 1-29, wherein the modified oligonucleotide comprises a modified nucleobase.
31. The oligomeric compound of claim 30, wherein the modified nucleobase is a 5-methyl cytosine.
32. The oligomeric compound of any of claims 1-31, wherein the modified oligonucleotide consists of 12-30, 12-22, 12-20,14-18, 14-20, 15-17, 15-25, 16-20, 18-22 or 18-20 linked nucleosides.
33. The oligomeric compound of any of claims 1-32, wherein the modified oligonucleotide consists of 18 linked nucleosides.
34. The oligomeric compound of any of claims 1-2, 4, or 6-32, wherein the modified oligonucleotide consists of 20 linked nucleosides.
35. The oligomeric compound of any of claims 1-34, consisting of the modified oligonucleotide.

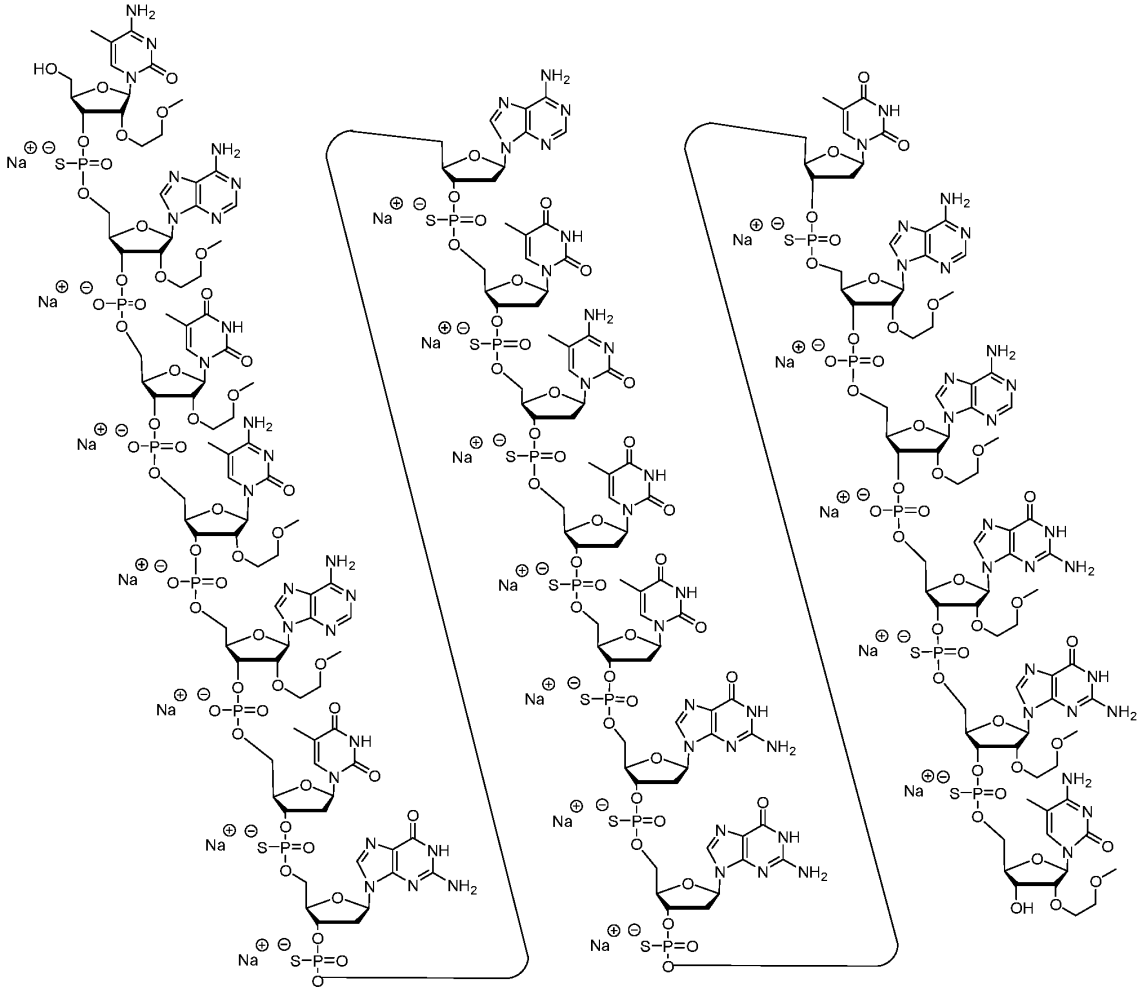
36. The oligomeric compound of any of claims 1-34, comprising a conjugate group comprising a conjugate moiety and a conjugate linker.
37. The oligomeric compound of claim 36, wherein the conjugate linker consists of a single bond.
38. The oligomeric compound of claim 36, wherein the conjugate linker is cleavable.
39. The oligomeric compound of claim 36, wherein the conjugate linker comprises 1-3 linker-nucleosides.
40. The oligomeric compound of any of claims 36-39, wherein the conjugate group is attached to the modified oligonucleotide at the 5'-end of the modified oligonucleotide.
41. The oligomeric compound of any of claims 36-39, wherein the conjugate group is attached to the modified oligonucleotide at the 3'-end of the modified oligonucleotide.
42. The oligomeric compound of any of claims 1-34 or 36-41, comprising a terminal group.
43. The oligomeric compound of any of claims 1-42 wherein the oligomeric compound is a singled-stranded oligomeric compound.
44. The oligomeric compound of any of claims 1-38 or 40-43, wherein the oligomeric compound does not comprise linker-nucleosides.
45. An oligomeric duplex comprising an oligomeric compound of any of claims 1-42 or 44.
46. An antisense compound comprising or consisting of an oligomeric compound of any of claims 1-44 or an oligomeric duplex of claim 45.
47. A pharmaceutical composition comprising an oligomeric compound of any of claims 1-44 or an oligomeric duplex of claim 45 and a pharmaceutically acceptable carrier or diluent.
48. The pharmaceutical composition of claim 47, wherein the pharmaceutically acceptable diluent is artificial cerebral spinal fluid.
49. The pharmaceutical composition of claim 48, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide and phosphate buffered saline.
50. A method comprising administering to a subject a pharmaceutical composition of any of claims 47-50.
51. A method of treating a disease associated with UBE3A-ATS comprising administering to an individual having or at risk for developing a disease associated with UBE3A-ATS a therapeutically effective amount of a pharmaceutical composition according to any of claims 47-49; and thereby treating the disease associated with UBE3A-ATS.
52. The method of claim 51, wherein the UBE3A-ATS-associated disease is Angelman Syndrome.
53. The method of any of claims 50-52, wherein at least one symptom or hallmark of the UBE3A-ATS-associated disease is ameliorated.
54. The method of claim 53, wherein the symptom or hallmark is developmental delays, ataxia, speech impairment, sleep problems, seizures, or EEG abnormalities.

