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(54) **Title:** COMPOUNDS AND METHODS FOR MODULATING EXPRESSION APOB

(57) **Abstract:** The present disclosure describes short antisense compounds, including such compounds comprising chemically-modified high-affinity monomers 8-16 monomers in length. Certain such short antisense compound are useful for the reduction of target nucleic acids and/or proteins in cells, tissues, and animals with increased potency and improved therapeutic index. Thus, provided herein are short antisense compounds comprising high-affinity nucleotide modifications useful for reducing a target RNA in vivo. Such short antisense compounds are effective at lower doses than previously described antisense compounds, allowing for a reduction in toxicity and cost of treatment. In addition, the described short antisense compounds have greater potential for oral dosing.

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COMPOUNDS AND METHODS FOR MODULATING EXPRESSION APOB

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 CORE0061WO7SEQ.txt, created on May 7, 2007 which is 700 Kb in size. The information in the electronic format of the sequence listing is incorporated herein by reference in its entirety.

BACKGROUND

Targeting disease-causing gene sequences was first suggested nearly 40 years ago (Belikova et al., Tet. Lett., 1967, 37, 3557-3562), and antisense activity was demonstrated in cell culture a decade later (Zamecnik et al., Proc. Natl. Acad. Sci. U.S.A., 1978, 75, 280-284). One advantage of antisense technology in the treatment of a disease or condition that stems from a disease-causing gene is that it is a direct genetic approach that has the ability to modulate expression of specific disease-causing genes.

Generally, the principle behind antisense technology is that an antisense compound hybridizes to a target nucleic acid and effects modulation of gene expression activity or function, such as transcription, translation or splicing. The modulation of gene expression can be achieved by, for example, target degradation or occupancy-based inhibition. An example of modulation of RNA target function by degradation is RNase H-based degradation of the target RNA upon hybridization with a DNA-like antisense compound. Another example of modulation of gene expression by target degradation is RNA interference (RNAi). RNAi is a form of antisense-mediated gene silencing involving the introduction of dsRNA leading to the sequence-specific reduction of targeted endogenous mRNA levels. Sequence-specificity makes antisense compounds extremely attractive as tools for target validation and gene functionalization, as well as research tools for identifying and characterizing nucleases and as therapeutics to selectively modulate the expression of genes involved in the pathogenesis of any one of a variety of diseases.

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

Despite the expansion of knowledge since the discovery of antisense technology, there remains an unmet need for antisense compounds with greater efficacy, reduced toxicity and lower cost. Until the present disclosure, high-affinity modifications have not been employed in the design of short antisense compounds for reducing target RNA *in vivo*. This is because of concerns regarding the degree of target specificity that a sequence 15 nucleotides or shorter would have when employed to reduce target in a living system. Previous studies have described that greater specificity, and therefore greater potential for potency, is achieved by antisense compounds between 16 and 20 nucleobases in length.

The present disclosure describes incorporation of chemically-modified high-affinity nucleotides into antisense compounds allows for short antisense compounds about 8-16 nucleobases in length useful in the reduction of target RNAs in animals with increased potency and improved therapeutic index. Thus, provided herein are short antisense compounds comprising high-affinity nucleotide modifications useful for reducing a target RNA *in vivo*. Such short antisense compounds are effective at lower doses than previously described antisense compounds, allowing for a reduction in toxicity and cost of treatment.

SUMMARY

Disclosed herein are short antisense compounds and methods of using said compounds to reduce target RNA expression in cells or tissues. In certain embodiments, provided herein is a method of reducing expression of a target in an animal, comprising administering to the animal a short antisense compound targeted to a nucleic acid of such target. In certain embodiments, shorts antisense compounds are oligonucleotide compounds. In certain embodiments short antisense oligonucleotides are about 8 to 16, preferably 9 to 15, more preferably 9 to 14, more preferably 10 to 14 nucleotides in length and comprises a gap region flanked on each side by a wing, wherein each wing independently consists of 1 to 3 nucleotides. Preferred motifs include but are not limited to wing – deoxy gap –wing motifs selected from 3-10-3, 2-10-3, 2-10-2, 1-10-1, 2-8-2, 1-8-1, 3-6-3 or 1-6-1. In a preferred embodiment, the short antisense oligonucleotide comprise at least one high-affinity modification. In a further embodiment, the high-affinity modification includes chemically-modified high-affinity nucleotides. In a preferred embodiment, each wing independently consists of 1 to 3 high-affinity modified nucleotides. In one embodiment the high affinity modified nucleotides are sugar-modified nucleotides.

In certain embodiments short antisense compounds exhibit greater uptake in the gut as compared to antisense compounds of greater length. Thus, also provided herein are methods of reducing a target in an animal, comprising orally administering the short antisense compounds of the present invention.

In certain embodiments, short antisense compounds are targeted to a nucleic acid encoding a protein selected from ApoB, SGLT2, PCSK9, SOD1, CRP, GCCR, GCGR, DGAT2, PTP1B and PTEN.

Further provided are methods of treating a metabolic disorder in an animal, comprising administering to an animal in need of such therapy a short antisense compound targeted to a nucleic acid involved in regulating glucose metabolism or clearance, lipid metabolism, cholesterol metabolism, or insulin signaling.

Also provided are methods of increasing insulin sensitivity, decreasing blood glucose or decreasing HbA_{1c} in an animal, comprising administering to said animal a short antisense compound targeted to a nucleic acid encoding a target involved in regulating glucose metabolism or clearance, lipid metabolism, cholesterol metabolism, or insulin signaling.

Further provided are methods of decreasing total serum cholesterol, serum LDL, serum VLDL, serum HDL, serum triglycerides, serum apolipoprotein(a) or free fatty acids in an animal, comprising administering to said animal a short antisense compound targeted to a nucleic acid encoding a target that is involved in regulating glucose metabolism or clearance, lipid metabolism, cholesterol metabolism, or insulin signaling, wherein said short antisense compound is 8 to 16 nucleotides in length and comprises a gap region flanked on each side by a wing, wherein each wing independently consists of 1 to 3 high-affinity modified nucleotides.

Certain targets involved in regulating glucose metabolism or clearance, lipid metabolism, cholesterol metabolism, or insulin signaling include, but are not limited to, GCGR and ApoB-100. Thus, provided are short antisense compounds targeting nucleic acids encoding GCGR and ApoB-100 and methods of reducing expression of said targets and/or target nucleic acids in animal. In addition, provided is the use of short antisense compounds targeting nucleic acids encoding GCGR, and ApoB-100 for the treatment of a metabolic or cardiovascular disease or condition.

In certain embodiments, short antisense compounds further comprise a conjugate group. Conjugate groups include, but are not limited to, C_{16} and cholesterol.

In certain embodiments short antisense compounds comprise at least one modified nucleobase, internucleoside linkage or sugar moiety. In certain embodiments, such modified internucleoside linkage is a phosphorothioate internucleoside linkage. In certain embodiments, each internucleoside linkage is a phosphorothioate internucleoside linkage.

In certain embodiments, short antisense compounds comprise at least one high affinity modification. In certain such embodiments, the high-affinity modification is a chemically-modified high-affinity nucleotide. In certain embodiments, chemically-modified high affinity nucleotides are sugar-modified nucleotides. In certain embodiments, at least one of the sugar-modified nucleotides comprises a bridge between the 4' and the 2' position of the sugar. Each of the sugar-modified nucleotides is, independently, in the β-D or α-L sugar conformation. In certain embodiments, each of said high-affinity modified nucleotides confers a T_m of at least 1 to 4 degrees per nucleotide. In certain embodiments, each of said sugar-modified nucleotides comprises a 2'-substituent group that is other than H or OH. Such sugar-modified nucleotides include those having a 4' to 2' bridged bicyclic sugar moiety. In certain embodiments, each of the 2'-substituent groups is, independently, alkoxy, substituted alkoxy, or halogen. In certain embodiments, each of the 2'-substituent groups is $OCH_2CH_2OCH_3$ (2'-MOE).

In certain embodiments, short antisense compounds have one or more sugar-modified nucleotides comprising a bridge between the 4' and 2' position of the sugar, wherein each of said bridges independently comprises from 2 to 4 linked groups independently selected from $-[C(R_1)(R_2)]_n-$, $-C(R_1)=C(R_2)-$, $-C(R_1)=N-$, $-C(=NR_1)-$, $-C(=O)-$, $-C(=S)-$, $-O-$, $-Si(R_1)_2-$, $-S(=O)_x-$ and $-N(R_1)-$;

wherein

x is 0, 1, or 2;

n is 1, 2, 3, or 4;

each R_1 and R_2 is, independently, H, a protecting group, hydroxyl, C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, substituted C_2-C_{12} alkenyl, C_2 The-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.

In one aspect, each of said bridges is, independently, -$[C(R_1)(R_2)]_n$-, -$[C(R_1)(R_2)]_n$-O-, -$C(R_1R_2)$-$N(R_1)$-O- or –$C(R_1R_2)$-O-$N(R_1)$-. In another aspect, each of said bridges is, independently, 4'-$(CH_2)_3$-2', 4'-$(CH_2)_2$-2', 4'-CH_2-O-2', 4'-$(CH_2)_2$-O-2', 4'-CH_2-O-$N(R_1)$-2' and 4'-CH_2-$N(R_1)$-O-2'- wherein each R_1 is, independently, H, a protecting group or C_1-C_{12} alkyl.

In certain embodiments, provided herein are short antisense compounds useful in the reduction of targets and/or target RNAs associated with disease states in animals. In certain embodiments, provided are methods of using the short antisense compounds for reducing expression of a target RNA in an animal. In certain embodiments, provided herein is the use of a short antisense compound in the preparation of a medicament for the treatment of a metabolic disorder in an animal. In certain embodiments, provided herein is the use of a short antisense compound in the preparation of a medicament for increasing insulin sensitivity, decreasing blood glucose or decreasing HbA_{1c} in an animal. Also provided is the use of a short antisense compound in the preparation of a medicament for decreasing total serum cholesterol, serum LDL, serum VLDL, serum HDL, serum triglycerides, serum apolipoprotein(a) or free fatty acids in an animal.

In certain embodiments, short antisense compounds provided herein exhibit equal or increased potency with regard to target RNA knockdown as compared to longer parent antisense oligonucleotide at least 20 nucleotides in length. In certain embodiments, short antisense compounds exhibit a faster onset of action (target RNA reduction) as compared to the parent antisense oligonucleotide. In certain embodiments, increased potency is in the kidney. In certain embodiments, target RNA is predominately expressed in the kidney. In certain embodiments, increased potency is in the liver. In certain embodiments, target RNA is predominately expressed in the liver.

DETAILED DESCRIPTION

It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed. Herein, the use of the singular includes the plural unless specifically stated otherwise. As used herein, the use of "or" means "and/or" unless stated otherwise. Furthermore, the use of the term "including" as well as other forms, such as "includes" and "included", is not limiting. 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 in their entirety for any purpose. US patent application serial nos 10/712,795 and 10/200,710 are hereby expressly incorporated by reference in their entirety for any purpose.

A. Definitions

Unless specific definitions are provided, the nomenclature utilized 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. Standard techniques may be used for chemical synthesis, chemical analysis, pharmaceutical preparation, formulation and delivery, and treatment of subjects. Certain such techniques and procedures may be found for example in "Carbohydrate Modifications in Antisense Research" Edited by Sangvi and Cook, American Chemical Society , Washington D.C., 1994; and "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, Pa., 18th edition, 1990; and which is hereby incorporated by reference for any purpose. Where permitted, all patents, applications, published applications and other publications and sequences from GenBank and other data bases referred to throughout in the disclosure herein are incorporated by reference in their entirety.

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

As used herein, the term "nucleoside" means a glycosylamine comprising a nucleobase and a sugar. Nucleosides includes, but are not limited to, naturally occurring nucleosides, abasic nucleosides, modified nucleosides, and nucleosides having mimetic bases and/or sugar groups.

As used herein, the term "nucleotide" refers to a glycosomine comprising a nucleobase and a sugur having a phosphate group covalently linked to the sugar. Nucleotides may be modified with any of a variety of substituents.

As used herein, the term "nucleobase" refers to the base portion of a nucleoside or nucleotide. A nucleobase may comprise any atom or group of atoms capable of hydrogen bonding to a base of another nucleic acid.

As used herein, the term "heterocyclic base moiety" refers to a nucleobase comprising a heterocycle.

As used herein, the term "deoxyribonucleotide" means a nucleotide having a hydrogen at the 2' position of the sugar portion of the nucleotide. Deoxyribonucleotides may be modified with any of a variety of substituents.

As used herein, the term "ribonucleotide" means a nucleotide having a hydroxy at the 2' position of the sugar portion of the nucleotide. Ribonucleotides may be modified with any of a variety of substituents.

As used herein, the term "oligomeric compound" refers to a polymeric structure comprising two or more sub-structures and capable of hybridizing to a region of a nucleic acid molecule. In certain embodiments, oligomeric compounds are oligonucleosides. In certain embodiments, oligomeric compounds are oligonucleotides. In certain embodiments, oligomeric compounds are antisense compounds. In certain embodiments, oligomeric compounds are antisense oligonucleotides. In certain embodiments, oligomeric compounds are short antisense compounds. In certain embodiments, oligomeric compounds are short antisense oligonucleotides. In certain embodiments, oligomeric compounds are chimeric oligonucleotides.

As used herein, the term "monomer" refers to a single unit of an oligomer. Monomers include, but are not limited to, nucleosides and nucleotides, whether naturally occuring or modified.

As used herein "oligonucleoside" refers to an oligonucleotide in which the internucleoside linkages do not contain a phosphorus atom.

As used herein, the term "oligonucleotide" refers to an oligomeric compound comprising a plurality of linked nucleotides. In certain embodiment, one or more nucleotides of an oligonucleotide is modified. In certain embodiments, an oligonucleotide comprises ribonucleic acid (RNA) or deoxyribonucleic acid (DNA). In certain embodiments, oligonucleotides are composed of naturally- and/or non-naturally-occurring nucleobases, sugars and covalent internucleotide linkages, and may further include non-nucleic acid conjugates.

As used herein "internucleotide linkage" refers to a covalent linkage between adjacent nucleotides.

As used herein, the term "monomeric linkage" refers to a covalent linkage between two monmers. Monomeric linkages include, but are not limited to internucleotide linkages and internucleoside linkages.

As used herein "naturally occuring internucleotide linkage" refers to a 3' to 5' phosphodiester linkage.

As used herein, the term "antisense compound" refers to an oligomeric compound that is at least partially complementary to a target nucleic acid molecule to which it hybridizes. In certain embodiments, an antisense compound modulates (increases or decreases) expression of a target nucleic acid. Antisense compounds include, but are not limited to, compounds that are oligonucleotides, oligonucleosides, oligonucleotide analogs, oligonucleotide mimetics, and chimeric combinations of these. Consequently, while all antisense compounds are oligomeric compounds, not all oligomeric compounds are antisense compounds.

As used herein, the term "antisense oligonucleotide" refers to an antisense compound that is an oligonucleotide.

As used herein, the term "parent antisense oligonucleotide" refers to an oligonucleotide 20 nucleotides in length having a deoxy gap region having ten 2'-deoxyribonucleotides, flanked by a first and a second wing region each having five 2'-O-(2-methoxyethyl) ribonucleotides (a 5-10-5 MOE gapmer) and comprising the sequence of the corresponding short antisense compound to which it is a parent.

As used herein, the term "short antisense compound" refers to an antisense compound about 8, 9, 10, 11, 12, 13, 14, 15 or 16 monomers in length. In certain embodiments, a short antisense compound has at least one high-affinity modification.

As used herein, the term "short antisense oligonucleotide" or refers to an antisense oligonucleotide about 8, 9, 10, 11, 12, 13, 14, 15 or 16 nucleotides in length. In certain embodiments, a short antisense oligonucleotide has at least one high-affinity modification.

As used herein, the term "short gapmer" refers to a short antisense oligonucleotide having a first and a second wing region each independently 1 to 3 nucleotides in length and a gap region 2 to 14 nucleobase in length.

As used herein, the term "motif" refers to the pattern of unmodified and modified nucleotides in a short antisense compound

As used herein, the term "chimeric antisense oligomer" refers to an antisense oligomeric compound, having at least one sugar, nucleobase or internucleoside linkage that is differentially modified as compared to at least on other sugar, nucleobase or internucleoside linkage within the same antisense oligomeric compound. The remainder of the sugars, nucleobases and internucleoside linkages can be independently modified or unmodified, the same or different.

As used herein, the term "chimeric antisense oligonucleotide" refers to an antisense oligonucleotide, having at least one sugar, nucleobase or internucleoside linkage that is differentially modified as compared to at least on other sugar, nucleobase or internucleoside linkage within the same antisense oligonucleotide. The remainder of the sugars, nucleobases and internucleoside linkages can be independently modified or unmodified, the same or different.

As used herein, the term "mixed-backbone antisense oligonucleotide" refers to an antisense oligonucleotide wherein at least one internucleoside linkage of the antisense oligonucleotide is different from at least one other internucleotide linkage of the antisense oligonucleotide.

As used herein, the term "target" refers to a protein, the modulation of which is desired.

As used herein, the term "target gene" refers to a gene encoding a target.

As used herein, the terms "target nucleic acid" and "nucleic acid molecule encoding a target" refer to any nucleic acid molecule the expression or activity of which is capable of being modulated by an antisense compound. Target nucleic acids include, but are not limited to, RNA (including, but not limited to pre-mRNA and mRNA or portions thereof) transcribed from DNA encoding a target, and also cDNA derived from such RNA, and miRNA. For example, the target nucleic acid can be a cellular gene (or mRNA transcribed from the gene) whose expression is associated with a particular disorder or disease state, or a nucleic acid molecule from an infectious agent.

As used herein, the term “targeting” or “targeted to” refers to the association of an antisense compound to a particular target nucleic acid molecule or a particular region of nucleotides within a target nucleic acid molecule.

As used herein, the term “5’ target site” refers to the nucleotide of a target nucleic acid which is complementary to the 5’-most nucleotide of a particular antisense compound.