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



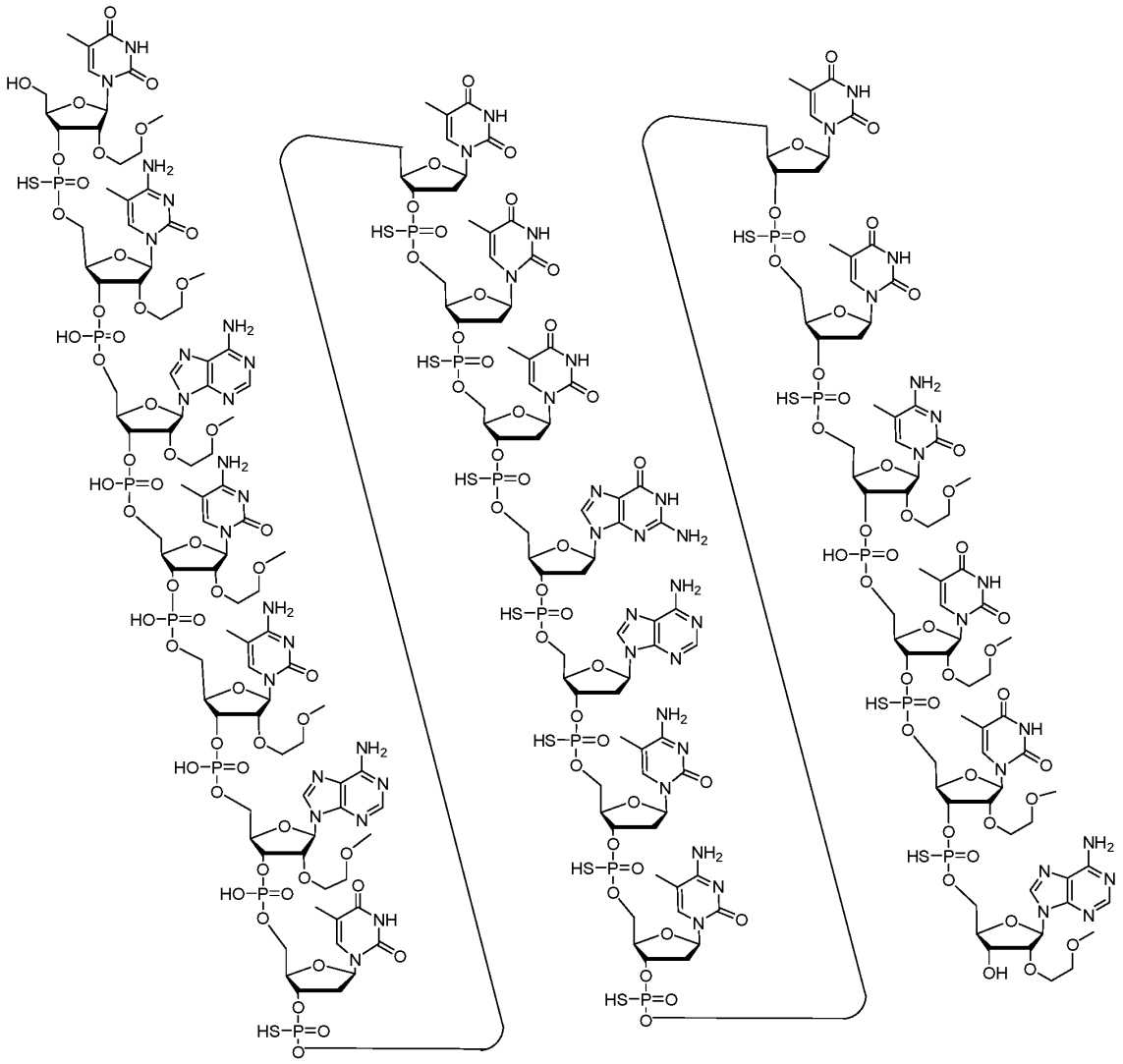
(SEQ ID NO: 1949), or a salt thereof.

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



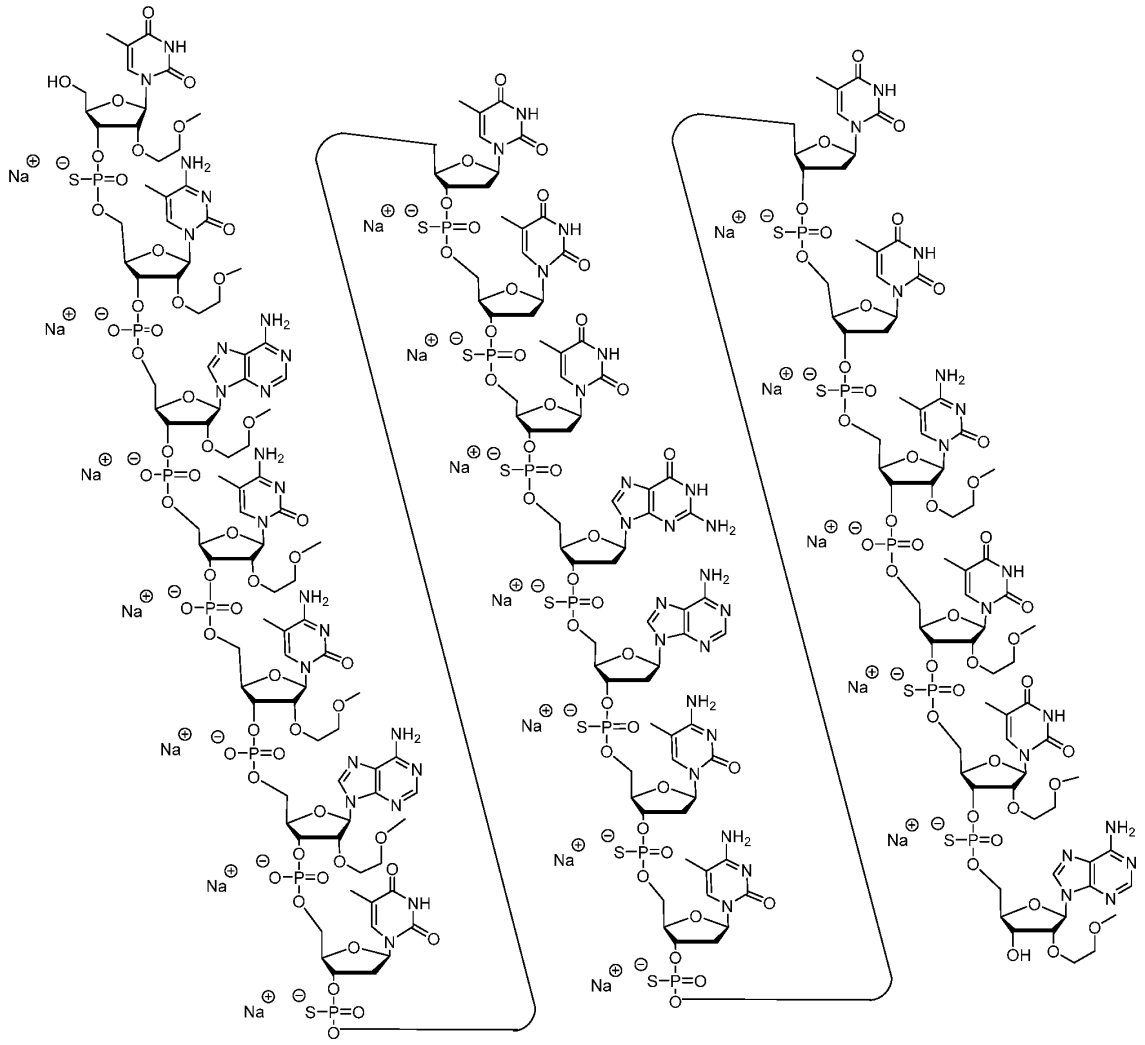
(SEQ ID NO: 1949).

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



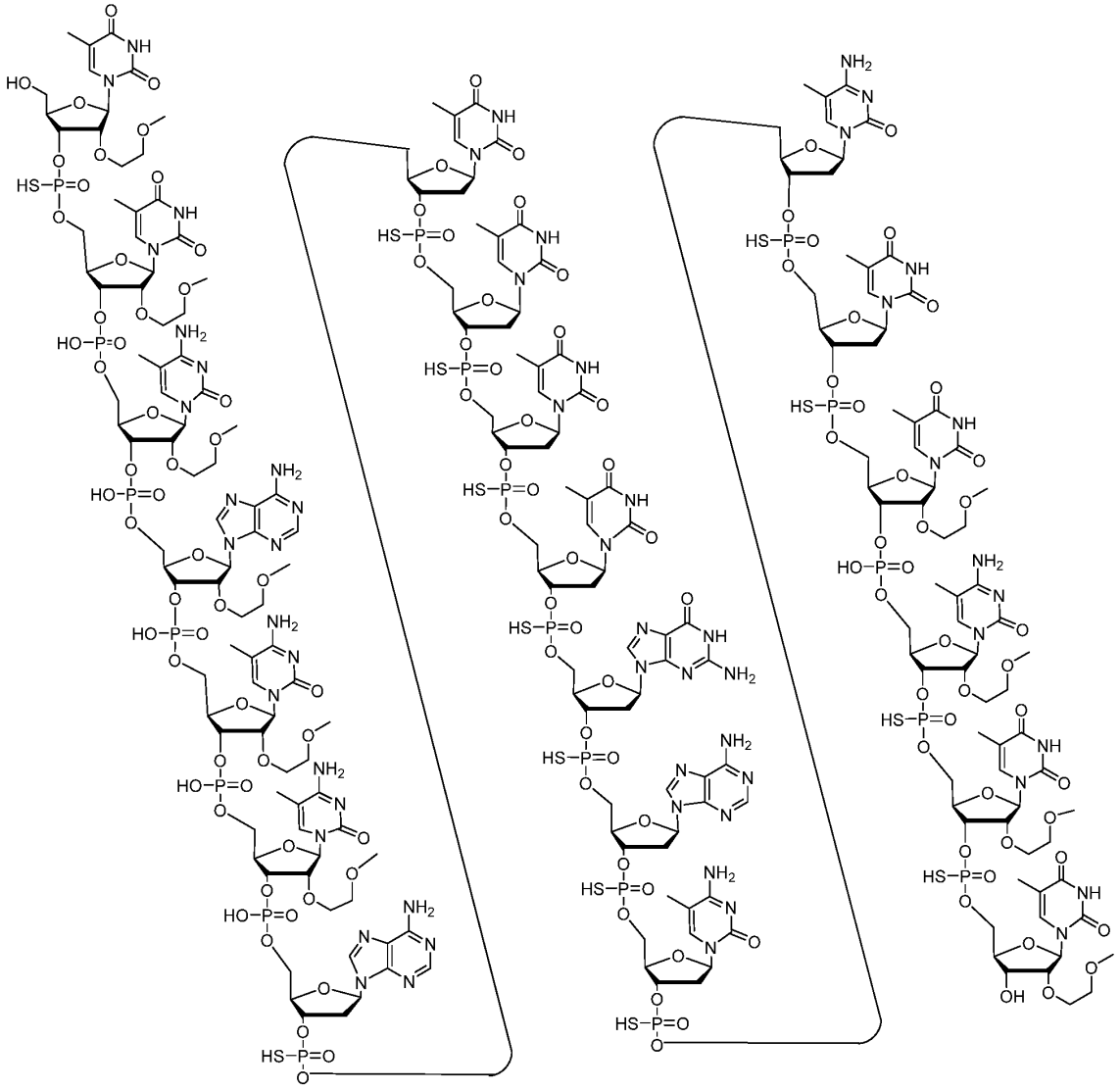
(SEQ ID NO: 2751), or a salt thereof.