As used herein, the term “3’ target site” refers to the nucleotide of a target nucleic acid which is complementary to the 3’-most nucleotide of a particular antisense compound.

As used herein, the term “target region,” refers to a portion of a target nucleic acid to which one or more antisense compounds is complementary.

As used herein, the term “target segment” refers to a smaller or sub-portions of a region within a target nucleic acid.

As used herein, the term “nucleobase complementarity” refers to a nucleobase that is capable of base pairing with another nucleobase. For example, in DNA, adenine (A) is complementary to thymine (T). For example, in RNA, adenine (A) is complementary to uracil (U). In certain embodiments, complementary nucleobase refers to a nucleobase of an antisense compound that is capable of base pairing with a nucleobase of its target nucleic acid. For example, if a nucleobase at a certain position of an antisense compound is capable of hydrogen bonding with a nucleobase at a certain position of a target nucleic acid, then the position of hydrogen bonding between the oligonucleotide and the target nucleic acid is considered to be complementary at that nucleobase pair.

As used herein, the term “non-complementary nucleobase” refers to a pair of nucleobases that do not form hydrogen bonds with one another or otherwise support hybridization.

As used herein, the term “complementary” refers to the capacity of an oligomeric compound to hybridize to another oligomeric compound or nucleic acid through nucleobase complementarity. In certain embodiments, an antisense compound and its target are complementary to each other when a sufficient number of corresponding positions in each molecule are occupied by nucleobases that can bond with each other to allow stable association between the antisense compound and the target. One skilled in the art recognizes that the inclusion of mismatches is possible without eliminating the ability of the oligomeric compounds to remain in association. Therefore, described herein are antisense compounds that may comprise up to about 20% nucleotides that are mismatched (i.e., are not nucleobase complementary to the corresponding nucleotides of the target). Preferably the antisense compounds contain no more than about 15%, more preferably not more than about 10%, most preferably not more than 5% or no mismatches. The remaining nucleotides are nucleobase complementary or otherwise do not disrupt hybridization (e.g., universal bases). One of ordinary skill in the art would recognize the compounds provided herein are at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or 100% complementary to a target nucleic acid.

As used herein, the term “mismatch” refers to a non-complementary nucleobase within a complementary oligomeric compound.

As used herein, "hybridization" means the pairing of complementary oligomeric compounds (e.g., an antisense compound and its target nucleic acid). While not limited to a particular mechanism, the most common mechanism of pairing involves hydrogen bonding, which may be Watson-Crick, Hoogsteen or reversed Hoogsteen hydrogen bonding, between complementary nucleoside or nucleotide bases (nucleobases). For example, the natural base adenine is nucleobase complementary to the natural nucleobases thymidine and uracil which pair through the formation of hydrogen bonds. The natural base guanine is nucleobase complementary to the natural bases cytosine and 5-methyl cytosine. Hybridization can occur under varying circumstances.

As used herein, the term “specifically hybridizes” refers to the ability of an oligomeric compound to hybridize to one nucleic acid site with greater affinity than it hybridizes to another nucleic acid site. In certain embodiments, an antisense oligonucleotide specifically hybridizes to more than one target site.

As used herein, “designing” or “designed to” refer to the process of designing an oligomeric compound that specifically hybridizes with a selected nucleic acid molecule.

As used herein, the term "modulation" refers to a perturbation of function or activity when compared to the level of the function or activity prior to modulation. For example, modulation includes the change, either an increase (stimulation or induction) or a decrease (inhibition or reduction) in gene expression. As further example, modulation of expression can include perturbing splice site selection of pre-mRNA processing.

As used herein, the term “expression” refers to all the functions and steps by which a gene’s coded information is converted into structures present and operating in a cell. Such structures include, but are not limited to the products of transcription and translation.

As used herein, “variant” refers to an alternative RNA transcript that can be produced from the same genomic region of DNA. Variants include, but are not limited to “pre-mRNA variants” which are transcripts produced from the same genomic DNA that differ from other transcripts produced from the same genomic DNA in either their start or stop position and contain both intronic and exonic sequence. Variants also include, but are not limited to, those with alternate splice junctions, or alternate initiation and termination codons.

As used herein, “high-affinity modified monomer” refers to a monomer having at least one modified nucleobase, internucleoside linkage or sugar moiety, when compared to naturally occurring monomers, such that the modification increases the affinity of an antisense compound comprising the high-affinity modified monomer to its target nucleic acid. High-affinity modifications include, but are not limited to, monomers (e.g., nucleosides and nucleotides) comprising 2’-modifed sugars.

As used herein, the term “2’-modified” or “2’-substituted” means a sugar comprising substituent at the 2' position other than H or OH. 2'-modified monomers, include, but are not limited to, BNA's and monomers (e.g., nucleosides and nucleotides) with 2'- substituents, such as allyl, amino, azido, thio, O-allyl, O-C_1-C_{10} alkyl, -OCF_3, O-$(CH_2)_2$-O-CH_3, 2'-O$(CH_2)_2SCH_3$, O-$(CH_2)_2$-O-N$(R_m)(R_n)$, or O-CH_2-C(=O)-N$(R_m)(R_n)$, where each R_m and R_n is, independently, H or substituted or unsubstituted C_1-C_{10} alkyl. In certain embodiments, short antisense compounds comprise a 2'modified monomer that does not have the formula 2'-O$(CH_2)_n$H, wherein n is one to six. In certain embodiments, short antisense compounds comprise a 2'modified monomer that does not have the formula 2'-OCH_3. In certain embodiments, short antisense compounds comprise a 2'modified monomer that does not have the formula or, in the alternative, 2'-O$(CH_2)_2OCH_3$.

As used herein, the term "bicyclic nucleic acid" or "BNA" or "bicyclic nucleoside" or "bicyclic nucleotide" refers to a nucleoside or nucleotide wherein the furanose portion of the nucleoside includes a bridge connecting two carbon atoms on the furanose ring, thereby forming a bicyclic ring system.

As used herein, unless otherwise indicated, the term "methyleneoxy BNA" alone refers to β-D-methyleneoxy BNA.

As used herein, the term "MOE" refers to a 2'-methoxyethyl substituent.

As used herein, the term "gapmer" refers to a chimeric oligomeric compound comprising a central region (a "gap") and a region on either side of the central region (the "wings"), wherein the gap comprises at least one modification that is different from that of each wing. Such modifications include nucleobase, monomeric linkage, and sugar modifications as well as the absence of modification (unmodified). Thus, in certain embodiments, the nucleotide linkages in each of the wings are different than the nucleotide linkages in the gap. In certain embodiments, each wing comprises nucleotides with high affinity modifications and the gap comprises nucleotides that do not comprise that modification. In certain embodiments the nucleotides in the gap and the nucleotides in the wings all comprise high affinity modifications, but the high affinity modifications in the gap are different than the high affinity modifications in the wings. In certain embodiments, the modifications in the wings are the same as one another. In certain embodiments, the modifications in the wings are different from each other. In certain embodiments, nucleotides in the gap are unmodified and nucleotides in the wings are modified. In certain embodiments, the modification(s) in each wing are the same. In certain embodiments, the modification(s) in one wing are different from the modification(s) in the other wing. In certain embodiments, short antisense compounds are gapmers having 2'-deoxynucleotides in the gap and nucleotides with high-affinity modifications in the wing.

As used herein, the term "prodrug" refers to a therapeutic agent that is prepared in an inactive form that is converted to an active form (i.e., drug) within the body or cells thereof by the action of endogenous enzymes or other chemicals and/or conditions.

As used herein, the term "pharmaceutically acceptable salts" refers to salts of active compounds that retain the desired biological activity of the active compound and do not impart undesired toxicological effects thereto.

As used herein, the term “cap structure” or “terminal cap moiety” refers to chemical modifications, which have been incorporated at either terminus of an antisense compound.

As used herein, the term “prevention” refers to delaying or forestalling the onset or development of a condition or disease for a period of time from hours to days, preferably weeks to months.

As used herein, the term “amelioration” refers to a lessening of at least one indicator of the severity of a condition or disease. The severity of indicators may be determined by subjective or objective measures which are known to those skilled in the art.

As used herein, the term “treatment” refers to administering a composition of the invention to effect an alteration or improvement of the disease or condition. Prevention, amelioration, and/or treatment may require administration of multiple doses at regular intervals, or prior to onset of the disease or condition to alter the course of the disease or condition. Moreover, a single agent may be used in a single individual for each prevention, amelioration, and treatment of a condition or disease sequentially, or concurrently.

As used herein, the term “pharmaceutical agent” refers to a substance provides a therapeutic benefit when administered to a subject.

As used herein, the term “therapeutically effective amount” refers to an amount of a pharmaceutical agent that provides a therapeutic benefit to an animal.

As used herein, “administering” means providing a pharmaceutical agent to an animal, and includes, but is not limited to administering by a medical professional and self-administering.

As used herein, the term “co-administration” refers to administration of two or more pharmaceutical agents to an animal. The two or more pharmaceutical agents may be in a single pharmaceutical composition, or may be in separate pharmaceutical compositions. Each of the two or more pharmaceutical agents may be administered through the same or different routes of administration. Co-administration encompasses administration in parallel or sequentially.

As used herein, the term “pharmaceutical composition” refers to a mixture of substances suitable for administering to an individual. For example, a pharmaceutical composition may comprise an antisense oligonucleotide and a sterile aqueous solution.

As used herein, the term “individual” refers to a human or non-human animal selected for treatment or therapy.

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

As used herein, the term “subject” refers to an animal, including, but not limited to a human, to whom a pharmaceutical composition is administered.

As used herein, the term “duration” refers to the period of time during which an activity or event continues. In certain embodiments, the duration of treatment is the period of time during which doses of a pharmaceutical agent are administered.

As used herein, the term "parenteral administration," refers to administration through injection or infusion. Parenteral administration includes, but is not limited to, subcutaneous administration, intravenous administration, or intramuscular administration.

As used herein, the term "subcutaneous administration" refers to administration just below the skin. "Intravenous administration" means administration into a vein.

As used herein, the term "dose" refers to a specified quantity of a pharmaceutical agent provided in a single administration. In certain embodiments, a dose may be administered in two or more boluses, tablets, or injections. For example, in certain embodiments, where subcutaneous administration is desired, the desired dose requires a volume not easily accommodated by a single injection. In such embodiments, two or more injections may be used to achieve the desired dose. In certain embodiments, a dose may be administered in two or more injections to minimize injection site reaction in an individual.

As used herein, the term "dosage unit" refers to a form in which a pharmaceutical agent is provided. In certain embodiments, a dosage unit is a vial comprising lyophilized antisense oligonucleotide. In certain embodiments, a dosage unit is a vial comprising reconstituted antisense oligonucleotide.

As used herein, the term "pharmaceutical agent" refers to a substance provides a therapeutic benefit when administered to an individual. For example, in certain embodiments, an antisense oligonucleotide is a pharmaceutical agent.

As used herein, the term "active pharmaceutical ingredient" refers to the substance in a pharmaceutical composition that provides a desired effect.

As used herein, the term "therapeutically effective amount" refers to an amount of a pharmaceutical agent that provides a therapeutic benefit to an individual. In certain embodiments, a therapeutically effective amount of an antisense compound is the amount that needs to be administered to result in an observable benefit.

As used herein, the term "hypercholesterolemia" refers to a condition characterized by elevated serum cholesterol.

As used herein, the term "hyperlipidemia" refers to a condition characterized by elevated serum lipids.

As used herein, the term "hypertriglyceridemia" refers to a condition characterized by elevated triglyceride levels.

As used herein, the term "non-familial hypercholesterolemia" refers to a condition characterized by elevated cholesterol that is not the result of a single inherited gene mutation.

As used herein, the term "polygenic hypercholesterolemia" refers to a condition characterized by elevated cholesterol that results from the influence of a variety of genetic factors. In certain embodiments, polygenic hypercholesterolemia may be exacerbated by dietary intake of lipids.

As used herein, the term "familial hypercholesterolemia (FH)" refers to an autosomal dominant metabolic disorder characterized by a mutation in the LDL-receptor (LDL-R) gene, markedly elevated LDL-C and premature onset of atherosclerosis. A diagnosis of familial hypercholesterolemia is made when a individual meets one or more of the following criteria: genetic testing confirming 2 mutated LDL-receptor genes; genetic testing confirming one mutated LDL-receptor gene; document history of untreated serum LDL-cholesterol greater than 500 mg/dL; tendinous and/or cutaneous xanthoma prior to age 10 years; or, both parents have documented elevated serum LDL-cholesterol prior to lipid-lowering therapy consistent with heterozygous familial hypercholesterolemia.

As used herein, the term "homozygous familial hypercholesterolemia" or "HoFH" refers to a condition characterized by a mutation in both maternal and paternal LDL-R genes.

As used herein, the term "heterozygous familial hypercholesterolemia" or "HeFH" refers to a condition characterized by a mutation in either the maternal or paternal LDL-R gene.

As used herein, the term "mixed dyslipidemia" refers to a condition characterized by elevated serum cholesterol and elevated serum triglycerides.

As used herein, the term "diabetic dyslipidemia" or "Type II diabetes with dyslipidemia" refers to a condition characterized by Type II diabetes, reduced HDL-C, elevated serum triglycerides, and elevated small, dense LDL particles.

As used herein, the term "CHD risk equivalents," refers to indicators of clinical atherosclerotic disease that confer a high risk for coronary heart disease. For example, in certain embodiments, CHD risk equivalents include, without limitation, clinical coronary heart disease, symptomatic carotid artery disease, peripheral arterial disease, and/or abdominal aortic aneurysm.

As used herein, the term "non-alcoholic fatty liver disease (NAFLD)" refers to a condition characterized by fatty inflammation of the liver that is not due to excessive alcohol use (for example, alcohol consumption of over 20 g/day). In certain embodiments, NAFLD is related to insulin resistance and the metabolic syndrome.

As used herein, the term "non-alcoholic steatohepatitis (NASH)" refers to a condition characterized by inflammation and the accumulation of fat and fibrous tissue in the liver, that is not due to excessive alcohol use. NASH is an extreme form of NAFLD.

As used herein, the term "major risk factors" refers to factors that contribute to a high risk for a particular disease or condition. In certain embodiments, major risk factors for coronary heart disease include, without limitation, cigarette smoking, hypertension, low HDL-C, family history of coronary heart disease, and age.

As used herein, the term "CHD risk factors" refers to CHD risk equivalents and major risk factors.

As used herein, the term "coronary heart disease (CHD)" refers to a narrowing of the small blood vessels that supply blood and oxygen to the heart, which is often a result of atherosclerosis.

As used herein, the term “reduced coronary heart disease risk” refers to a reduction in the likelihood that a individual will develop coronary heart disease. In certain embodiments, a reduction in coronary heart disease risk is measured by an improvement in one or more CHD risk factors, for example, a decrease in LDL-C levels.

As used herein, the term “atherosclerosis” refers to a hardening of the arteries affecting large and medium-sized arteries and is characterized by the presence of fatty deposits. The fatty deposits are called "atheromas" or “plaques,” which consist mainly of cholesterol and other fats, calcium and scar tissue, and damage the lining of arteries.

As used herein, the term “history of coronary heart disease” refers to the occurrence of clinically evident coronary heart disease in the medical history of a individual or a individual’s family member.

As used herein, the term “Early onset coronary heart disease” refers to a diagnosis of coronary heart disease prior to age 50.

As used herein, the term “statin intolerant individual” refers to a individual who as a result of statin therapy experiences one or more of creatine kinase increases, liver function test abnormalities, muscle aches, or central nervous system side effects.

As used herein, the term “efficacy” refers to the ability to produce a desired effect. For example, efficacy of a lipid-lowering therapy may be reduction in the concentration of one or more of LDL-C, VLDL-C, IDL-C, non-HDL-C, ApoB, lipoprotein(a), or triglycerides.

As used herein, the term “acceptable safety profile” refers to a pattern of side effects that is within clinically acceptable limits.

As used herein, the term “side effects” refers to physiological responses attributable to a treatment other than desired effects. In certain embodiments, side effects include, without limitation, injection site reactions, liver function test abnormalities, renal function abnormalities, liver toxicity, renal toxicity, central nervous system abnormalities, and myopathies. For example, increased aminotransferase levels in serum may indicate liver toxicity or liver function abnormality. For example, increased bilirubin may indicate liver toxicity or liver function abnormality.

As used herein, the term “injection site reaction” refers to inflammation or abnormal redness of skin at a site of injection in an individual.

As used herein, the term “individual compliance” refers to adherence to a recommended or prescribed therapy by an individual.

As used herein, the term “lipid-lowering therapy” refers to a therapeutic regimen provided to a individual to reduce one or more lipids in a individual. In certain embodiments, a lipid-lowering therapy is provide to reduce one or more of ApoB, total cholesterol, LDL-C, VLDL-C, IDL-C, non-HDL-C, triglycerides, small dense LDL particles, and Lp(a) in an individual.

As used herein, the term "lipid-lowering agent" refers to a pharmaceutical agent provided to a individual to achieve a lowering of lipids in the individual. For example, in certain embodiments, a lipid-lowering agent is provided to an individual to reduce one or more of ApoB, LDL-C, total cholesterol, and triglycerides.

As used herein, the term "LDL-C target" refers to an LDL-C level that is desired following lipid-lowering therapy.

As used herein, the term "comply" refers to the adherence with a recommended therapy by an individual.

As used herein, the term "recommended therapy" refers to a therapeutic regimen recommended by a medical professional for the treatment, amelioration, or prevention of a disease.

As used herein, the term "low LDL-receptor activity" refers to LDL-receptor activity that is not sufficiently high to maintain clinically acceptable levels of LDL-C in the bloodstream.

As used herein, the term "cardiovascular outcome" refers to the occurrence of major adverse cardiovascular events.

As used herein, the term "improved cardiovascular outcome" refers to a reduction in the occurrence of major adverse cardiovascular events, or the risk thereof. Examples of major adverse cardiovascular events include, without limitation, death, reinfarction, stroke, cardiogenic shock, pulmonary edema, cardiac arrest, and atrial dysrhythmia.

As used herein, the term "surrogate markers of cardiovascular outcome" refers to indirect indicators of cardiovascular events, or the risk thereof. For example, surrogate markers of cardiovascular outcome include carotid intimal media thickness (CIMT). Another example of a surrogate marker of cardiovascular outcome includes atheroma size. Atheroma size may be determined by intravascular ultrasound (IVUS).

As used herein, the term "increased HDL-C" refers to an increase in serum HDL-C in an individual over time.

As used herein, the term "lipid-lowering" refers to a reduction in one or more serum lipids in an individual over time.

As used herein, the term "metabolic disorder" refers to a condition characterized by an alteration or disturbance in metabolic function. "Metabolic" and "metabolism" are terms well know in the art and generally include the whole range of biochemical processes that occur within a living organism. Metabolic disorders include, but are not limited to, hyperglycemia, prediabetes, diabetes (type I and type II), obesity, insulin resistance and metabolic syndrome.

As used herein, the term "metabolic syndrome" refers to a clustering of lipid and non-lipid cardiovascular risk factors of metabolic origin. It has been closely linked to the generalized metabolic disorder known as insulin resistance. The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATPIII) established criteria for diagnosis of metabolic syndrome when three or more of five risk determinants are present. The five risk determinants are abdominal obesity defined as waist circumference of greater than 102 cm for men or greater than 88cm for women, triglyceride levels greater than or equal to 150 mg/dL, HDL cholesterol levels of less than 40 mg/dL for men and less than 50 mg/dL for women, blood pressure greater than or equal to 130/85 mm Hg and fasting glucose levels greater than or equal to 110 mg/dL. These determinants can be readily measured in clinical practice (JAMA, 2001, 285: 2486-2497).

The term "alkyl," as used herein, refers to a saturated straight or branched hydrocarbon radical containing up to twenty four carbon atoms. Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl, butyl, isopropyl, n-hexyl, octyl, decyl, dodecyl and the like. Alkyl groups typically include from 1 to about 24 carbon atoms, more typically from 1 to about 12 carbon atoms (C_1-C_{12} alkyl) with from 1 to about 6 carbon atoms being more preferred. The term "lower alkyl" as used herein includes from 1 to about 6 carbon atoms. Alkyl groups as used herein may optionally include one or more further substituent groups.

The term "alkenyl," as used herein, refers to a straight or branched hydrocarbon chain radical containing up to twenty four carbon atoms and having at least one carbon-carbon double bond. Examples of alkenyl groups include, but are not limited to, ethenyl, propenyl, butenyl, 1-methyl-2-buten-1-yl, dienes such as 1,3-butadiene and the like. Alkenyl groups typically include from 2 to about 24 carbon atoms, more typically from 2 to about 12 carbon atoms with from 2 to about 6 carbon atoms being more preferred. Alkenyl groups as used herein may optionally include one or more further substituent groups.

The term "alkynyl," as used herein, refers to a straight or branched hydrocarbon radical containing up to twenty four carbon atoms and having at least one carbon-carbon triple bond. Examples of alkynyl groups include, but are not limited to, ethynyl, 1-propynyl, 1-butynyl, and the like. Alkynyl groups typically include from 2 to about 24 carbon atoms, more typically from 2 to about 12 carbon atoms with from 2 to about 6 carbon atoms being more preferred. Alkynyl groups as used herein may optionally include one or more further substitutent groups.

The term "aminoalkyl" as used herein, refers to an amino substituted alkyl radical. This term is meant to include C_1-C_{12} alkyl groups having an amino substituent at any position and wherein the alkyl group attaches the aminoalkyl group to the parent molecule. The alkyl and/or amino portions of the aminoalkyl group can be further substituted with substituent groups.

The term "aliphatic," as used herein, refers to a straight or branched hydrocarbon radical containing up to twenty four carbon atoms wherein the saturation between any two carbon atoms is a single, double or triple bond. An aliphatic group preferably contains from 1 to about 24 carbon atoms, more typically from 1 to about 12 carbon atoms with from 1 to about 6 carbon atoms being more preferred. The straight or branched chain of an aliphatic group may be interrupted with one or more heteroatoms that include nitrogen, oxygen, sulfur and phosphorus. Such aliphatic groups interrupted by heteroatoms include without limitation polyalkoxys, such as polyalkylene glycols, polyamines, and polyimines. Aliphatic groups as used herein may optionally include further substituent groups.

The term "alicyclic" or "alicyclyl" refers to a cyclic ring system wherein the ring is aliphatic. The ring system can comprise one or more rings wherein at least one ring is aliphatic. Preferred alicyclics include rings having from about 5 to about 9 carbon atoms in the ring. Alicyclic as used herein may optionally include further substituent groups.

The term "alkoxy," as used herein, refers to a radical formed between an alkyl group and an oxygen atom wherein the oxygen atom is used to attach the alkoxy group to a parent molecule. Examples of alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, *n*-butoxy, sec-butoxy, *tert*-butoxy, n-pentoxy, neopentoxy, n-hexoxy and the like. Alkoxy groups as used herein may optionally include further substituent groups.

The terms "halo" and "halogen," as used herein, refer to an atom selected from fluorine, chlorine, bromine and iodine.

The terms "aryl" and "aromatic," as used herein, refer to a mono- or polycyclic carbocyclic ring system radicals having one or more aromatic rings. Examples of aryl groups include, but are not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, idenyl and the like. Preferred aryl ring systems have from about 5 to about 20 carbon atoms in one or more rings. Aryl groups as used herein may optionally include further substituent groups.

The terms "aralkyl" and "arylalkyl," as used herein, refer to a radical formed between an alkyl group and an aryl group wherein the alkyl group is used to attach the aralkyl group to a parent molecule. Examples include, but are not limited to, benzyl, phenethyl and the like. Aralkyl groups as used herein may optionally include further substituent groups attached to the alkyl, the aryl or both groups that form the radical group.

The term "heterocyclic radical" as used herein, refers to a radical mono-, or poly-cyclic ring system that includes at least one heteroatom and is unsaturated, partially saturated or fully saturated, thereby including heteroaryl groups. Heterocyclic is also meant to include fused ring systems wherein one or more of the fused rings contain at least one heteroatom and the other rings can contain one or more heteroatoms or optionally contain no heteroatoms. A heterocyclic group typically includes at least one atom selected from sulfur, nitrogen or oxygen. Examples of heterocyclic groups include, [1,3]dioxolane, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl, tetrahydrofuryl and the like. Heterocyclic groups as used herein may optionally include further substituent groups.

The terms "heteroaryl," and "heteroaromatic," as used herein, refer to a radical comprising a mono- or poly-cyclic aromatic ring, ring system or fused ring system wherein at least one of the rings is aromatic and includes one or more heteroatom. Heteroaryl is also meant to include fused ring systems including systems where one or more of the fused rings contain no heteroatoms. Heteroaryl groups typically include one ring atom selected from sulfur, nitrogen or oxygen. Examples of heteroaryl groups include, but are not limited to, pyridinyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isooxazolyl, thiadiazolyl, oxadiazolyl, thiophenyl, furanyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzooxazolyl, quinoxalinyl, and the like. Heteroaryl radicals can be attached to a parent molecule directly or through a linking moiety such as an aliphatic group or hetero atom. Heteroaryl groups as used herein may optionally include further substitutent groups.

The term "heteroarylalkyl," as used herein, refers to a heteroaryl group as previously defined having an alky radical that can attach the heteroarylalkyl group to a parent molecule. Examples include, but are not limited to, pyridinylmethyl, pyrimidinylethyl, napthyridinylpropyl and the like. Heteroarylalkyl groups as used herein may optionally include further substitutent groups on one or both of the heteroaryl or alkyl portions.

The term "mono or poly cyclic structure" as used in the present invention includes all ring systems that are single or polycyclic having rings that are fused or linked and is meant to be inclusive of single and mixed ring systems individually selected from aliphatic, alicyclic, aryl, heteroaryl, aralkyl, arylalkyl, heterocyclic, heteroaryl, heteroaromatic, heteroarylalkyl. Such mono and poly cyclic structures can contain rings that are uniform or have varying degrees of saturation including fully saturated, partially saturated or fully unsaturated. Each ring can comprise ring atoms selected from C, N, O and S to give rise to heterocyclic rings as well as rings comprising only C ring atoms which can be present in a mixed motif such as for example benzimidazole wherein one ring has only carbon ring atoms and the fused ring has two nitrogen atoms. The mono or poly cyclic structures can be further substituted with substituent groups such as for example phthalimide which has two =O groups attached to one of the rings. In another aspect, mono or poly cyclic structures can be attached to a parent molecule directly through a ring atom, through a substituent group or a bifunctional linking moiety.

The term "acyl," as used herein, refers to a radical formed by removal of a hydroxyl group from an organic acid an d has the general formula -C(O)-X where X is typically aliphatic, alicyclic or aromatic. Examples include aliphatic carbonyls, aromatic carbonyls, aliphatic sulfonyls, aromatic sulfinyls, aliphatic sulfinyls, aromatic phosphates, aliphatic phosphates and the like. Acyl groups as used herein may optionally include further substitutent groups.

The term "hydrocarbyl" includes groups comprising C, O and H. Included are straight, branched and cyclic groups having any degree of saturation. Such hydrocarbyl groups can include one or more heteroatoms selected from N, O and S and can be further mono or poly substituted with one or more substituent groups.

The terms "substituent" and "substituent group," as used herein, include groups that are typically added to other groups or parent compounds to enhance desired properties or give desired effects. Substituent groups can be protected or unprotected and can be added to one available site or to many available sites in a parent compound. Substituent groups may also be further substituted with other substituent groups and may be attached directly or via a linking group such as an alkyl or hydrocarbyl group to a parent compound. Such groups include without limitation, halogen, hydroxyl, alkyl, alkenyl, alkynyl, acyl (-C(O)R_{aa}), carboxyl (-C(O)O-R_{aa}), aliphatic groups, alicyclic groups, alkoxy, substituted oxo (-O-R_{aa}), aryl, aralkyl, heterocyclic, heteroaryl, heteroarylalkyl, amino (-N$R_{bb}R_{cc}$), imino(=NR_{bb}), amido (-C(O)N$R_{bb}R_{cc}$or -N(R_{bb})C(O)R_{aa}), azido (-N_3), nitro (-NO_2), cyano (-CN), carbamido (-OC(O)N$R_{bb}R_{cc}$ or -N(R_{bb})C(O)OR_{aa}), ureido (-N(R_{bb})C(O)N$R_{bb}R_{cc}$), thioureido (-N(R_{bb})C(S)N$R_{bb}R_{cc}$), guanidinyl (-N(R_{bb})C(=NR_{bb})N$R_{bb}R_{cc}$), amidinyl (-C(=NR_{bb})N$R_{bb}R_{cc}$ or -N(R_{bb})C(NR_{bb})R_{aa}), thiol (-SR_{bb}), sulfinyl (-S(O)R_{bb}), sulfonyl (-S(O)$_2R_{bb}$), sulfonamidyl (-S(O)$_2$N$R_{bb}R_{cc}$ or -N(R_{bb})S(O)$_2R_{bb}$) and conjugate groups. Wherein each R_{aa}, R_{bb} and R_{cc} is, independently, H, an optionally linked chemical functional group or a further substituent group with a preferred list including without limitation H, alkyl, alkenyl, alkynyl, aliphatic, alkoxy, acyl, aryl, aralkyl, heteroaryl, alicyclic, heterocyclic and heteroarylalkyl.

B. Certain Oligomeric Compounds

In certain embodiments, it is desirable to chemically modify oligomeric compounds, compared to naturally occuring oligomers, such as DNA or RNA. Certain such modifications alter the activity of the oligomeric compound. Certain such chemical modifications can alter activity by, for example: increasing affinity of an antisense compound for its target nucleic acid, increasing its resistance to one or more nucleases, and/or altering the pharmacokinetics or tissue distribution of the oligomeric compound. In certain instances, the use of chemistries that increase the affinity of an oligomeric compound for its target can allow for the use of shorter oligomeric compounds.

1. Certain monomers

In certain embodiment, oligomeric compounds comprise one or more modified monomer. In certain such embodiments, oligomeric compounds comprise one or more high affinity monomer. In certain embodiments, such high-affinity monomer is selected from monomers (e.g., nucleosides and nucleotides) comprising 2'-modifed sugars, including, but not limited to: BNA's and monomers (e.g., nucleosides and nucleotides) with 2'- substituents such as allyl, amino, azido, thio, O-allyl, O-C_1-C_{10} alkyl, -OCF_3, O-$(CH_2)_2$-O-CH_3, 2'-O$(CH_2)_2SCH_3$, O-$(CH_2)_2$-O-N(R_m)(R_n), or O-CH_2-C(=O)-N(R_m)(R_n), where each R_m and R_n is, independently, H or substituted or unsubstituted C_1-C_{10} alkyl.

In certain embodiments, the oligomeric compounds including, but no limited to short antisense compounds of the present invention, comprise one or more high affinity monomers provided that the oligomeric compound does not comprise a nucleotide comprising a 2'-O$(CH_2)_n$H, wherein n is one to six.

In certain embodiments, the oligomeric compounds including, but no limited to short antisense compounds of the present invention, comprise one or more high affinity monomer provided that the oligomeric compound does not comprise a nucleotide comprising a 2'-OCH_3 or a 2'-O$(CH_2)_2OCH_3$.

In certain embodiments, the oligomeric compounds including, but no limited to short antisense compounds of the present invention, comprise one or more high affinity monomer provided that the oligomeric compound does not comprise a α-L-Methyleneoxy (4'-CH_2-O-2') BNA.

In certain embodiments, the oligomeric compounds including, but no limited to short antisense compounds of the present invention, comprise one or more high affinity monomer provided that the oligomeric compound does not comprise a β-D-Methyleneoxy (4'-CH_2-O-2') BNA.

In certain embodiments, the oligomeric compounds including, but no limited to short antisense compounds of the present invention, comprise one or more high affinity monomer provided that the oligomeric compound does not comprise a α-L-Methyleneoxy (4'-CH_2-O-2') BNA or a β-D-Methyleneoxy (4'-CH_2-O-2') BNA.

a. Certain Nucleobases

The naturally occurring base portion of a nucleoside is typically a heterocyclic base. The two most common classes of such heterocyclic bases are the purines and the pyrimidines. For those nucleosides that include a pentofuranosyl sugar, a phosphate group can be linked to the 2', 3' or 5' hydroxyl moiety of the sugar. In forming oligonucleotides, those phosphate groups covalently link adjacent nucleosides to one another to form a linear polymeric compound. Within oligonucleotides, the phosphate groups are commonly referred to as forming the internucleotide backbone of the oligonucleotide. The naturally occurring linkage or backbone of RNA and of DNA is a 3' to 5' phosphodiester linkage.

In addition to "unmodified" or "natural" nucleobases such as the purine nucleobases adenine (A) and guanine (G), and the pyrimidine nucleobases thymine (T), cytosine (C) and uracil (U), many modified nucleobases or nucleobase mimetics known to those skilled in the art are amenable with the compounds described herein. In certain embodiments, a modified nucleobase is a nucleobase that is fairly similar in structure to the parent nucleobase, such as for example a 7-deaza purine, a 5-methyl cytosine, or a G-clamp. In certain embodiments, nucleobase mimetic include more complicated structures, such as for example a tricyclic phenoxazine nucleobase mimetic. Methods for preparation of the above noted modified nucleobases are well known to those skilled in the art.

b. Certain sugars

Oligomeric compounds provided herein may comprise one or more monomer, including a nucleoside or nucleotide, having a modified sugar moiety. For example, the furanosyl sugar ring of a nucleoside can be modified in a number of ways including, but not limited to, addition of a substituent group, bridging of two non-geminal ring atoms to form a bicyclic nucleic acid (BNA).

In certain embodiments, oligomeric compounds comprise one or more monomers that is a BNA. In certain such embodiments, BNA s include, but are not limited to, (A) α-L-Methyleneoxy (4'-CH_2-O-2') BNA , (B) β-D-Methyleneoxy (4'-CH_2-O-2') BNA , (C) Ethyleneoxy (4'-$(CH_2)_2$-O-2') BNA , (D) Aminooxy (4'-CH_2-O-N(R)-2') BNA and (E) Oxyamino (4'-CH_2-N(R)-O-2') BNA, as depicted in Figure 1.

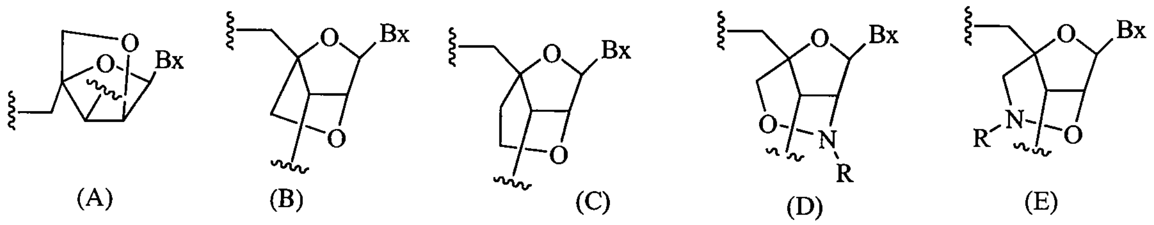


Figure 1. Certain BNA Structures

In certain embodimnents, BNA compounds include, but are not limited to, compounds having at least one bridge between the 4' and the 2' position of the sugar wherein each of the bridges independently comprises 1 or from 2 to 4 linked groups independently selected from $-[C(R_1)(R_2)]_n-$, $-C(R_1)=C(R_2)-$, $-C(R_1)=N-$, $-C(=NR_1)-$, -C(=O)-, -C(=S)-, -O-, $-Si(R_1)_2-$, $-S(=O)_x-$ and $-N(R_1)-$;

wherein:

x is 0, 1, or 2;

n is 1, 2, 3, or 4;

each R_1 and R_2 is, independently, H, a protecting group, hydroxyl, C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, substituted C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, substituted C_2-C_{12} alkynyl, C_5-C_{20} aryl, substituted C_5-C_{20} aryl, 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.