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



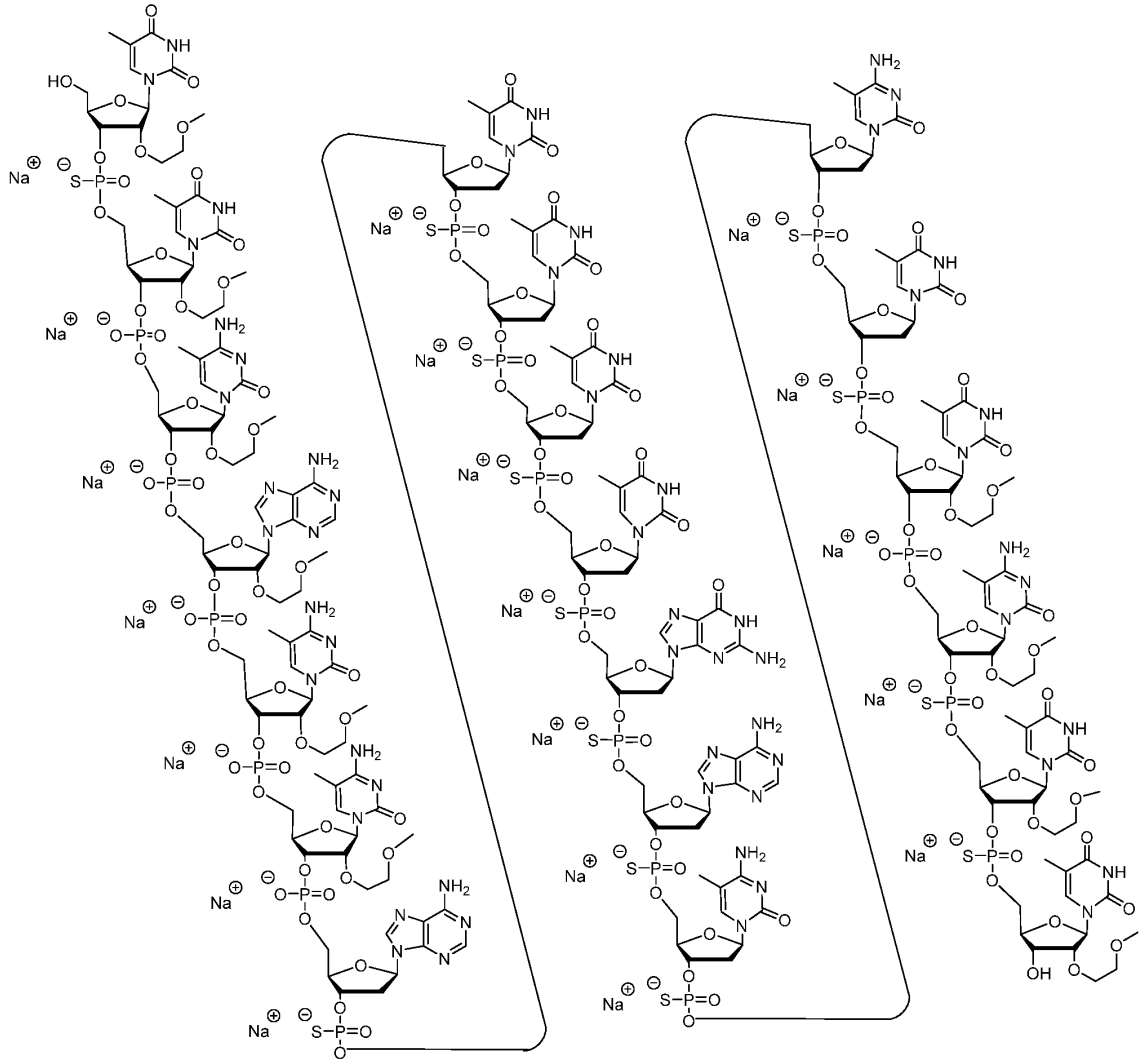
(SEQ ID NO: 2751).

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



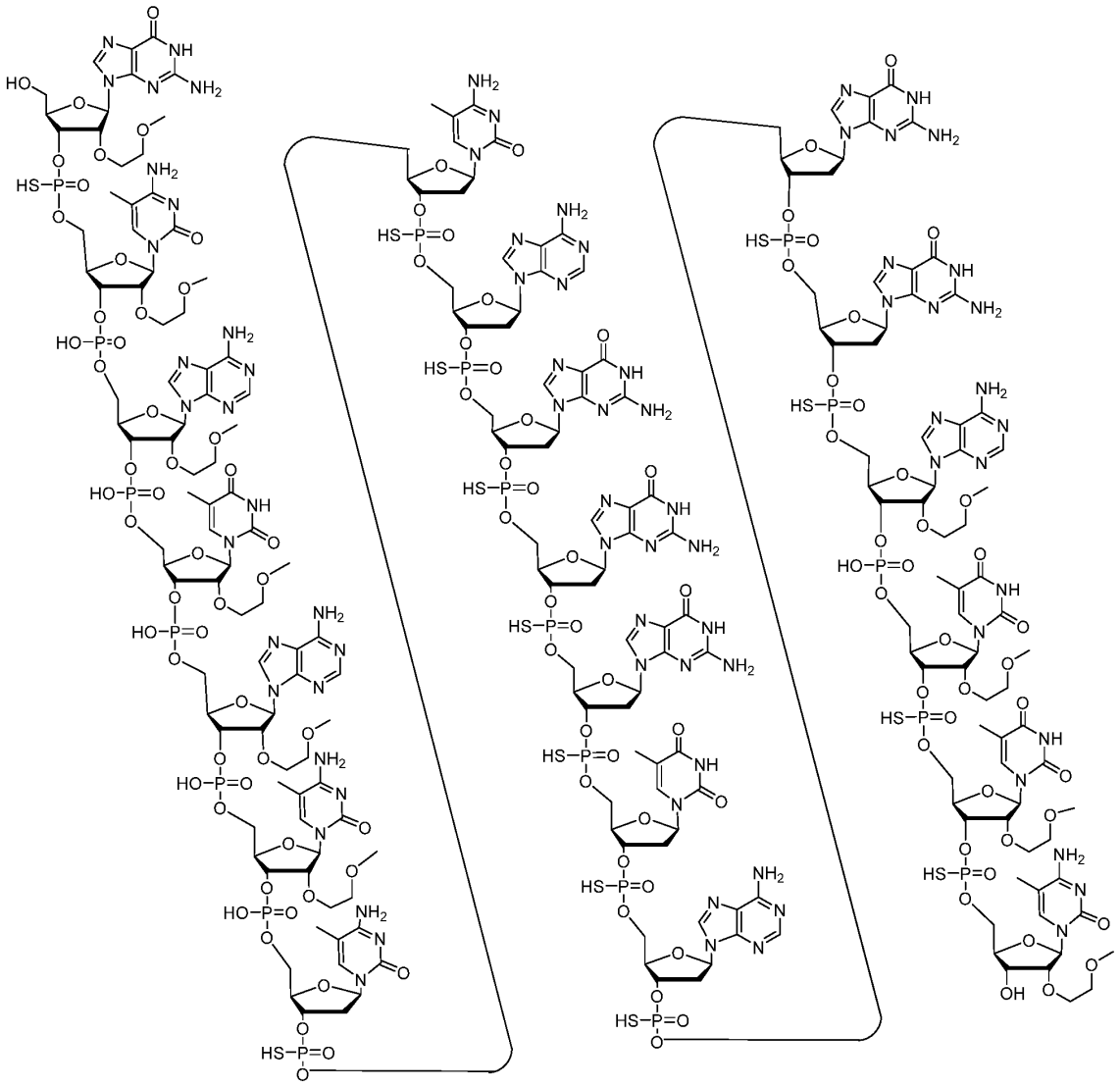
(SEQ ID NO: 2752), or a salt thereof.