In one embodiment, each of the bridges of the BNA compounds is, independently, $-[C(R_1)(R_2)]_n-$, $-[C(R_1)(R_2)]_n-O-$, $-C(R_1R_2)-N(R_1)-O-$ or $-C(R_1R_2)-O-N(R_1)-$. In another embodiment, each of said bridges is, independently, 4'-CH_2-2', 4'-$(CH_2)_2$-2', 4'-$(CH_2)_3$-2', 4'-CH_2-O-2', 4'-$(CH_2)_2$-O-2', 4'-CH_2-O-N(R_1)-2' and 4'-CH_2-N(R_1)-O-2'- wherein each R_1 is, independently, H, a protecting group or C_1-C_{12} alkyl.

Certain BNA's have been prepared and disclosed in the patent literature as well as in scientific literature (Singh et al., Chem. Commun., 1998, 4, 455-456; Koshkin et al., Tetrahedron, 1998, 54, 3607-3630; Wahlestedt et al., Proc. Natl. Acad. Sci. U. S. A., 2000, 97, 5633-5638; Kumar et al., Bioorg. Med. Chem. Lett., 1998, 8, 2219-2222; WO 94/14226; WO 2005/021570; Singh et al., J. Org. Chem., 1998, 63, 10035-10039; Examples of issued US patents and published applications that disclose BNA s include, for example, U.S. Patent Nos. 7,053,207; 6,268,490; 6,770,748; 6,794,499; 7,034,133; and 6,525,191; and U.S. Pre-Grant Publication Nos. 2004-0171570; 2004-0219565; 2004-0014959; 2003-0207841; 2004-0143114;

and 20030082807.

Also provided herein are BNAs in which the 2'-hydroxyl group of the ribosyl sugar ring is linked to the 4' carbon atom of the sugar ring thereby forming a methyleneoxy (4'-CH_2-O-2') linkage to form the bicyclic sugar moiety (reviewed in Elayadi *et al., Curr. Opinion Invens. Drugs,* 2001, 2, 558-561; Braasch *et al., Chem. Biol.,* 2001, *8* 1-7; and Orum *et al., Curr. Opinion Mol. Ther.,* 2001, *3*, 239-243; see also U.S. Patents: 6,268,490 and 6,670,461). The linkage can be a methylene (-CH_2-) group bridging the 2' oxygen atom and the 4' carbon atom, for which the term methyleneoxy (4'-CH_2-O-2') BNA is used for the bicyclic moiety; in the case of an ethylene group in this position, the term ethyleneoxy (4'-CH_2CH_2-O-2') BNA is used (Singh et al., Chem. Commun., 1998, 4, 455-456: Morita *et al., Bioorganic Medicinal Chemistry,* 2003, *11*, 2211-2226). Methyleneoxy (4'-CH_2-O-2') BNA and other bicyclic sugar analogs display very high duplex thermal stabilities with complementary DNA and RNA (Tm = +3 to +10° C), stability towards 3'-exonucleolytic degradation and good solubility properties. Potent and nontoxic antisense oligonucleotides compriseing BNAs have been described (Wahlestedt et al., *Proc. Natl. Acad. Sci. U. S. A.*, 2000, 97, 5633-5638).

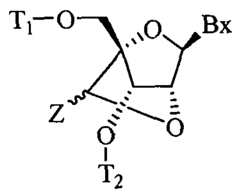
An isomer of methyleneoxy (4'-CH_2-O-2') BNA that has also been discussed is alpha-L-methyleneoxy (4'-CH_2-O-2') BNA which has been shown to have superior stability against a 3'-exonuclease. The alpha-L- methyleneoxy (4'-CH_2-O-2') BNA's were incorporated into antisense gapmers and chimeras that showed potent antisense activity (Frieden *et al., Nucleic Acids Research,* **2003**, *21*, 6365-6372).

The synthesis and preparation of the methyleneoxy (4'-CH_2-O-2') BNA monomers adenine, cytosine, guanine, 5-methyl-cytosine, thymine and uracil, along with their oligomerization, and nucleic acid recognition properties have been described (Koshkin et al., Tetrahedron, 1998, 54, 3607-3630). BNAs and preparation thereof are also described in WO 98/39352 and WO 99/14226.

Analogs of methyleneoxy (4'-CH_2-O-2') BNA, phosphorothioate- methyleneoxy (4'-CH_2-O-2') BNA and 2'-thio-BNAs, have also been prepared (Kumar et al., Bioorg. Med. Chem. Lett., 1998, 8, 2219-2222). Preparation of locked nucleoside analogs compriseing oligodeoxyribonucleotide duplexes as substrates for nucleic acid polymerases has also been described (Wengel et al., WO 99/14226). Furthermore, synthesis of 2'-amino-BNA, a novel comformationally restricted high-affinity oligonucleotide analog has been described in the art (Singh et al., J. Org. Chem., 1998, 63, 10035-10039). In addition, 2'-Amino- and 2'-methylamino-BNA's have been prepared and the thermal stability of their duplexes with complementary RNA and DNA strands has been previously reported.

Modified sugar moieties are well known and can be used to alter, typically increase, the affinity of the antisense compound for its target and/or increase nuclease resistance. A representative list of preferred modified sugars includes but is not limited to bicyclic modified sugars (BNA's), including methyleneoxy (4'-CH_2-O-2') BNA and ethyleneoxy (4'-$(CH_2)_2$-O-2' bridge) BNA ; substituted sugars, especially 2'-substituted sugars having a 2'-F, 2'-OCH_3 or a 2'-$O(CH_2)_2$-OCH_3 substituent group; and 4'-thio modified sugars. Sugars can also be replaced with sugar mimetic groups among others. Methods for the preparations of modified sugars are well known to those skilled in the art. Some representative patents and publications that teach the preparation of such modified sugars include, but are not limited to, U.S. Patents: 4,981,957; 5,118,800; 5,319,080; 5,359,044; 5,393,878; 5,446,137; 5,466,786; 5,514,785; 5,519,134; 5,567,811; 5,576,427; 5,591,722; 5,597,909; 5,610,300; 5,627,053; 5,639,873; 5,646,265; 5,658,873; 5,670,633; 5,792,747; 5,700,920; 6,531,584; and 6,600,032; and WO 2005/121371.

In certain embodiments, BNA's include bicyclic nucleoside having the formula:



wherein:

Bx is a heterocyclic base moiety;

T_1 is H or a hydroxyl protecting group;

T_2 is H, a hydroxyl protecting group or a reactive phosphorus group;

Z is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, substituted C_1-C_6 alkyl, substituted C_2-C_6 alkenyl, substituted C_2-C_6 alkynyl, acyl, substituted acyl, or substituted amide.

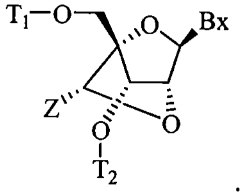
In one embodiment, each of the substituted groups, is, independently, mono or poly substituted with optionally protected substituent groups independently selected from halogen, oxo, hydroxyl, OJ_1, NJ_1J_2, SJ_1, N_3, $OC(=X)J_1$, $OC(=X)NJ_1J_2$, $NJ_3C(=X)NJ_1J_2$ and CN, wherein each J_1, J_2 and J_3 is, independently, H or C_1-C_6 alkyl, and X is O, S or NJ_1.

In certain such embodiments, each of the substituted groups, is, independently, mono or poly substituted with substituent groups independently selected from halogen, oxo, hydroxyl, OJ_1, NJ_1J_2, SJ_1, N_3, $OC(=X)J_1$, and $NJ_3C(=X)NJ_1J_2$, wherein each J_1, J_2 and J_3 is, independently, H, C_1-C_6 alkyl, or substituted C_1-C_6 alkyl and X is O or NJ_1.

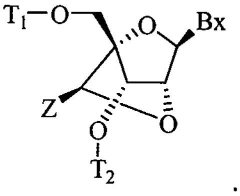
In certain embodiments, the Z group is C_1-C_6 alkyl substituted with one or more X^x, wherein each X^x is independently OJ_1, NJ_1J_2, SJ_1, N_3, $OC(=X)J_1$, $OC(=X)NJ_1J_2$, $NJ_3C(=X)NJ_1J_2$ or CN; wherein each J_1, J_2 and J_3 is, independently, H or C_1-C_6 alkyl, and X is O, S or NJ_1. In another embodiment, the Z group is C_1-C_6 alkyl substituted with one or more X^x, wherein each X^x is independently halo (e.g., fluoro), hydroxyl, alkoxy (e.g., CH_3O-), substituted alkoxy or azido.

In certain embodiments, the Z group is $-CH_2X^x$, wherein X^x is OJ_1, NJ_1J_2, SJ_1, N_3, $OC(=X)J_1$, $OC(=X)NJ_1J_2$, $NJ_3C(=X)NJ_1J_2$ or CN; wherein each J_1, J_2 and J_3 is, independently, H or C_1-C_6 alkyl, and X is O, S or NJ_1. In another embodiment, the Z group is $-CH_2X^x$, wherein X^x is halo (e.g., fluoro), hydroxyl, alkoxy (e.g., CH_3O-) or azido.

In certain such embodiments, the Z group is in the (*R*)-configuration:



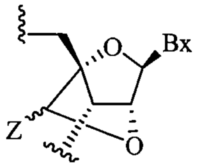
In certain such embodiments, the Z group is in the (*S*)-configuration:



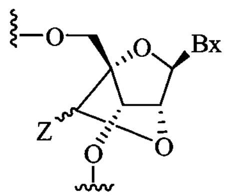
In certain embodiments, each T_1 and T_2 is a hydroxyl protecting group. A preferred list of hydroxyl protecting groups includes benzyl, benzoyl, 2,6-dichlorobenzyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, mesylate, tosylate, dimethoxytrityl (DMT), 9-phenylxanthine-9-yl (Pixyl) and 9-(p-methoxyphenyl)xanthine-9-yl (MOX). In certain embodiments, T_1 is a hydroxyl protecting group selected from acetyl, benzyl, t-butyldimethylsilyl, t-butyldiphenylsilyl and dimethoxytrityl wherein a more preferred hydroxyl protecting group is T_1 is 4,4'-dimethoxytrityl.

In certain embodiments, T_2 is a reactive phosphorus group wherein preferred reactive phosphorus groups include diisopropylcyanoethoxy phosphoramidite and H-phosphonate. In certain embodiments T_1 is 4,4'-dimethoxytrityl and T_2 is diisopropylcyanoethoxy phosphoramidite.

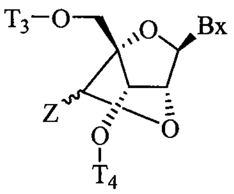
In certain embodiments, oligomeric compounds have at least one monomer of the formula:



or of the formula:



or of the formula:



wherein

Bx is a heterocyclic base moiety;

T_3 is H, a hydroxyl protecting group, a linked conjugate group or an internucleoside linking group attached to a nucleoside, a nucleotide, an oligonucleoside, an oligonucleotide, a monomeric subunit or an oligomeric compound;

T_4 is H, a hydroxyl protecting group, a linked conjugate group or an internucleoside linking group attached to a nucleoside, a nucleotide, an oligonucleoside, an oligonucleotide, a monomeric subunit or an oligomeric compound;

wherein at least one of T_3 and T_4 is an internucleoside linking group attached to a nucleoside, a nucleotide, an oligonucleoside, an oligonucleotide, a monomeric subunit or an oligomeric compound; and

Z is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, substituted C_1-C_6 alkyl, substituted C_2-C_6 alkenyl, substituted C_2-C_6 alkynyl, acyl, substituted acyl, or substituted amide.

In one embodiment, each of the substituted groups, is, independently, mono or poly substituted with optionally protected substituent groups independently selected from halogen, oxo, hydroxyl, OJ_1, 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 each J_1, J_2 and J_3 is, independently, H or C_1-C_6 alkyl, and X is O, S or NJ_1.

In one embodiment, each of the substituted groups, is, independently, mono or poly substituted with substituent groups independently selected from halogen, oxo, hydroxyl, OJ_1, NJ_1J_2, SJ_1, N_3, $OC(=X)J_1$, and $NJ_3C(=X)NJ_1J_2$, wherein each J_1, J_2 and J_3 is, independently, H or C_1-C_6 alkyl, and X is O or NJ_1.

In certain such embodiments, at least one Z is C_1-C_6 alkyl or substituted C_1-C_6 alkyl. In certain embodiments, each Z is, independently, C_1-C_6 alkyl or substituted C_1-C_6 alkyl. In certain embodiments, at least one Z is C_1-C_6 alkyl. In certain embodiments, each Z is, independently, C_1-C_6 alkyl. In certain embodiments, at least one Z is methyl. In certain embodiments, each Z is methyl. In certain embodiments, at least one Z is ethyl. In certain embodiments, each Z is ethyl. In certain embodiments, at least one Z is substituted C_1-C_6 alkyl. In certain embodiments, each Z is, independently, substituted C_1-C_6 alkyl. In certain embodiments, at least one Z is substituted methyl. In certain embodiments, each Z is substituted methyl. In certain embodiments, at least one Z is substituted ethyl. In certain embodiments, each Z is substituted ethyl.

In certain embodiments, at least one substituent group is C_1-C_6 alkoxy (e.g., at least one Z is C_1-C_6 alkyl substituted with one or more C_1-C_6 alkoxy). In another embodiment, each substituent group is, independently, C_1-C_6 alkoxy (e.g., each Z is, independently, C_1-C_6 alkyl substituted with one or more C_1-C_6 alkoxy).

In certain embodiments, at least one C_1-C_6 alkoxy substituent group is CH_3O- (e.g., at least one Z is CH_3OCH_2-). In another embodiment, each C_1-C_6 alkoxy substituent group is CH_3O- (e.g., each Z is CH_3OCH_2-).

In certain embodiments, at least one substituent group is halogen (e.g., at least one Z is C_1-C_6 alkyl substituted with one or more halogen). In certain embodiments, each substituent group is, independently, halogen (e.g., each Z is, independently, C_1-C_6 alkyl substituted with one or more halogen). In certain embodiments, at least one halogen substituent group is fluoro (e.g., at least one Z is CH_2FCH_2-, CHF_2CH_2- or CF_3CH_2-). In certain embodiments, each halo substituent group is fluoro (e.g., each Z is, independently, CH_2FCH_2-, CHF_2CH_2- or CF_3CH_2-).

In certain embodiments, at least one substituent group is hydroxyl (e.g., at least one Z is C_1-C_6 alkyl substituted with one or more hydroxyl). In certain embodiments, each substituent group is, independently, hydroxyl (e.g., each Z is, independently, C_1-C_6 alkyl substituted with one or more hydroxyl). In certain embodiments, at least one Z is $HOCH_2$-. In another embodiment, each Z is $HOCH_2$-.

In certain embodiments, at least one Z is CH_3-, CH_3CH_2-, CH_2OCH_3-, CH_2F- or $HOCH_2$-. In certain embodiments, each Z is, independently, CH_3-, CH_3CH_2-, CH_2OCH_3-, CH_2F- or $HOCH_2$-.

In certain embodiments, at least one Z group is C_1-C_6 alkyl substituted with one or more X^x, wherein each X^x is, independently, OJ_1, NJ_1J_2, SJ_1, N_3, $OC(=X)J_1$, $OC(=X)NJ_1J_2$, $NJ_3C(=X)NJ_1J_2$ or CN; wherein each J_1, J_2 and J_3 is, independently, H or C_1-C_6 alkyl, and X is O, S or NJ_1. In another embodiment, at least one Z group is C_1-C_6 alkyl substituted with one or more X^x, wherein each X^x is, independently, halo (e.g., fluoro), hydroxyl, alkoxy (e.g., CH_3O-) or azido.

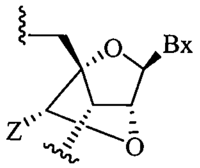
In certain embodiments, each Z group is, independently, C_1-C_6 alkyl substituted with one or more X^x, wherein each X^x is independently OJ_1, NJ_1J_2, SJ_1, N_3, $OC(=X)J_1$, $OC(=X)NJ_1J_2$, $NJ_3C(=X)NJ_1J_2$ or CN; wherein each J_1, J_2 and J_3 is, independently, H or C_1-C_6 alkyl, and X is O, S or NJ_1. In another embodiment, each Z group is, independently, C_1-C_6 alkyl substituted with one or more X^x, wherein each X^x is independently halo (e.g., fluoro), hydroxyl, alkoxy (e.g., CH_3O-) or azido.

In certain embodiments, at least one Z group is –CH_2X^x, wherein X^x is OJ_1, NJ_1J_2, SJ_1, N_3, $OC(=X)J_1$, $OC(=X)NJ_1J_2$, $NJ_3C(=X)NJ_1J_2$ or CN; wherein each J_1, J_2 and J_3 is, independently, H or C_1-C_6 alkyl, and X is O, S or NJ_1 In certain embodiments, at least one Z group is –CH_2X^x, wherein X^x is halo (e.g., fluoro), hydroxyl, alkoxy (e.g., CH_3O-) or azido.

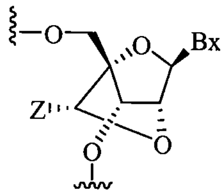
In certain embodiments, each Z group is, independently, –CH_2X^x, wherein each X^x is, independently, OJ_1, NJ_1J_2, SJ_1, N_3, $OC(=X)J_1$, $OC(=X)NJ_1J_2$, $NJ_3C(=X)NJ_1J_2$ or CN; wherein each J_1, J_2 and J_3 is, independently, H or C_1-C_6 alkyl, and X is O, S or NJ_1. In another embodiment, each Z group is, independently, –CH_2X^x, wherein each X^x is, independently, halo (e.g., fluoro), hydroxyl, alkoxy (e.g., CH_3O-) or azido.

In certain embodiments, at least one Z is CH_3-. In another embodiment, each Z is, CH_3-.

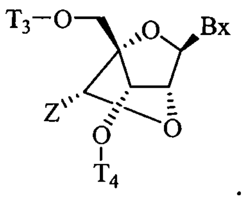
In certain embodiments, the Z group of at least one monomer is in the (*R*)- configuration represented by the formula:



or the formula:

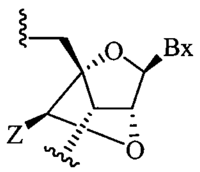


or the formula:

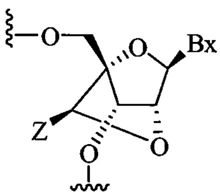


In certain embodiments, the Z group of each monomer of the formula is in the (*R*)- configuration.

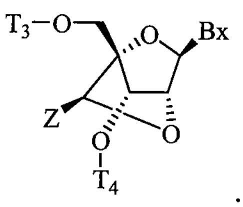
In certain embodiments, the Z group of at least one monomer is in the (*S*)- configuration represented by the formula:



or the formula:



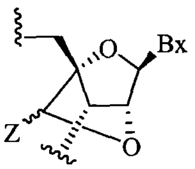
or the formula:



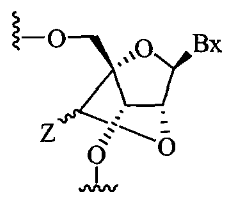
In certain embodiments, the Z group of each monomer of the formula is in the (*S*)- configuration.

In certain embodiments, T_3 is H or a hydroxyl protecting group. In certain embodiments, T_4 is H or a hydroxyl protecting group. In a further embodiment T_3 is an internucleoside linking group attached to a nucleoside, a nucleotide or a monomeric subunit. In certain embodiments, T_4 is an internucleoside linking group attached to a nucleoside, a nucleotide or a monomeric subunit. In certain embodiments,T_3 is an internucleoside linking group attached to an oligonucleoside or an oligonucleotide. In certain embodiments, T_4 is an internucleoside linking group attached to an oligonucleoside or an oligonucleotide. In certain embodiments, T_3 is an internucleoside linking group attached to an oligomeric compound. In certain embodiments, T_4 is an internucleoside linking group attached to an oligomeric compound. In In certain embodiments, at least one of T_3 and T_4 comprises an internucleoside linking group selected from phosphodiester or phosphorothioate.

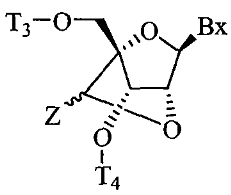
In certain embodiments, oligomeric compounds have at least one region of at least two contiguous monomers of the formula:



or of the formula:



or of the formula:



to .

In certain embodiments, the oligomeric compound comprises at least two regions of at least two contiguous monomers of the above formula. In certain embodiments, the oligomeric compound comprises a gapped oligomeric compound. In certain embodiments, the oligmeric compound comprises at least one region of from about 8 to about 14 contiguous β-D-2'-deoxyribofuranosyl nucleosides. In certain embodiments, the oligomeric compound comprises at least one region of from about 9 to about 12 contiguous β-D-2'-deoxyribofuranosyl nucleosides.

In certain embodiments, monmers include sugar mimetics. In certain such embodiments, a mimetic is used in place of the sugar or sugar-internucleoside linkage combination, and the nucleobase is maintained for hybridization to a selected target. Representative examples of a sugar mimetics include, but are not limited to, cyclohexenyl or morpholino. Representative examples of a mimetic for a sugar-internucleoside linkage combination include, but are not limited to, peptide nucleic acids (PNA) and morpholino groups linked by uncharged achiral linkages. In some instances a mimetic is used in place of the nucleobase. Representative nucleobase mimetics are well known in the art and include, but are not limited to, tricyclic phenoxazine analogs and universal bases (Berger et al., Nuc Acid Res. 2000, 28:2911-14, incorporated herein by reference). Methods of synthesis of sugar, nucleoside and nucleobase mimetics are well known to those skilled in the art.

3. Monomeric Linkages

Described herein are linking groups that link monomers (including, but not limited to, modified and unmodified nucleosides and nucleotides) together, thereby forming an oligomeric compound. The two main classes of linking groups are defined by the presence or absence of a phosphorus atom. Representative phosphorus containing linkages include, but are not limited to, phosphodiesters (P=O), phosphotriesters, methylphosphonates, phosphoramidate, and phosphorothioates (P=S). Representative non-phosphorus containing linking groups include, but are not limited to, methylenemethylimino ($-CH_2-N(CH_3)-O-CH_2-$), thiodiester (-O-C(O)-S-), thionocarbamate (-O-C(O)(NH)-S-); siloxane (-O-Si(H)2-O-); and N,N'-dimethylhydrazine ($-CH_2-N(CH_3)-N(CH_3)-$). Oligomeric compounds having non-phosphorus linking groups are referred to as oligonucleosides. Modified linkages, compared to natural phosphodiester linkages, can be used to alter, typically increase, nuclease resistance of the oligomeric compound. In certain embodiments, linkages having a chiral atom can be prepared a racemic mixtures, as separate enantomers. Representative chiral linkages include, but are not limited to, alkylphosphonates and phosphorothioates. Methods of preparation of phosphorous-containing and non-phosphorous-containing linkages are well known to those skilled in the art.

The oligomeric compounds described herein contain one or more asymmetric centers and thus give rise to enantiomers, diastereomers, and other stereoisomeric configurations that may be defined, in terms of absolute stereochemistry, as (R) or (S), α or β such as for sugar anomers, or as (D) or (L) such as for amino acids et al. Included in the antisense compounds provided herein are all such possible isomers, as well as their racemic and optically pure forms.

4. Oligomeric Compounds

In certain embodiments, provided herein are oligomeric compounds having reactive phosphorus groups useful for forming linkages including for example phosphodiester and phosphorothioate internucleoside linkages. Methods of preparation and/or purification of precursors or oligomeric compounds are not a limitation of the compositions or methods provided herein. Methods for synthesis and purification of oligomeric compounds including DNA, RNA, oligonucleotides, oligonucleosides, and antisense compounds are well known to those skilled in the art.

Generally, oligomeric compounds comprise a plurality of monomeric subunits linked together by linking groups. Nonlimiting examples of oligomeric compounds include primers, probes, antisense compounds, antisense oligonucleotides, external guide sequence (EGS) oligonucleotides, alternate splicers, and siRNAs. As such, these compounds can be introduced in the form of single-stranded, double-stranded, circular, branched or hairpins and can contain structural elements such as internal or terminal bulges or loops. Oligomeric double-stranded compounds can be two strands hybridized to form double-stranded compounds or a single strand with sufficient self complementarity to allow for hybridization and formation of a fully or partially double-stranded compound.

In certain embodiments, the present invention provides chimeric oligomeric compounds. In certain such embodiments, chimeric oligomeric compounds are chimeric oligonucleotides. In certain such embodiments, the chimeric oligonucleotides comprise differently modified nucleotides. In certain embodiments, chimeric oligonucleotides are mixed-backbone antisense oligonucleotides.

In general a chimeric oligomeric compound will have modified nucleosides that can be in isolated positions or grouped together in regions that will define a particular motif. Any combination of modifications and/or mimetic groups can comprise a chimeric oligomeric compound as described herein.

In certain embodiments, chimeric oligomeric compounds typically comprise at least one region modified so as to confer increased resistance to nuclease degradation, increased cellular uptake, and/or increased binding affinity for the target nucleic acid. In certain embodiments, an additional region of the oligomeric compound may serve as a substrate for enzymes capable of cleaving RNA:DNA or RNA:RNA hybrids. By way of example, RNase H is a cellular endonuclease that cleaves the RNA strand of an RNA:DNA duplex. Activation of RNase H, therefore, results in cleavage of the RNA target, thereby greatly enhancing the efficiency of inhibition of gene expression. Consequently, comparable results can often be obtained with shorter oligomeric compounds when chimeras are used, compared to for example phosphorothioate deoxyoligonucleotides hybridizing to the same target region. Cleavage of the RNA target can be routinely detected by gel electrophoresis and, if necessary, associated nucleic acid hybridization techniques known in the art.

In certain embodiments, chimeric oligomeric compounds are gapmers. In certain embodiments, chimeric compounds are short antisense compounds. In certain embodiments, short antisense compounds are gapmers. In certain such embodiments, a mixed-backbone antisense oligomer has one type of internucleotide linkages in one or both wings and a different type of internucleotide linkages in the gap. In certain such embodiments, the mixed-backbone antisense oligonucleotide has phosphodiester linkages in the wings and phosphorothioate linkages in the gap. In certain embodiments in which the internucleotide linkages in a wing is different from the internucleotide linkages in the gap, the internucleotide linkage bridging that wing and the gap is the same as the internucleotide linkage in the wing. In certain embodiments in which the internucleotide linkages in a wing is different from the internucleotide linkages in the gap, the internucleotide linkage bridging that wing and the gap is the same as the internucleotide linkage in the gap.

C. Certain Short Antisense Compounds

Disclosed herein are short antisense compounds 8 to 16, preferably 9 to 15, more preferably 9 to 14, more preferably 10 to 14 nucleotides in length. In certain embodiments, short antisense compounds are 9 to 14 nucleotides in length. In certain embodiments, short antisense compounds are 10 to 14 nucleotides in length. In certain embodiments, such short antisense compounds are short antisense oligonucleotides.

In certain embodiments, short antisense compounds comprise one or more chemical modifications. In certain such embodiments, short antisense compounds comprise at least one modified nucleotide. In certain embodiments short antisense compounds comprise at least two or more modified nucleotides. In certain embodiments, short antisense compounds comprise at least one modified internucleotide linkage. In certain embodiments, short antisense compounds are mixed-backbone oligonucleotides. In certain embodiments, short antisense compounds are chimeric oligonucleotides. In certain embodiments, short antisense oligonucleotides are uniformly modified. In certain embodiments, short antisense oligonucleotides comprise modifications independently selected at each nucleobase and at each linkage.

In certain embodiments, short antisense compounds are short gapmers. In certain such embodiments, short gapmers comprise at least one high affinity modification in one or more wings of the compound. In certain embodiments, short antisense compounds comprise 1 to 3 high-affinity modifications in each wing. In certain embodiments, high affinity modifications of the short antisense compounds allow for a target affinity similar to, or even greater than, the target affinity of longer antisense compounds. In certain embodiments, the high-affinity modified nucleotides are sugar modified nucleotides. Such sugar modified nucleotides include those comprising a bridge between the 4' and 2' position of the sugar. Exemplary high affinity sugar modifications include, but are not limited to, BNA s and other 2'-modifications such as 2'-MOE. In an alternate embodiment of the invention, the high affinity modification is not a 2'-O-$(CH_2)_nH$ (n=1-6) sugar-modified nucleotide. In an additional alternate embodiment, the high affinity modified nucleotide is not a 2'-OCH_3 or a 2'-$OCH_2CH_2OCH_3$ nucleotide. In certain embodiments, the high-affinity modified nucleotides confer a T_m of at least 1, at least 1.5, at least 2, at least 2.5, at least 3.0, at least 3.5 or at least 4.0 degrees per nucleotide. Some high-affinity nucleotide modifications are known in the art to increase toxicity. As shown herein, short antisense compounds having a limited number (generally 2 to 6) of high affinity modifications exhibit little to no increase in toxicity but retain or increase affinity for the target RNA, while also significantly reducing expression of the RNA target. Short antisense compounds of the invention may optionally comprise a conjugate group, such as, for example, cholesterol or C_{16}.

1. Certain Wings

In certain embodiments, the short antisense compounds comprise a 5' wing and/or a 3' wing. In such embodiments, the features of the 3' wing and the features of the 5' wing are selected independently. Thus, in such embodiments, the number of monomers in the 5' wing and the number of monomers (length) in the 3' wing may be the same or may be different; the modifications, if any, in the 5' wing may be the same as the modifications, if any, in the 3' wing or such modifications, if any, may be different; and the monomeric linkages in the 5' wing and the monomeric linkages in the 3' wing may be the same or they may be different.

In certain embodiments a wing comprises one, two or three monomers (i.e. has a length of 1, 2, or 3). In certain embodiments, the monomers of a wing are modified. In certain such embodiments, the monomers of the wing are modified to increase affinity of the antisense compound for its target nucleic acid. In certain embodiments, the monomers of a wing are nucleosides or nucleotides. In certain such embodiments, the nucleosides or nucleotides of the wing comprise a 2' modification. In certain such embodiments, the monomers (nucleosides or nucleotides) of the wing are BNA's. In certain such embodiments, the monomers of the wing are selected from α-L-Methyleneoxy (4'-CH_2-O-2') BNA , β-D-Methyleneoxy (4'-CH_2-O-2') BNA , Ethyleneoxy (4'-$(CH_2)_2$-O-2') BNA , Aminooxy (4'-CH_2-O-N(R)-2') BNA and Oxyamino (4'-CH_2-N(R)-O-2') BNA. In certain embodiments, the monomers of a wing comprise a substituent at the 2' position selected from allyl, amino, azido, thio, O-allyl, O-C_1-C_{10} alkyl, -OCF_3, O-$(CH_2)_2$-O-CH_3, 2'-O$(CH_2)_2SCH_3$, O-$(CH_2)_2$-O-N(R_m)(R_n), and O-CH_2-C(=O)-N(R_m)(R_n), where each R_m and R_n is, independently, H or substituted or unsubstituted C_1-C_{10} alkyl. In certain embodiments, the monomers of a wing are 2'MOE nucleotides.

In certain embodiments, the monomeric linkages in a wing are naturally occurring internucleotide linkages. In certain embodiments, the monomeric linkages in a wing are non-naturally occurring internucleotide or internucleoside linkages. In certain such embodiments, the monomeric linkages in the wing are more resistant to one or more nucleases than naturally occurring internucleotide linkages. In certain such embodiments, the monomeric linkages in the wing are phosphorothioate linkages (P=S). In certain embodiments where a wing has more than one monomeric linkage, the monomeric linkages are the same as one another. In certain embodiments where a wing has more than one monomers linkage, the monomers linkages are different from each other.

One of ordinary skill in the art will recognize that the features and modifications discussed above may be used in any combination to prepare a wing. The table below provides non-limiting examples showing how one might prepare a wing by selecting a certain number of monomers, monomeric modifications (if any), and monomeric linkages both within the wing.

Length	Monomer type/ modifications	monomeric linkages within wing
1	2' MOE	None

1	BNA	None
1	Methyleneoxy BNA	None
1	ENA	None
2	2' MOE	P=S
2	BNA	P=S
2	Methyleneoxy BNA	P=S
2	ENA	P=S
2	2' MOE	P=O
2	BNA	P=O
2	Methyleneoxy BNA	P=O
2	ENA	P=O
3	2' MOE	P=S
3	BNA	P=S
3	Methyleneoxy BNA	P=S
3	ENA	P=S
3	2' MOE	P=O
3	BNA	P=O
3	Methyleneoxy BNA	P=O
3	ENA	P=O

In certain embodiments in which a wing comprises two, three or four monomers, those two, three or four monomers all comprise the same modifications, if any. In certain embodiments in which a wing comprises two, three or four monomers, one or more of those two, three or four nucleobases comprises one or more modifications that is different from one or more of the modifications of one or more of the remaining monomers.

2. Certain Gaps

In certain embodiments, the short antisense compounds comprise a gap between the 5' wing and the 3' wing. In certain embodiments the gap comprises five, six, seven, eight, nine, ten, eleven, twelve, thirteen, or fourteen monomers. In certain embodiments, the monomers of the gap are unmodified deoxyribonucleotides. In certain embodiments, the monomers of the gap are unmodified ribonucleotides. In certain embodiments, gap modifications (if any) gap result in an antisense compound that, when bound to its target nucleic acid, supports cleavage by an RNase, including, but not limited to, RNase H.

In certain embodiments, the monomeric linkages in the gap are naturally occurring internucleotide linkages. In certain embodiments, the monomeric linkages in the gap are non-naturally occurring linkages. In certain such embodiments, the monomeric linkages in the gap are more resistant to one or more nuclease than naturally occurring internucleotide linkages. In certain such embodiments, the monomeric linkages in the gap are phosphorothioate linkages (P=S). In certain embodiments, the monomeric linkages in the gap are all the same as one another. In certain embodiments, the monomeric linkages within the gap are not all the same.

One of ordinary skill in the art will recognize that the features and modifications discussed above may be used in any combination to prepare a gap. The table below provides non-limiting examples showing how one might prepare a gap by selecting a certain number of monomers, monomeric modifications (if any), and monomeric linkages within the gap region.

Length	Monomer type/ modifications	Monomeric linkages within gap
5	DNA	P=S
6	DNA	P=S
7	DNA	P=S
8	DNA	P=S
9	DNA	P=S
10	DNA	P=S
11	DNA	P=S
12	DNA	P=S
13	DNA	P=S
14	DNA	P=S
6	DNA	P=O
7	DNA	P=O
8	DNA	P=O
9	DNA	P=O
10	DNA	P=O
11	DNA	P=O
12	DNA	P=O

8	RNA	P=S
9	RNA	P=S
10	RNA	P=S
11	RNA	P=S
12	RNA	P=S

3. Certain Gapped Antisense Oligomeric Compounds

One of ordinary skill in the art will recognize that the wings and the gaps discussed above may be selected and then combined in a variety of combinations to generate gapped oligomeric compounds, including, but not limited to, gapped antisense oligomeric compounds, and gapped antisense oligonucleotides. The features (length, modifications, linkages) of the 5' wing and the 3' wing may be selected independently of one another. The features of the gap include at least one difference in modification compared to the features of the 5' wing and at least one difference compared to the features of the 3' wing (i.e., there must be at least one difference in modification between neighboring regions to distinguish those neighboring regions from one another). The features of the gap may otherwise be selected independently.

In certain embodiments, the monomeric linkages within a wing and the monomeric linkages within the gap are the same. In certain embodiments, the monomeric linkages within a wing and the monomeric linkages within the gap are different. In certain such embodiments, the monomeric linkage bridging the wing and the gap are the same as the monomeric linkages in the wing. In certain embodiments, the monomeric linkage bridging the wing and the gap are the same as the monomeric linkages in the gap. In certain embodiments, short antisense compounds have uniform linkages throughout the compound. In certain such embodiments, all of the linkages are phosphorothioate (P=S) linkages.