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



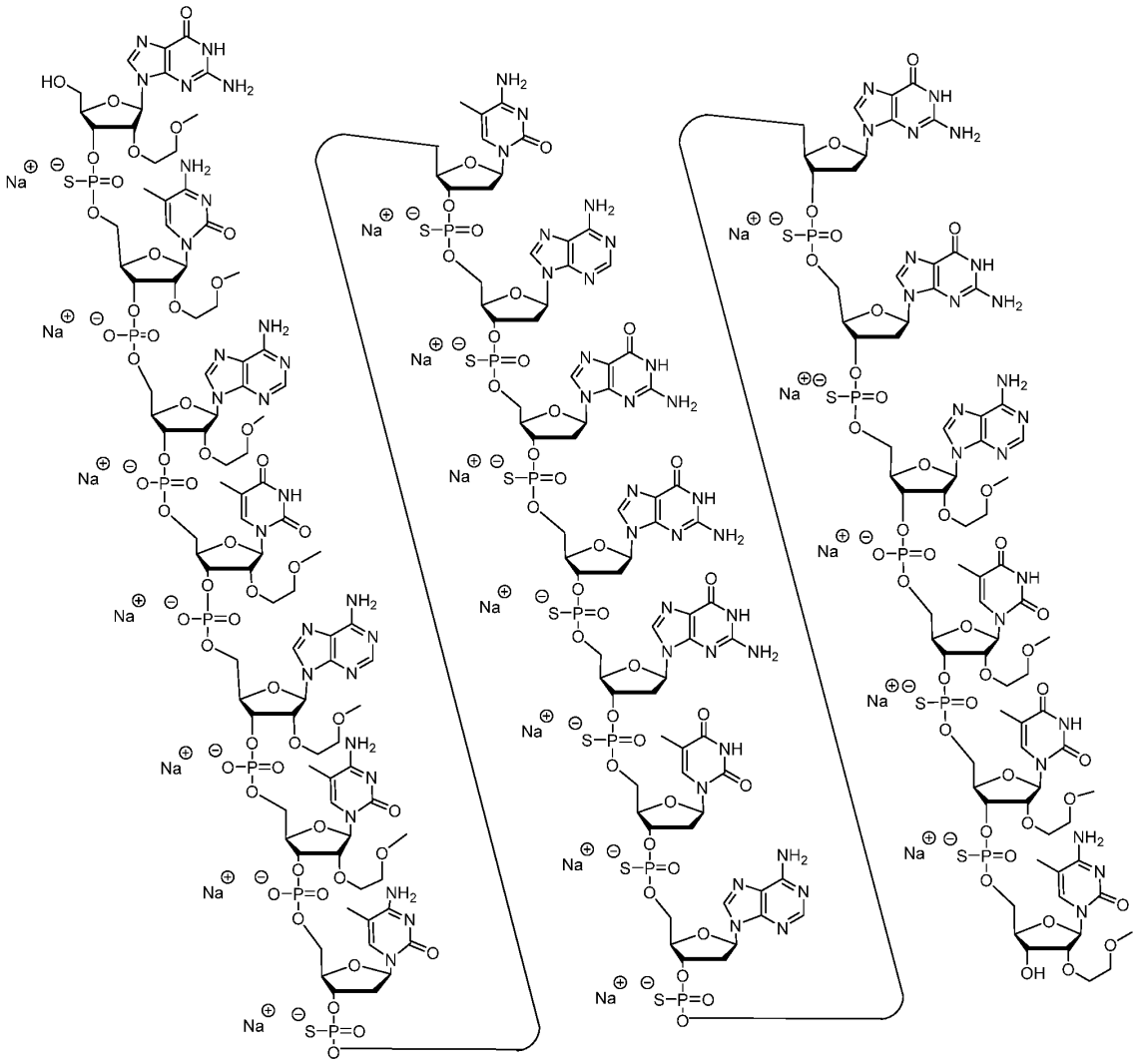
(SEQ ID NO: 2752).