One of ordinary skill in the art will recognize that the 3' wings, 5' wings, gaps, and linkages discussed above may be used in any combination to prepare a gapmer. The table below provides non-limiting examples showing how one might prepare a gapmer by selecting a certain 5' wing, a gap, a 3' wing and certain linkages bridging the gap and each wing.

5' Wing			5'Bridge	Gap			3' Bridge	3' Wing		
Length	Monomer	Link	Link	Length	Monomer	Link	Link	Length	Monomer	Link
2	MOE	P=S	P=S	6	DNA	P=S	P=S	2	MOE	P=S
2	BNA	P=S	P=O	8	DNA	P=O	P=S	3	BNA	P=S
1	MOE	None	P=S	10	DNA	P=S	P=S	1	MOE	P=S
2	MOE	P=S	P=S	8	RNA	P=S	P=S	2	MOE	P=S

3	Methyleneoxy BNA	P=S	P=S	8	RNA	P=S	P=S	3	MOE	P=S
3	DNA	P=O	P=O	10	RNA	P=S	P=O	3	2'OH	P=O
2	2-F	P=S	P=S	5	RNA	P=S	P=S	2	2'-F	P=S
1	MOE	P=O	P=S	5	DNA	P=O	P=S	4	MOE	P=S

In certain embodiments, the oligomeric compounds disclosed herein may comprise from about 8 to about 16, preferably 9 to 15, more preferably 9 to 14, more preferably 10 to 14 monomers (i.e. from about 8 to about 16 linked monomers). One of ordinary skill in the art will appreciate that this comprehends antisense compounds of 8, 9, 10, 11, 12, 13, 14, 15 or 16 nucleobases. In certain embodiments, oligomeric compounds are antisense compounds.

In certain embodiments, short antisense compounds are 8 nucleobases in length.

In certain embodiments, short antisense compounds are 9 nucleobases in length.

In certain embodiments, short antisense compounds are 10 nucleobases in length.

In certain embodiments, short antisense compounds are 11 nucleobases in length.

In certain embodiments, short antisense compounds are 12 nucleobases in length.

In certain embodiments, short antisense compounds are 13 nucleobases in length.

In certain embodiments, short antisense compounds are 14 nucleobases in length.

In certain embodiments, short antisense compounds are 15 nucleobases in length.

In certain embodiments, short antisense compounds are 16 nucleobases in length.

In certain embodiments, short antisense compounds are 8 monomers in length. In certain embodiments, short antisense compounds are 9 monomers in length. In certain embodiments, short antisense compounds are 10 monomers in length. In certain embodiments, short antisense compounds are 11 monomers in length. In certain embodiments, short antisense compounds are monomers in length. In certain embodiments, short antisense compounds are 13 monomers in length. In certain embodiments, short antisense compounds are 14 monomers in length. In certain embodiments, short antisense compounds are 15 monomers in length. In certain embodiments, short antisense compounds are 16 monomers in length. In certain embodiments, short antisense compounds comprise 9 to 15 monomers. In certain embodiments, short antisense compounds comprise 10 to 15 monomers. In certain embodiments, short antisense compounds comprise 12 to 14 monomers. In certain embodiments, short antisense compounds comprise 12 to 14 nucleotides or nucleosides.

One having skill in the art and informed by the short antisense compounds illustrated herein will be able, without undue experimentation, to identify further short antisense compounds.

In certain embodiments, short antisense compounds comprise a gap flanked by more than one wing on either or both sides. Thus, in certain embodiments, a short antisense compound comprises two or more 5' wings and two or more 3' wings. In certain embodiments, a short antisense compound comprises one 5' wing and two or more 3' wings. In certain embodiments, a short antisense compound comprises one 3' wing and two or more 5' wings. Certain such embodiments comprise, for example, the following regions: a first 5' wing – a bridge – a second 5' wing – a bridge – a gap – a bridge – a second 3' wing – a bridge – a first 3'wing. In such embodiments, each region has at least one difference in modification when compared to its neighboring region. Thus, in such embodiments, the second 5' wing and the second 3' wing each independently comprises one or more differences in modification compared to the gap and compared to the first 5' wing and the first 3' wing. In such embodiments, the modifications of the first 3' wing and first 5' wing may either or both be the same or different from the modifications of the gap, if any.

4. Certain Conjugate Groups

In one aspect, oligomeric compounds are modified by covalent attachment of one or more conjugate groups. In general, conjugate groups modify one or more properties of the attached oligomeric compound including but not limited to pharmacodynamic, pharmacokinetic, binding, absorption, cellular distribution, cellular uptake, charge and clearance. Conjugate groups are routinely used in the chemical arts and are linked directly or via an optional linking moiety or linking group to a parent compound such as an oligomeric compound. A preferred list of conjugate groups includes without limitation, intercalators, reporter molecules, polyamines, polyamides, polyethylene glycols, thioethers, polyethers, cholesterols, thiocholesterols, cholic acid moieties, folate, lipids, phospholipids, biotin, phenazine, phenanthridine, anthraquinone, adamantane, acridine, fluoresceins, rhodamines, coumarins and dyes.

Preferred conjugate groups amenable to the present invention include lipid moieties such as a cholesterol moiety (Letsinger et al., Proc. Natl. Acad. Sci. USA, 1989, 86, 6553); cholic acid (Manoharan et al., Bioorg. Med. Chem. Lett., 1994, 4, 1053); a thioether, e.g., hexyl-S-tritylthiol (Manoharan et al., Ann. N.Y. Acad. Sci., 1992, 660, 306; Manoharan et al., Bioorg. Med. Chem. Let., 1993, 3, 2765); a thiocholesterol (Oberhauser et al., Nucl. Acids Res., 1992, 20, 533); an aliphatic chain, e.g., dodecandiol or undecyl residues (Saison-Behmoaras et al., EMBO J., 1991, 10, 111; Kabanov et al., FEBS Lett., 1990, 259, 327; Svinarchuk et al., Biochimie, 1993, 75, 49); 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; Shea et al., Nucl. Acids Res., 1990, 18, 3777); a polyamine or a polyethylene glycol chain (Manoharan et al., Nucleosides & Nucleotides, 1995, 14, 969); adamantane acetic acid (Manoharan et al., Tetrahedron Lett., 1995, 36, 3651); a palmityl moiety (Mishra et al., Biochim. Biophys. Acta, 1995, 1264, 229); or an octadecylamine or hexylamino-carbonyl-oxycholesterol moiety (Crooke et al., J. Pharmacol. Exp. Ther., 1996, 277, 923).

Linking groups or bifunctional linking moieties such as those known in the art are amenable to the compounds provided herein. Linking groups are useful for attachment of chemical functional groups, conjugate groups, reporter groups and other groups to selective sites in a parent compound such as for example an oligomeric compound. In general a bifunctional linking moiety comprises a hydrocarbyl moiety having two functional groups. One of the functional groups is selected to bind to a parent molecule or compound of interest and the other is selected to bind essentially any selected group such as chemical functional group or a conjugate group. In some embodiments, the linker comprises a chain structure or an oligomer of repeating units such as ethylene glycol or amino acid units. Examples of functional groups that are routinely 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 some embodiments, bifunctional linking moieties include amino, hydroxyl, carboxylic acid, thiol, unsaturations (e.g., double or triple bonds), and the like. Some nonlimiting examples of bifunctional linking moieties include 8-amino-3,6-dioxaoctanoic acid (ADO), succinimidyl 4-(N-maleimidomethyl) cyclohexane-1-carboxylate (SMCC) and 6-aminohexanoic acid (AHEX or AHA). Other linking groups include, but are not limited to, substituted 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.

5. Synthesis, Purification and Analysis

Oligomerization of modified and unmodified nucleosides and nucleotides can be routinely performed according to literature procedures for DNA (Protocols for Oligonucleotides and Analogs, Ed. Agrawal (1993), Humana Press) and/or RNA (Scaringe, Methods (2001), 23, 206-217. Gait et al., Applications of Chemically synthesized RNA in RNA: Protein Interactions, Ed. Smith (1998), 1-36. Gallo et al., Tetrahedron (2001), 57, 5707-5713).

Oligomeric compounds provided herein can be conveniently and routinely made through the well-known technique of solid phase synthesis. Equipment for such synthesis is sold by several vendors including, for example, Applied Biosystems (Foster City, CA). Any other means for such synthesis known in the art may additionally or alternatively be employed. It is well known to use similar techniques to prepare oligonucleotides such as the phosphorothioates and alkylated derivatives. The invention is not limited by the method of antisense compound synthesis.

Methods of purification and analysis of oligomeric compounds are known to those skilled in the art. Analysis methods include capillary electrophoresis (CE) and electrospray-mass spectroscopy. Such synthesis and analysis methods can be performed in multi-well plates. The method of the invention is not limited by the method of oligomer purification.

D. Antisense

Antisense mechanisms are all those involving the hybridization of a compound with target nucleic acid, wherein the outcome or effect of the hybridization is either target degradation or target occupancy with concomitant stalling of the cellular machinery involving, for example, transcription or splicing.

One type of antisense mechanism involving target degradation includes an RNase H. RNase H is a cellular endonuclease which cleaves the RNA strand of an RNA:DNA duplex. It is known in the art that single-stranded antisense compounds which are "DNA-like" elicit RNAse H activity in mammalian cells. Activation of RNase H, therefore, results in cleavage of the RNA target, thereby greatly enhancing the efficiency of DNA-like oligonucleotide-mediated inhibition of gene expression.

In certain embodiments, chemically-modified antisense compounds have a higher affinity for target RNAs than does non-modified DNA. In certain such embodiments, that higher affinity in turn provides increased potency allowing for the administration of lower doses of such compounds, reduced potential for toxicity and improvement in therapeutic index and decreased overall cost of therapy.

The present disclosure demonstrates that the incorporation of chemically-modified high-affinity nucleotides and nucleosides into antisense compounds allows for the design of short antisense compounds 8-16 nucleobases in length useful for the reduction of target RNAs and/or target proteins in cells, tissues, and animals, including, but not limited to, humans with increased potency and improved therapeutic index. Thus, in certain embodiments, provided herein are short antisense compounds comprising high-affinity nucleotide modifications useful for reducing a target RNA *in vivo*. Certain such short antisense compounds are effective at lower doses than previously described antisense compounds, allowing for a reduction in toxicity and cost of treatment. In addition, certain short antisense compounds have greater potential for oral dosing.

To address the need for more potent antisense compounds, provided herein are short antisense compounds (8-16, preferably 9 to 15, more preferably 9 to 14, more preferably 10 to 14 nucleotides in length) with increased activity *in vivo* relative to longer compounds. Certain short antisense compounds are gapmer compounds comprising high-affinity chemically-modified nucleotides on the 3' and 5' ends (wings) of the compound. In certain embodiments, the addition of high-affinity modified nucleotides allows antisense compounds to be active against, and specific for, their intended target RNA *in vivo* despite being shorter in length. Contemplated herein are short antisense compounds wherein each of the wings independently comprises 1 to 3 high-affinity modified nucleotides. In certain embodiments, the high-affinity modifications are sugar modifications. High-affinity modified nucleotides include, but are not limited to, BNA s or other 2'-modified nucleotides, such as 2'-MOE nucleotides. Also contemplated are short antisense compounds having at least one modified internucleotide linkage, such as a phosphorothioate internucleotide linkage. In certain embodiments, the short antisense compounds of the present invention can have all phosphorothioate internucleoside linkages. The short antisense compounds optionally comprise a conjugate group. As shown herein, short antisense compounds have greater affinity for target RNA than they have for DNA and are significantly more potent *in vivo* as shown by reduction of target mRNA as well as by amelioration of a variety of disease indications.

As used herein, an RNA which is involved in regulating glucose metabolism or clearance, lipid metabolism, cholesterol metabolism or insulin metabolism is any RNA involved in the biochemical pathways that regulate these processes. Such RNAs are well known in the art. Examples of target genes include, but are not limited to, ApoB-100 (also known as APOB; Ag(x) antigen; apoB-48; apolipoprotein B; apolipoprotein B-100; apolipoprotein B-48) and GCGR (also known as glucagon receptor; GR), CRP, DGAT2, GCCR, PCSK9, PTEN, PTP1B, SGLT2, and SOD1.

1. Modulation of Target Expression

In certain embodiments, a target is identified and antisense oligonucleotides are designed to modulate that target or its expression. In certain embodiments, designing an oligomeric compound to a target nucleic acid molecule can be a multistep process. Typically the process begins with the identification of a target protein, the activity of which is to be modulated, and then identifying the nucleic acid the expression of which yields the target protein. In certain embodiments, designing of an antisense compound results in an antisense compound that is hybridizable to the targeted nucleic acid molecule. In certain embodiments, the antisense compound is an antisense oligonucleotide or antisense oligonucleoside. In certain embodiments, an antisense compound and a target nucleic acid are complementary to one another. In certain such embodiments, an antisense compound is perfectly complementary to a target nucleic acid. In certain embodiments, an antisense compound includes one mismatch. In certain embodiments, an antisense compound includes two mismatches. In certain embodiments, an antisense compound includes three or more mismatches.

Modulation of expression of a target nucleic acid can be achieved through alteration of any number of nucleic acid functions. In certain embodiments, the functions of RNA to be modulated include, but are not limited to, translocation functions, which include, but are not limited to, translocation of the RNA to a site of protein translation, translocation of the RNA to sites within the cell which are distant from the site of RNA synthesis, and translation of protein from the RNA. RNA processing functions that can be modulated include, but are not limited to, splicing of the RNA to yield one or more RNA species, capping of the RNA, 3' maturation of the RNA and catalytic activity or complex formation involving the RNA which may be engaged in or facilitated by the RNA. Modulation of expression can result in the increased level of one or more nucleic acid species or the decreased level of one or more nucleic acid species, either temporally or by net steady state level. Thus, in one embodiment modulation of expression can mean increase or decrease in target RNA or protein levels. In another embodiment modulation of expression can mean an increase or decrease of one or more RNA splice products, or a change in the ratio of two or more splice products.

In certain embodiments, expression of a target gene is modulated using an oligomeric compound comprising from about 8 to about 16, preferably 9 to 15, more preferably 9 to 14, more preferably 10 to 14 monomers (i.e. from about 8 to about 16 linked monomers). One of ordinary skill in the art will appreciate that this comprehends methods of modulating expression of a target gene using one or more antisense compounds of 8, 9, 10, 11, 12, 13, 14, 15 or 16 nucleobases.

In certain embodiments, methods of modulating a target gene comprises use of a short antisense compound that is 8 nucleobases in length. In certain embodiments, methods of modulating a target gene comprises use of a short antisense compound that is 9 nucleobases in length. In certain embodiments, methods of modulating a target gene comprises use of a short antisense compound that is 8 nucleobases in length. In certain embodiments, methods of modulating a target gene comprises use of a short antisense compound that is 10 nucleobases in length. In certain embodiments, methods of modulating a target gene comprises use of a short antisense compound that is 10 nucleobases in length. In certain embodiments, methods of modulating a target gene comprises use of a short antisense compound that is 11 nucleobases in length. In certain embodiments, methods of modulating a target gene comprises use of a short antisense compound that is 12 nucleobases in length. In certain embodiments, methods of modulating a target gene comprises use of a short antisense compound that is 13 nucleobases in length. In certain embodiments, methods of modulating a target gene comprises use of a short antisense compound that is 14 nucleobases in length. In certain embodiments, methods of modulating a target gene comprises use of a short antisense compound that is 15 nucleobases in length. In certain embodiments, methods of modulating a target gene comprises use of a short antisense compound that is 16 nucleobases in length.

In certain embodiments, methods of modulating expression of a target gene comprises use of a short antisense compound comprising 9 to 15 monomers. In certain embodiments, methods of modulating expression of a target gene comprises use of a short antisense compound comprising 10 to 15 monomers. In certain embodiments, methods of modulating expression of a target gene comprises use of a short antisense compound comprising 12 to 14 monomers. In certain embodiments, methods of modulating expression of a target gene comprises use of a short antisense compound comprising 12 or 14 nucleotides or nucleosides.

2. Hybridization

In certain embodiments, antisense compounds specifically hybridize when there is a sufficient degree of complementarity to avoid non-specific binding of the antisense compound to non-target nucleic acid sequences under conditions in which specific binding is desired, i.e., under physiological conditions in the case of *in vivo* assays or therapeutic treatment, and under conditions in which assays are performed in the case of *in vitro* assays.

As used herein, “stringent hybridization conditions” or “stringent conditions” refers to conditions under which an antisense compound will hybridize to its target sequence, but to a minimal number of other sequences. Stringent conditions are sequence-dependent and will be different in different circumstances, and “stringent conditions” under which antisense compounds hybridize to a target sequence are determined by the nature and composition of the antisense compounds and the assays in which they are being investigated.

3. Complementarity

It is understood in the art that incorporation of nucleotide affinity modifications may allow for a greater number of mismatches compared to an unmodified compound. Similarly, certain oligonucleotide sequences may be more tolerant to mismatches than other oligonucleotide sequences. One of ordinary skill in the art is capable of determining an appropriate number of mismatches between oligonucleotides, or between an oligonucleotide and a target nucleic acid, such as by determining melting temperature (T_m). T_m or T_m can be calculated by techniques that are familiar to one of ordinary skill in the art. For example, techniques described in Freier et al. (*Nucleic Acids Research*, *1997*, **25**, *22*: 4429-4443) allow one of ordinary skill in the art to evaluate nucleotide modifications for their ability to increase the melting temperature of an RNA:DNA duplex.

4. <u>Identity</u>

Antisense compounds, or a portion thereof, may have a defined percent identity to a SEQ ID NO, or a compound having a specific Isis number. As used herein, a sequence is identical to the sequence disclosed herein if it has the same nucleobase pairing ability. For example, an RNA which contains uracil in place of thymidine in the disclosed sequences of the compounds described herein would be considered identical as they both pair with adenine. This identity may be over the entire length of the oligomeric compound, or in a portion of the antisense compound (e.g., nucleobases 1-20 of a 27-mer may be compared to a 20-mer to determine percent identity of the oligomeric compound to the SEQ ID NO. It is understood by those skilled in the art that an antisense compound need not have an identical sequence to those described herein to function similarly to the antisense compound described herein. Shortened versions of antisense compounds taught herein, or non-identical versions of the antisense compounds taught herein, are also provided herein. Non-identical versions are those wherein each base does not have the same pairing activity as the antisense compounds disclosed herein. Bases do not have the same pairing activity by being shorter or having at least one abasic site. Alternatively, a non-identical version can include at least one base replaced with a different base with different pairing activity (e.g., G can be replaced by C, A, or T). Percent identity is calculated according to the number of bases that have identical base pairing corresponding to the SEQ ID NO or antisense compound to which it is being compared. The non-identical bases may be adjacent to each other, dispersed through out the oligonucleotide, or both.

For example, a 16-mer having the same sequence as nucleobases 2-17 of a 20-mer is 80% identical to the 20-mer. Alternatively, a 20-mer containing four nucleobases not identical to the 20-mer is also 80% identical to the 20-mer. A 14-mer having the same sequence as nucleobases 1-14 of an 18-mer is 78% identical to the 18-mer. Such calculations are well within the ability of those skilled in the art.

The percent identity is based on the percent of nucleobases in the original sequence present in a portion of the modified sequence. Therefore, a 30 nucleobase antisense compound comprising the full sequence of the complement of a 20 nucleobase active target segment would have a portion of 100% identity with the complement of the 20 nucleobase active target segment, while further comprising an additional 10 nucleobase portion. In the context of the instant description, the complement of an active target segment may constitute a single portion. In preferred embodiments, the oligonucleotides provided herein are at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or 100% identical to at least a portion of the complement of the active target segments presented herein.

E. Target Nucleic Acids, Regions and Segments

In certain embodiments, short antisense compounds may be designed to target any target nucleic acid. In certain embodiments, the target nucleic acid encodes a target that is clinically relevant. In such embodiments, modulation of the target nucleic acid results in clinical benefit. Certain target nucleic acids include, but are not limited to, the target nucleic acids illustrated in Table 1.

In certain embodiments, a target nucleic acid is a nucleic acid molecule encoding ApoB. Nucleic acid molecules that encode ApoB include, without limitation, SEQ ID NO: 1 and SEQ ID NO: 2.

In certain embodiments, a target nucleic acid is a nucleic acid molecule encoding SGLT2. Nucleic acid molecules that encode SGLT2 include, without limitation, SEQ ID NO: 3.

In certain embodiments, a target nucleic acid is a nucleic acid molecule encoding PCSK9. Nucleic acid molecules that encode PCSK9 include, without limitation, SEQ ID NO: 4.

In certain embodiments, a target nucleic acid is a nucleic acid molecule encoding SOD1. Nucleic acid molecules that encode SOD1 include, without limitation, SEQ ID NO: 5.

In certain embodiments, a target nucleic acid is a nucleic acid molecule encoding CRP. Nucleic acid molecules that encode CRP include, without limitation, SEQ ID NO: 6.

In certain embodiments, a target nucleic acid is a nucleic acid molecule encoding GCCR. Nucleic acid molecules that encode GCCR include, without limitation, SEQ ID NO: 7 and SEQ ID NO: 8.

In certain embodiments, a target nucleic acid is a nucleic acid molecule encoding GCGR. Nucleic acid molecules that encode GCGR include, without limitation, SEQ ID NO: 9.

In certain embodiments, a target nucleic acid is a nucleic acid molecule encoding DGAT2. Nucleic acid molecules that encode DGAT2 include, without limitation, SEQ ID NO: 10.

In certain embodiments, a target nucleic acid is a nucleic acid molecule encoding PTP1B. Nucleic acid molecules that encode PTP1B include, without limitation, SEQ ID NO: 11 and SEQ ID NO: 12.

In certain embodiments, a target nucleic acid is a nucleic acid molecule encoding PTEN. Nucleic acid molecules that encode PTEN include, without limitation, SEQ ID NO: 14 or SEQ ID NO: 15.

Table 1: Certain Target Nucleic Acids

Target	Species	GENBANK® Accession Number	SEQ ID NO
ApoB	Human	NM_000384.1	1
ApoB	Mouse	XM_137955.5	2
SGLT2	Human	NM_003041.1	3
PCSK9	Human	NM_174936.2	4
SOD1	Human	X02317.1	5
CRP	Human	NM_000567.1	6
GCCR	Mouse	BC031885.1	7

GCCR	Human	Nucleotides 1 to 10600 of AC012634	8
GCGR	Human	NM_000160.1	9
DGAT2	Human	NM_032564.2	10
PTP1B	Human	NM_002827.2	11
PTP1B	Human	Nucleotides 1417800 to 1425600 of NT_011362.9	12
PTEN	Mouse	U92437.1	13
PTEN	Human	NM_000314.4	14
PTEN	Human	Nucleotides 8063255 to 8167140 of NT_033890.3	15

The targeting process usually includes determination of at least one target region, segment, or site within the target nucleic acid for the antisense interaction to occur such that the desired effect will result.

In certain embodiments, the 5'-most nucleotide of a target region is the 5' target site of a short antisense compound and the 3'-most nucleotide of a target region is the 3' target site of the same short antisense compound. In certain embodiments, the 5'-most nucleotide of a target region is the 5' target site of a short antisense compound and the 3'-most nucleotide of a target region is the 3' target site of a different short antisense compound. In certain embodiments, a target region comprises a nucleotide sequence within 10, 15, or 20 nucleotides of a 5' target site or a 3' target site.

In certain embodiments, a target region is a structurally defined region of the nucleic acid. For example, in certain such embodiments, a target region may encompass a 3' UTR, a 5' UTR, an exon, an intron, a coding region, a translation initiation region, translation termination region, or other defined nucleic acid region.

The locations on the target nucleic acid defined by having one or more active short antisense compounds targeted thereto are referred to as "active target segments." In certain embodiments, the target nucleic acid having one or more active short antisense compounds targeted thereto is a target RNA. When an active target segment is defined by multiple short antisense compounds, the compounds are preferably separated by no more than about 10 nucleotides on the target sequence, more preferably no more than about 5 nucleotides on the target sequence, even more preferably the short antisense compounds are contiguous, most preferably the short antisense compounds are overlapping. There may be substantial variation in activity (e.g., as defined by percent inhibition) of the short antisense compounds within an active target segment. Active short antisense compounds are those that modulate the expression of their target nucleic acid, including but not limited to a target RNA. Active short antisense compounds inhibit expression of their target RNA at least 10%, preferably 20%. In a preferred embodiment, at least about 50%, preferably about 70% of the short antisense compounds targeted to the active target segment modulate expression of their target RNA at least 40%. In a more preferred embodiment, the level of inhibition required to define an active short antisense compound is defined based on the results from the screen used to define the active target segments.

A suitable target segment is at least about an 8-nucleobase portion of a target region to which an active short antisense compound is targeted. Target segments can include DNA or RNA sequences that comprise at least the 8 consecutive nucleobases from the 5'-terminus of one of the illustrative target segments (the remaining nucleobases being a consecutive stretch of the same DNA or RNA beginning immediately upstream of the 5'-terminus of the target segment and continuing until the DNA or RNA comprises about 8 to about 16 nucleobases). Target segments are also represented by DNA or RNA sequences that comprise at least the 8 consecutive nucleobases from the 3'-terminus of one of the illustrative target segments (the remaining nucleobases being a consecutive stretch of the same DNA or RNA beginning immediately downstream of the 3'-terminus of the target segment and continuing until the DNA or RNA comprises about 8 to about 16 nucleobases). It is also understood that antisense target segments may be represented by DNA or RNA sequences that comprise at least 8 consecutive nucleobases from an internal portion of the sequence of an illustrative target segment, and may extend in either or both directions until the short antisense compound comprises about 8 to about 16 nucleobases. One having skill in the art armed with the target segments illustrated herein will be able, without undue experimentation, to identify further target segments.

Once one or more target regions, segments or sites have been identified, short antisense compounds are chosen which are sufficiently complementary to the target, i.e., hybridize sufficiently well and with sufficient specificity, to give the desired effect.

The short antisense compounds may also be targeted to regions of the target nucleobase sequence comprising any consecutive nucleobases 8 to 16 nucleobases in length along the target nucleic acid molecule.

Target segments 8-16 nucleobases in length comprising a stretch of at least eight (8) consecutive nucleobases selected from within the illustrative target segments are considered to be suitable for targeting as well. Thus, the short antisense compounds may also encompass 8-16 nucleobases within those segments identified herein as beginning at a particular 5' target site. Any segment of 8, 9, 10, 11, or more preferably 12, 13, 14, 15 or 16 contiguous nucleobases in a 50, preferably 25, more preferably 16 nucleobase perimeter around these regions are also considered to be suitable for targeting.

In a further embodiment, the "suitable target segments" identified herein may be employed in a screen for additional short antisense compounds that modulate the expression of a target nucleic acid. "Modulators" are those compounds that decrease or increase the expression of a target nucleic acid and which comprise at least an 8-nucleobase portion which is complementary to a target segment. The screening method comprises the steps of contacting a target segment of a nucleic acid with one or more candidate modulators, and selecting for one or more candidate modulators which decrease or increase the expression of a target nucleic acid. Once it is shown that the candidate modulator or modulators are capable of modulating (e.g. either decreasing or increasing) the expression of a target nucleic acid, the modulator may then be employed in further investigative studies of the function of the target, or for use as a research, diagnostic, or therapeutic agent in accordance with the present invention.

For all short antisense compounds discussed herein, sequence, monomer, monomeric modification, and monomeric linkage may each be selected independently. In certain embodiments, short antisense compounds are described by a motif. In such embodiments, any motif may be used with any sequence, whether or not the sequence and/or the motif is specifically disclosed herein. In certain embodiments, short antisense compounds comprise modifications that are not amenable to description by motif (for example, short antisense compounds comprising several different modifications and/or linkages at various positions throughout the compound). Such combinations may be incorporated for any sequence, whether or not it is disclosed herein. The sequence listing accompanying this filing provides certain nucleic acid sequences independent of chemical modification. Though that listing identifies each sequence as either "RNA" or "DNA" as required, in reality, those sequences may be modified with any combination of chemical modifications and/or motifs.

In certain embodiments, short antisense compounds comprise at least one high-affinity modified monomer. In certain embodiments, provided are short antisense compounds targeted to nucleic acid molecules encoding targets including, but not limited to, ApoB-100 (also known as APOB; Ag(x) antigen; apoB-48; apolipoprotein B; apolipoprotein B-100; apolipoprotein B-48), GCGR (also known as glucagon receptor; GR), CRP, DGAT2, GCCR, PCSK9, PTEN, PTP1B, SGLT2, and SOD1. In certain such embodiments, such short antisense compounds are targeted to a nucleic acid molecule encoding any of those targets.

F. Certain Targets

In certain embodiments, short antisense compounds may be designed to modulate any target. In certain embodiments, the target is clinically relevant. In such embodiments, modulation of the target results in clinical benefit. Certain targets are preferentially expressed in the kidney. Certain targets are preferentially expressed in the liver. Certain targets are associated with a metabolic disorder. Certain targets are associated to a cardiovascular disorder. In certain embodiments, a target is selected from: ApoB, SGLT2, PCSK9, SOD1, CRP, GCCR, GCGR, DGAT2, PTP1B, and PTEN. In certain embodiments, a target is selected from: ApoB, SGLT2, PCSK9, SOD1, CRP, GCCR, GCGR, DGAT2, and PTP1B. In certain embodiments, a target is any protein other than SGLT2.

In certain embodiments, short antisense compounds exhibit liver and kidney-specific target RNA reduction *in vivo*. Such property renders those short antisense compounds particularly useful for inhibition of many target RNAs involved in metabolic and cardiovascular diseases. Thus, provided herein are methods of treating cardiovascular or metabolic disorders by contacting said kidney or liver tissues with short antisense compounds targeted to RNAs associated with said disorders. Thus, also provided are methods for ameliorating any of a variety of metabolic or cardiovascular disease indications with the short antisense compounds of the present invention.

1. ApoB

ApoB (also known as apolipoprotein B-100; ApoB-100, apolipoprotein B-48; ApoB-48 and Ag(x) antigen), is a large glycoprotein that serves an indispensable role in the assembly and secretion of lipids and in the transport and receptor-mediated uptake and delivery of distinct classes of lipoproteins. ApoB performs a variety of activities, from the absorption and processing of dietary lipids to the regulation of circulating lipoprotein levels (Davidson and Shelness, *Annu. Rev. Nutr.*, 2000, *20*, 169-193). This latter property underlies its relevance in terms of atherosclerosis susceptibility, which is highly correlated with the ambient concentration of ApoB-containing lipoproteins (Davidson and Shelness, Annu. Rev. Nutr., 2000, 20, 169-193). ApoB-100 is the major protein component of LDL-C and contains the domain required for interaction of this lipoprotein species with the LDL receptor. Elevated levels of LDL-C are a risk factor for cardiovascular disease, including atherosclerosis.

Definitions

"ApoB" is the gene product or protein of which expression is to be modulated by administration of a short antisense compound.

"ApoB nucleic acid" means any nucleic acid encoding ApoB. For example, in certain embodiments, a ApoB nucleic acid includes, without limitation, a DNA sequence encoding ApoB, an RNA sequence transcribed from DNA encoding ApoB, and an mRNA sequence encoding ApoB.

"ApoB mRNA" means an mRNA encoding ApoB.

ApoB Therapeutic Indications

In certain embodiments, the invention provides methods of modulating the expression of ApoB in an individual comprising administering a short antisense compound targeted to an ApoB nucleic acid. In certain embodiments, the invention provides methods of treating an individual comprising administering one or more pharmaceutical compositions comprising a short antisense compound targeted to an ApoB nucleic acid. In certain embodiments, the individual has hypercholesterolemia, non-familial hypercholesterolemia, familial hypercholesterolemia, heterozygous familial hypercholesterolemia, homozygous familial hypercholesterolemia, mixed dyslipidemia, atherosclerosis, a risk of developing atherosclerosis, coronary heart disease, a history of coronary heart disease, early onset coronary heart disease, one or more risk factors for coronary heart disease, type II diabetes, type II diabetes with dyslipidemia, dyslipidemia, hypertriglyceridemia, hyperlipidemia, hyperfattyacidemia, hepatic steatosis, non-alcoholic steatohepatitis, or non-alcoholic fatty liver disease.

Guidelines for lipid-lowering therapy were established in 2001 by Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP), and updated in 2004 (Grundy et al., Circulation, 2004, 110, 227-239). The guidelines include obtaining a complete lipoprotein profile, typically after a 9 to 12 hour fast, for determination of LDL-C, total cholesterol, and HDL-C levels. According to the most recently established guidelines, LDL-C levels of 130-159 mg/dL, 160-189 mg/dL, and greater than or equal to 190 mg/dL are considered borderline high, high, and very high, respectively. Total cholesterol levels of 200-239 and greater than or equal to 240 mg/dL are considered borderline high and high, respectively. HDL-C levels of less than 40 mg/dL are considered low.

In certain embodiments, the individual has been identified as in need of lipid-lowering therapy. In certain such embodiments, the individual has been identified as in need of lipid-lowering therapy according to the guidelines established in 2001 by Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP), and updated in 2004 (Grundy et al., Circulation, 2004, 110, 227-239). In certain such embodiments, the individual in need of lipid-lowering therapy has LDL-C above 190 mg/dL. In certain such embodiments, the individual in need of lipid-lowering therapy has LDL-C above 160 mg/dL. In certain such embodiments, the individual in need of lipid-lowering therapy has LDL-C above 130 mg/dL. In certain such embodiments the individual in need of lipid-lowering therapy has LDL-C above 100 mg/dL. In certain such embodiments the individual in need of lipid-lowering therapy should maintain LDL-C below 160 mg/dL. In certain such embodiments the individual in need of lipid-lowering therapy should maintain LDL-C below 130 mg/dL. In certain such embodiments the individual in need of lipid-lowering therapy should maintain LDL-C below 100 mg/dL. In certain such embodiments the individual should maintain LDL-C below 70 mg/dL.

In certain embodiments the invention provides methods for reducing ApoB in an individual. In certain embodiments the invention provides methods for reducing ApoB-containing lipoprotein in an individual. In certain embodiments the invention provides methods for reducing LDL-C in an individual. In certain embodiments the invention provides methods for reducing VLDL-C in an individual. In certain embodiments the invention provides methods for reducing IDL-C in an individual. In certain embodiments the invention provides methods for reducing non-HDL-C in an individual. In certain embodiments the invention provides methods for reducing Lp(a) in an individual. In certain embodiments the invention provides methods for reducing serum triglyceride in an individual. In certain embodiments the invention provides methods for reducing liver triglyceride in an individual. In certain embodiments the invention provides methods for reducing Ox-LDL-C in an individual. In certain embodiments the invention provides methods for reducing small LDL particles in an individual. In certain embodiments the invention provides methods for reducing small VLDL particles in an individual. In certain embodiments the invention provides methods for reducing phospholipids in an individual. In certain embodiments the invention provides methods for reducing oxidized phospholipids in an individual.

In certain embodiments the invention provides methods for reducing Ox-LDL-C concentration in a subject. In certain such embodiments, the reduction in ApoB, LDL-C, VLDL-C, IDL-C, total cholesterol, non-HDL-C, Lp(a), triglyerides, or Ox-LDL-C is, independently, selected from at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, and at least 100%. In certain such embodiments, the reduction in ApoB, LDL-C, VLDL-C, IDL-C, total cholesterol, non-HDL-C, Lp(a), triglyerides, or Ox-LDL-C is, independently, selected from at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, and at least 70%. In certain such embodiments, the reduction in ApoB, LDL-C, VLDL-C, IDL-C, total cholesterol, non-HDL-C, Lp(a), triglyerides, or Ox-LDL-C is, independently, selected from at least 40%, at least 50%, at least 60%, and at least 70%.

In certain embodiments, the invention provides method for raising HDL-C concentration in a subject.

In certain embodiments, the methods provided by the present invention do not lower HDL-C. In certain embodiments, the methods provided by the present invention do not result in accumulation of lipids in the liver. In certain embodiments, the methods provided by the present invention do not cause hepatic steatosis.