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



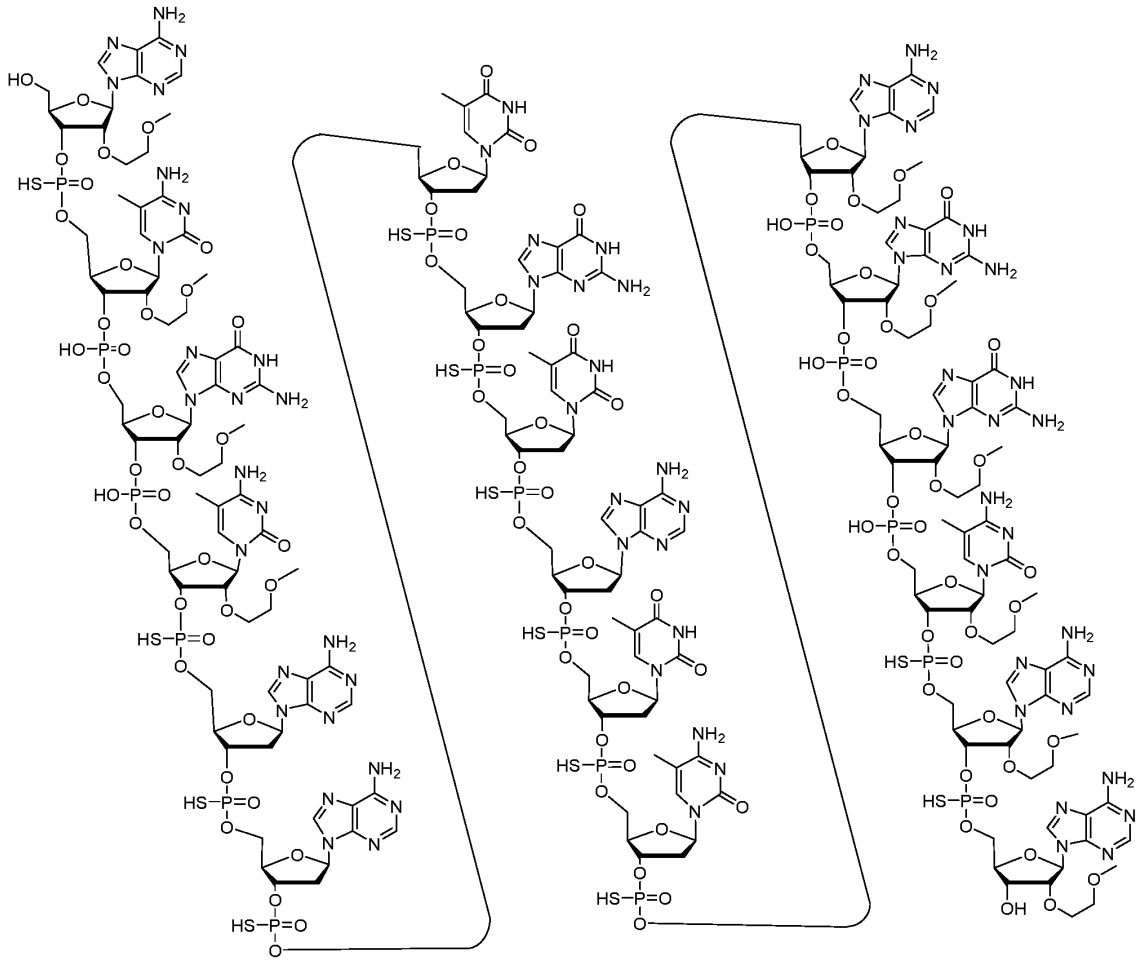
(SEQ ID NO: 765), or a salt thereof.

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



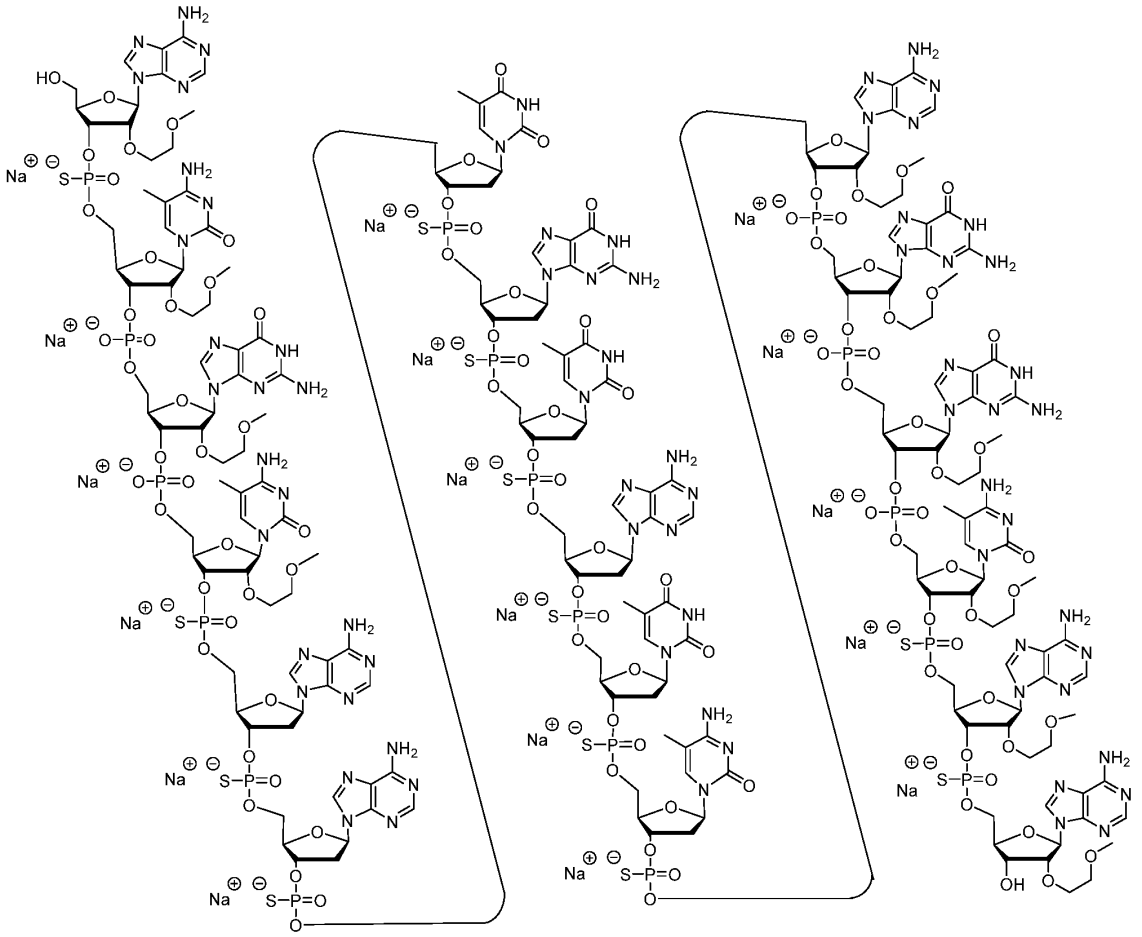
(SEQ ID NO: 765).