In certain embodiments, the invention provides methods for lowering ApoB concentration in a subject while reducing side effects associated with treatment. In certain such embodiments, a side effect is liver toxicity. In certain such embodiments, a side effect is abnormal liver function. In certain such embodiments, a side effect is elevated alanine aminotransferase (ALT). In certain such embodiments, a side effect is elevated aspartate aminotransferase (AST).

In certain embodiments, the invention provides methods for lowering ApoB concentration in a subject who is not reaching target LDL-C levels as a result of lipid-lowering therapy. In certain such embodiments, a short antisense compound targeted to an ApoB nucleic acid is the only lipid-lowering agent administered to the subject. In certain such embodiments, the subject has not complied with recommended lipid-lowering therapy. In certain such embodiments, a pharmaceutical composition of the invention is co-administered with an additional different lipid-lowering therapy. In certain such embodiments, an additional lipid-lowering therapy is LDL-apheresis. In certain such embodiments, an additional lipid-lowering therapy is a statin. In certain such embodiments, an additional lipid-lowering therapy is ezetimibe.

In certain embodiments, the invention provides methods for lowering ApoB concentration in a statin-intolerant subject. In certain such embodiments, the subject has creatine kinase concentration increases as a result of statin administration. In certain such embodiments, the subject has liver function abnormalities as a result of statin administration. In certain such embodiments the subject has muscle aches as a result of statin administration. In certain such embodiments the subject has central nervous system side effects as a result of statin administration. In certain embodiments, the subject has not complied with recommended statin administration.

In certain embodiments, the invention provides methods for lowering liver triglycerides in a subject. In certain such embodiments, the subject has elevated liver triglycerides. In certain such embodiments, the subject has steatohepatitis. In certain such embodiments, the subject has steatosis. In certain such embodiments, liver triglyceride levels are measured by magnetic resonance imaging.

In certain embodiments, the invention provides methods for reducing coronary heart disease risk in a subject. In certain embodiments the invention provides methods for slowing the progression of atherosclerosis in a subject. In certain such embodiments the invention provides methods for stopping the progression of atherosclerosis in a subject. In certain such embodiments the invention provides methods for reducing the size and/or prevalence of atherosclerotic plaques in a subject. In certain embodiments the methods provided reduce a subject's risk of developing atherosclerosis.

In certain embodiments the methods provided improve the cardiovascular outcome in a subject. In certain such embodiments improved cardiovascular outcome is the reduction of the risk of developing coronary heart disease. In certain such embodiments, improved cardiovascular outcome is a reduction in the occurrence of one or more major cardiovascular events, which include, but are not limited to, death, myocardial infarction, reinfarction, stroke, cardiogenic shock, pulmonary edema, cardiac arrest, and atrial dysrhythmia. In certain such embodiments, the improved cardiovascular outcome is evidenced by improved carotid intimal media thickness. In certain such embodiments, improved carotid intimal media thickness is a decrease in thickness. In certain such embodiments, improved carotid intimal media thickness is a prevention an increase of intimal media thickness.

In certain embodiments a pharmaceutical composition comprising a short antisense compound targeted to an ApoB nucleic acid is for use in therapy. In certain embodiments, the therapy is the reduction of LDL-C, ApoB, VLDL-C, IDL-C, non-HDL-C, Lp(a) , serum triglyceride, liver triglyceride, Ox-LDL-C, small LDL particles, small VLDL, phospholipids, or oxidized phospholipids in an individual. In certain embodiments, the therapy is the treatment of hypercholesterolemia, non-familial hypercholesterolemia, familial hypercholesterolemia, heterozygous familial hypercholesterolemia, homozygous familial hypercholesterolemia, mixed dyslipidemia, atherosclerosis, a risk of developing atherosclerosis, coronary heart disease, a history of coronary heart disease, early onset coronary heart disease, one or more risk factors for coronary heart disease, type II diabetes, type II diabetes with dyslipidemia, dyslipidemia, hypertriglyceridemia, hyperlipidemia, hyperfattyacidemia, hepatic steatosis, non-alcoholic steatohepatitis, or non-alcoholic fatty liver disease. In additional embodiments, the therapy is the reduction of CHD risk. In certain the therapy is prevention of atherosclerosis. In certain embodiments, the therapy is the prevention of coronary heart disease.

In certain embodiments a pharmaceutical composition comprising a short antisense compound targeted to an ApoB nucleic acid is used for the preparation of a medicament for reducing LDL-C, ApoB, VLDL-C, IDL-C, non-HDL-C, Lp(a) , serum triglyceride, liver triglyceride, Ox-LDL-C, small LDL particles, small VLDL, phospholipids, or oxidized phospholipids in an individual. In certain embodiments pharmaceutical composition comprising a short antisense compound targeted to an ApoB nucleic acid is used for the preparation of a medicament for reducing coronary heart disease risk. In certain embodiments a short antisense compound targeted to an ApoB nucleic acid is used for the preparation of a medicament for the treatment of hypercholesterolemia, non-familial hypercholesterolemia, familial hypercholesterolemia, heterozygous familial hypercholesterolemia, homozygous familial hypercholesterolemia, mixed dyslipidemia, atherosclerosis, a risk of developing atherosclerosis, coronary heart disease, a history of coronary heart disease, early onset coronary heart disease, one or more risk factors for coronary heart disease, type II diabetes, type II diabetes with dyslipidemia, dyslipidemia, hypertriglyceridemia, hyperlipidemia, hyperfattyacidemia, hepatic steatosis, non-alcoholic steatohepatitis, or non-alcoholic fatty liver disease.

ApoB Combination Therapies

In certain embodiments, one or more pharmaceutical compositions comprising a short antisense compound targeted to an ApoB nucleic acid are co-administered with one or more other pharmaceutical agents. In certain embodiments, such one or more other pharmaceutical agents are designed to treat the same disease or condition as the one or more pharmaceutical compositions of the present invention. In certain such embodiments, the one or more pharmaceutical agents are lipid-lowering agents. In certain embodiments, such one or more other pharmaceutical agents are designed to treat a different disease or condition as the one or more pharmaceutical compositions of the present invention. In certain embodiments, such one or more other pharmaceutical agents are designed to treat an undesired effect of one or more pharmaceutical compositions of the present invention. In certain embodiments, one or more pharmaceutical compositions of the present invention are co-administered with another pharmaceutical agent to treat an undesired effect of that other pharmaceutical agent. In certain embodiments, one or more pharmaceutical compositions of the present invention and one or more other pharmaceutical agents are administered at the same time. In certain embodiments, one or more pharmaceutical compositions of the present invention and one or more other pharmaceutical agents are administered at different times. In certain embodiments, one or more pharmaceutical compositions of the present invention and one or more other pharmaceutical agents are prepared together in a single formulation. In certain embodiments, one or more pharmaceutical compositions of the present invention and one or more other pharmaceutical agents are prepared separately.

In certain embodiments, pharmaceutical agents that may be co-administered with a pharmaceutical composition comprising a short antisense compound targeted to an ApoB nucleic acid include lipid-lowering agents. In certain such embodiments, pharmaceutical agents that may be co-administered with a pharmaceutical composition of the present invention include, but are not limited to atorvastatin, simvastatin, rosuvastatin, and ezetimibe. In certain such embodiments, the lipid-lowering agent is administered prior to administration of a pharmaceutical composition of the present invention. In certain such embodiments, the lipid-lowering agent is administered following administration of a pharmaceutical composition of the present invention. In certain such embodiments the lipid-lowering agent is administered at the same time as a pharmaceutical composition of the present invention. In certain such embodiments the dose of a co-administered lipid-lowering agent is the same as the dose that would be administered if the lipid-lowering agent was administered alone. In certain such embodiments the dose of a co-administered lipid-lowering agent is lower than the dose that would be administered if the lipid-lowering agent was administered alone. In certain such embodiments the dose of a co-administered lipid-lowering agent is greater than the dose that would be administered if the lipid-lowering agent was administered alone.

In certain embodiments, a co-administered lipid-lowering agent is a HMG-CoA reductase inhibitor. In certain such embodiments the HMG-CoA reductase inhibitor is a statin. In certain such embodiments the statin is selected from atorvastatin, simvastatin, pravastatin, fluvastatin, and rosuvastatin.

In certain embodiments, a co-administered lipid-lowering agent is a cholesterol absorption inhibitor. In certain such embodiments, cholesterol absorption inhibitor is ezetimibe.

In certain embodiments, a co-administered lipid-lowering agent is a co-formulated HMG-CoA reductase inhibitor and cholesterol absorption inhibitor. In certain such embodiments the co-formulated lipid-lowering agent is ezetimibe/simvastatin.

In certain embodiments, a co-administered lipid-lowering agent is a microsomal triglyceride transfer protein inhibitor (MTP inhibitor).

In certain embodiments, a co-administered pharmaceutical agent is a bile acid sequestrant. In certain such embodiments, the bile acid sequestrant is selected from cholestyramine, colestipol, and colesevelam.

In certain embodiments, a co-administered pharmaceutical agent is a nicotinic acid. In certain such embodiments, the nicotinic acid is selected from immediate release nicotinic acid, extended release nicotinic acid, and sustained release nicotinic acid.

In certain embodiments, a co-administered pharmaceutical agent is a fibric acid. In certain such embodiments, a fibric acid is selected from gemfibrozil, fenofibrate, clofibrate, bezafibrate, and ciprofibrate.

Further examples of pharmaceutical agents that may be co-administered with a pharmaceutical composition comprising a short antisense compound targeted to an ApoB nucleic acid include, but are not limited to, corticosteroids, including but not limited to prednisone; immunoglobulins, including, but not limited to intravenous immunoglobulin (IVIg); analgesics (e.g., acetaminophen); anti-inflammatory agents, including, but not limited to non-steroidal anti-inflammatory drugs (e.g., ibuprofen, COX-1 inhibitors, and COX-2, inhibitors); salicylates; antibiotics; antivirals; antifungal agents; antidiabetic agents (e.g., biguanides, glucosidase inhibitors, insulins, sulfonylureas, and thiazolidenediones); adrenergic modifiers; diuretics; hormones (e.g., anabolic steroids, androgen, estrogen, calcitonin, progestin, somatostan, and thyroid hormones); immunomodulators; muscle relaxants; antihistamines; osteoporosis agents (e.g., biphosphonates, calcitonin, and estrogens); prostaglandins, antineoplastic agents; psychotherapeutic agents; sedatives; poison oak or poison sumac products; antibodies; and vaccines.

In certain embodiments, a pharmaceutical composition comprising a short antisense compound targeted to an ApoB nucleic acid may be administered in conjunction with a lipid-lowering therapy. In certain such embodiments, a lipid-lowering therapy is therapeutic lifestyle change. In certain such embodiments, a lipid-lowering therapy is LDL apheresis.

In one embodiment, the antisense compounds provided herein can be used to lower the level of apolipoprotein B-containing lipoproteins in a human subject. As used herein, "apolipoprotein B-containing lipoprotein" refers to any lipoprotein that has apolipoprotein B as its protein component, and is understood to include LDL, VLDL, IDL, and lipoprotein(a). LDL, VLDL, IDL and lipoprotein(a) each contain one molecule of apolipoprotein B, thus a serum apolipoprotein B measurement reflects the total number of these lipoproteins. As is known in the art, each of the aforementioned lipoproteins is atherogenic. Thus, lowering one or more apolipoprotein B-containing lipoproteins in serum may provide a therapeutic benefit to a human subject. Small LDL particles are considered to be particularly atherogenic relative to large LDL particles, thus lowering small LDL particles can provide a therapeutic benefit to a human subject. Additional lipid parameters can also be determined in a subject. Reduction of total cholesterol:HDL ratio or LDL:HDL ratio is a clinically desirable improvement in cholesterol ratio. Similarly, it is clinically desirable to reduce serum triglycerides in humans who exhibit elevated lipid levels.

Other indications of cardiovascular disease that can be measured in a subject include serum LDL particle size; serum LDL cholesteryl ester concentration; serum LDL cholesteryl ester composition; the extent of polyunsaturation of serum LDL cholesteryl esters; and serum HDL cholesterol levels. As used herein, "serum LDL particle size" refers to the classification of serum LDL particle size, which may be very small, small, medium, or large, and is typically expressed in g/μmol. In the context of the present invention, "serum LDL cholesteryl ester concentration" means the amount of cholesteryl ester present in LDL particles, and is typically measured as mg/dL. In the context of the present invention, "serum LDL cholesteryl ester composition" is a measurement of the percentage of saturated, monounsaturated and polyunsaturated cholesteryl ester fatty acids present in serum LDL particles. "Polyunsaturation of serum LDL cholesteryl esters" means the percentage of polyunsaturated cholesteryl ester fatty acids in serum LDL particles.

Methods of obtaining serum or plasma samples for analysis and methods of preparation of the serum samples to allow for analysis are well known to those skilled in the art. With regard to measurements of lipoproteins, cholesterol, triglyceride and cholesteryl esters, the terms "serum" and "plasma" are herein used interchangeably.

In another embodiment, the antisense compounds provided herein can be used to treat metabolic disorders. A variety of biomarkers can be used for evaluating metabolic disease. For example, blood glucose levels can be determined by a physician or even by the patient using a commonly available test kit or glucometer (for example, the Ascensia ELITE™ kit, Ascensia (Bayer), Tarrytown NY, or Accucheck, Roche Diagnostics). Glycated hemoglobin (HbA_{1c}) can also be measured. HbA_{1c} is a stable minor hemoglobin variant formed *in vivo* via posttranslational modification by glucose, and it contains predominantly glycated

NH_2-terminal ß-chains. There is a strong correlation between levels of HbA_{1c} and the average blood glucose levels over the previous 3 months. Thus HbA_{1c} is often viewed as the "gold standard" for measuring sustained blood glucose control (Bunn, H.F. et al., 1978, Science. 200, 21-7). HbA_{1c} can be measured by ion-exchange HPLC or immunoassay; home blood collection and mailing kits for HbA_{1c} measurement are now widely available. Serum fructosamine is another measure of stable glucose control and can be measured by a colorimetric method (Cobas Integra, Roche Diagnostics).

Certain Short Antisense Compounds Targeted to an ApoB Nucleic Acid

In certain embodiments, short antisense compounds are targeted to an ApoB nucleic acid having the sequence of GENBANK® Accession No. NM_000384.1, incorporated herein as SEQ ID NO: 1. In certain such embodiments, a short antisense compound targeted to SEQ ID NO: 1 is at least 90% complementary to SEQ ID NO: 1. In certain such embodiments, a short antisense compound targeted to SEQ ID NO: 1 is at least 95% complementary to SEQ ID NO: 1. In certain such embodiments, a short antisense compound targeted to SEQ ID NO: 1 is 100% complementary to SEQ ID NO: 1. In certain embodiments, a short antisense compound targeted to SEQ ID NO: 1 comprises a nucleotide sequence selected from the nucleotide sequences set forth in Table 2 and Table 3.

The nucleotide sequence set forth in each SEQ ID NO in Tables 2 and 3 is independent of any modification to a sugar moiety, a monomeric linkage, or a nucleobase. As such, short antisense compounds defined by a SEQ ID NO may comprise, independently, one or more modifications to a sugar moiety, an internucleoside linkage, or a nucleobase. Antisense compounds described by Isis Number (Isis NO.) indicate a combination of nucleobase sequence and one or more modifications to a sugar moiety, an internucleoside linkage, or a nucleobase.

Tables 2 and 3 illustrate examples of short antisense compounds targeted to SEQ ID NO: 1. Table 2 illustrates short antisense compounds that are 100% complementary to SEQ ID NO: 1. Table 3 illustrates short antisense compounds that have one or two mismatches with respect to SEQ ID NO: 1. The column labeled 'gapmer motif' indicates the wing-gap-wing motif of each short antisense compounds. The gap segment comprises 2'-deoxynucleotides and each nucleotide of each wing segment comprises a 2'-modified sugar. The particular 2'-modified sugar is also indicated in the 'gapmer motif' column. For example, '2-10-2 MOE' means a 2-10-2 gapmer motif, where a gap segment of ten 2'-deoxynucleotides is flanked by wing segments of two nucleotides, where the nucleotides of the wing segments are 2'-MOE nucleotides. Internucleoside linkages are phosphorothioate. The short antisense compounds comprise 5-methylcytidine in place of unmodified cytosine, unless "unmodified cytosine" is listed in the gapmer motif column, in which case the indicated cytosines are unmodified cytosines. For example, "5-mC in gap only" indicates that the gap segment has 5-methylcytosines, while the wing segments have unmodified cytosines.

Table 2: Short Antisense Compounds targeted to SEQ ID NO: 1

ISIS No	5' Target Site	3' Target Site	Sequence (5'-3')	Gapmer Motif	SEQ ID NO
372816	263	278	CCGGAGGTGCTTGAAT	3-10-3 MOE	16
372894	264	277	CGGAGGTGCTTGAA	2-10-2 MOE	17
372817	428	443	GAAGCCATACACCTCT	3-10-3 MOE	18
372895	429	442	AAGCCATACACCTC	2-10-2 MOE	19
372818	431	446	GTTGAAGCCATACACC	3-10-3 MOE	20
372896	432	445	TTGAAGCCATACAC	2-10-2 MOE	21
372819	438	453	CCTCAGGGTTGAAGCC	3-10-3 MOE	22
372897	439	452	CTCAGGGTTGAAGC	2-10-2 MOE	23
372820	443	458	TTTGCCCTCAGGGTTG	3-10-3 MOE	24
372898	444	457	TTGCCCTCAGGGTT	2-10-2 MOE	25
372821	468	483	AGTTCTTGGTTTTCTT	3-10-3 MOE	26
372899	469	482	GTTCTTGGTTTTCT	2-10-2 MOE	27
372822	587	602	CCTCTTGATGTTCAGG	3-10-3 MOE	28
372900	588	601	CTCTTGATGTTCAG	2-10-2 MOE	29
372823	592	607	ATGCCCCTCTTGATGT	3-10-3 MOE	30
372