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



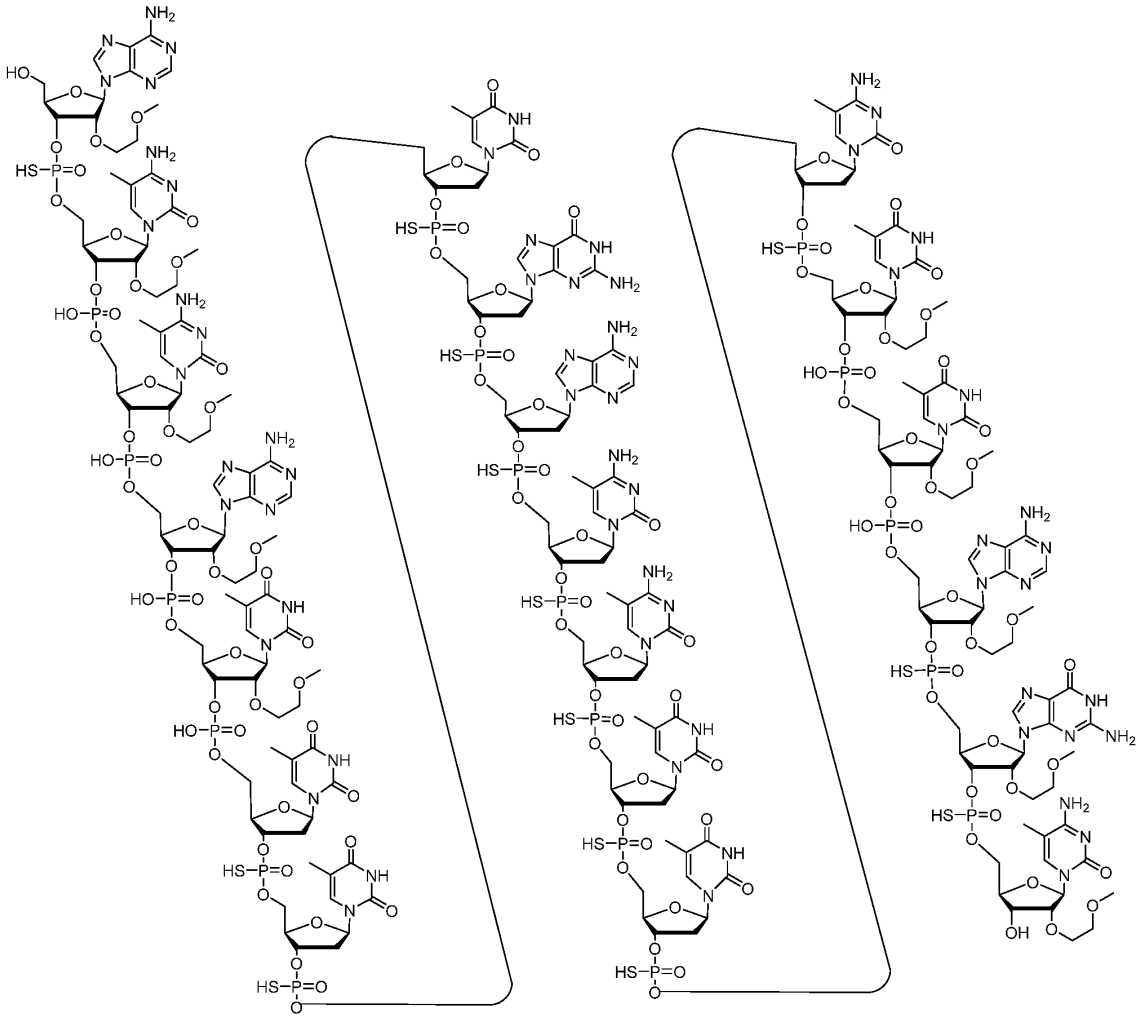
(SEQ ID NO: 2866), or a salt thereof.

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



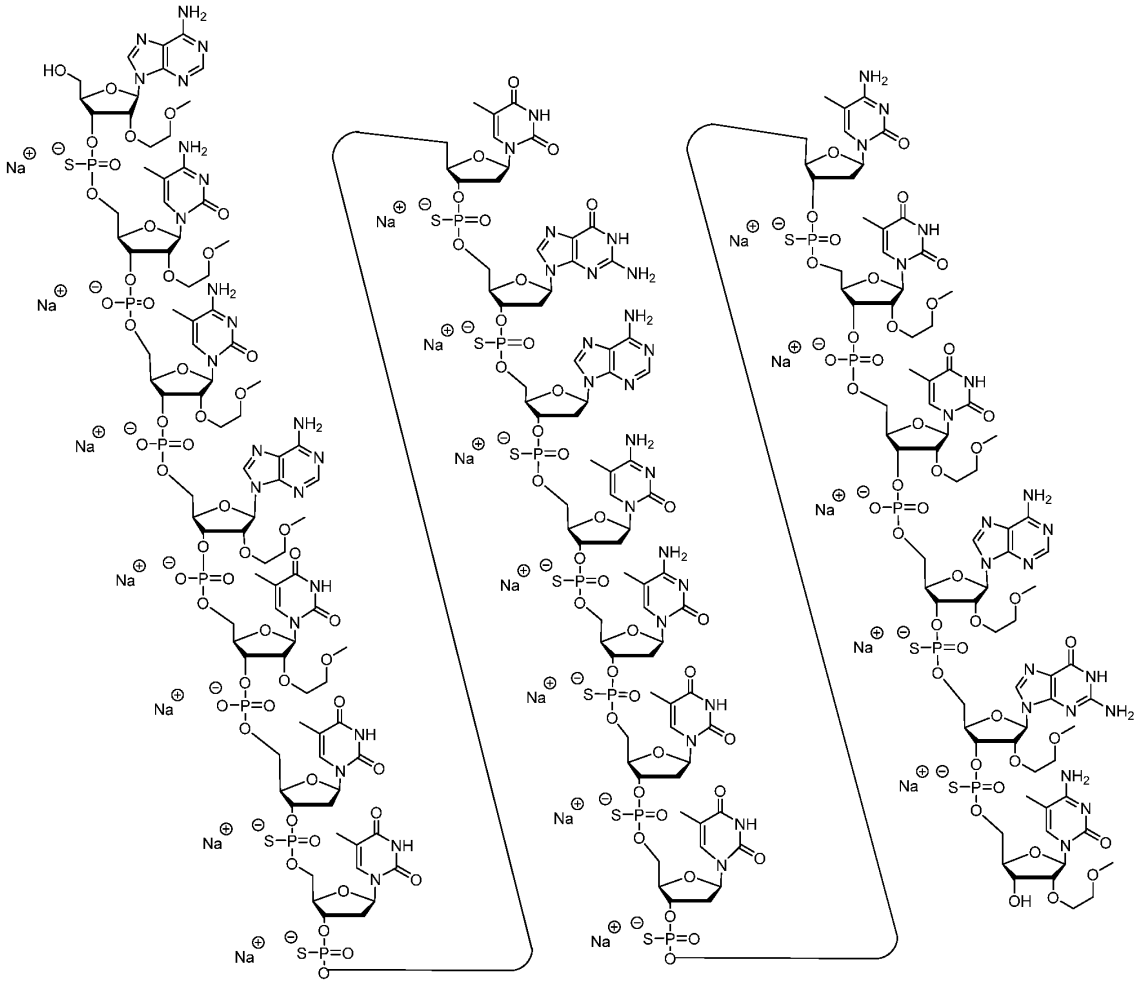
(SEQ ID NO: 2866).

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



(SEQ ID NO: 2873), or a salt thereof.

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



(SEQ ID NO: 2873).

67. The modified oligonucleotide of any of claims 55, 57, 59, 61, 63, or 65, which is the sodium salt or the potassium salt.

68. A pharmaceutical composition comprising the modified oligonucleotide of any of claims 55-67 and a pharmaceutically acceptable carrier or diluent.

69. The pharmaceutical composition of claim 68, wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid.

70. The pharmaceutical composition of claim 69, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide and artificial cerebrospinal fluid.

71. A compound comprising a modified oligonucleotide according to the following chemical notation: $^{m}C_{es}A_{eo}T_{eo}{}^{m}C_{eo}A_{eo}T_{ds}G_{ds}A_{ds}T_{ds}{}^{m}C_{ds}T_{ds}T_{ds}G_{ds}G_{ds}T_{ds}A_{eo}A_{eo}G_{es}G_{es}{}^{m}C_{e}$ (SEQ ID NO: 1949), wherein:

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

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

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

72. A compound comprising a modified oligonucleotide according to the following chemical notation: $T_{es}{}^{m}C_{eo}A_{eo}{}^{m}C_{eo}{}^{m}C_{eo}A_{eo}T_{ds}T_{ds}T_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{ds}{}^{m}C_{eo}T_{es}T_{es}A_{e}$ (SEQ ID NO: 2751), wherein:

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

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

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

73. A compound comprising a modified oligonucleotide according to the following chemical notation: $T_{es}T_{eo}{}^{m}C_{eo}A_{eo}{}^{m}C_{eo}{}^{m}C_{eo}A_{ds}T_{ds}T_{ds}T_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{eo}{}^{m}C_{es}T_{es}T_{e}$ (SEQ ID NO: 2752), wherein:

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

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

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

74. A compound comprising a modified oligonucleotide according to the following chemical notation: $G_{es}{}^{m}C_{eo}A_{eo}T_{eo}A_{eo}{}^{m}C_{eo}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}G_{ds}G_{ds}G_{ds}T_{ds}A_{ds}G_{ds}G_{ds}A_{eo}T_{es}T_{es}{}^{m}C_{e}$ (SEQ ID NO: 765), wherein:

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

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

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

75. A compound comprising a modified oligonucleotide according to the following chemical notation: $A_{es}{}^{m}C_{eo}G_{eo}{}^{m}C_{es}A_{ds}A_{ds}T_{ds}G_{ds}T_{ds}A_{ds}T_{ds}{}^{m}C_{ds}A_{eo}G_{eo}G_{eo}{}^{m}C_{es}A_{es}A_{e}$ (SEQ ID NO: 2866), wherein:

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

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

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

76. A compound comprising a modified oligonucleotide according to the following chemical notation: $A_{es}{}^{m}C_{eo}{}^{m}C_{eo}A_{eo}T_{eo}T_{ds}T_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{ds}{}^{m}C_{ds}T_{eo}T_{eo}A_{es}G_{es}{}^{m}C_{e}$ (SEQ ID NO: 2873), wherein:

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

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

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

77. The compound of any of claims 71-76, comprising the modified oligonucleotide covalently linked to a conjugate group.

78. A pharmaceutical composition of any of claims 71-77, and a pharmaceutically acceptable diluent or carrier.

79. The pharmaceutical composition of claim 78, wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid.

80. The pharmaceutical composition of claim 79, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide and artificial cerebrospinal fluid.

81. A chirally enriched population of modified oligonucleotides of any of claims 55-67, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having a particular setereochemical configuration.

82. The chirally enriched population of claim 81, wherein the population is enriched for modified oligonucleotides comprising at least one particular phorphorothioate internucleoside linkage having the (Sp) configuration.

83. The chirally enriched population of claim 81, wherein the population is enriched for modified oligonucleotides comprising at least one particular phorphorothioate internucleoside linkage having the (Rp) configuration.

84. The chirally enriched population of claim 81, wherein the population is enriched for modified oligonucleotides having a particular, independently selected stereochemical configuration at each phosphorothioate internucleoside linkage

85. The chirally enriched population of claim 84, wherein the population is enriched for modified oligonucleotides having the (Sp) configuration at each phosphorothioate internucleoside linkage.

86. The chirally enriched population of claim 84, wherein the population is enriched for modified oligonucleotides having the (Rp) configuration at each phosphorothioate internucleoside linkage.

87. The chirally enriched population of claim 84, wherein the population is enriched for modified oligonucleotides having the (Rp) configuration at one particular phosphorothioate internucleoside linkage and the (Sp)

configuration at each of the remaining phosphorothioate internucleoside linkages.

88. The chirally enriched population of claim 81 or claim 84 wherein the population is enriched for modified oligonucleotides having at least 3 contiguous phosphorothioate internucleoside linkages in the Sp, Sp, and Rp configurations, in the 5' to 3' direction.

89. A chirally enriched population of modified oligonucleotides of any of claims 55-67, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom.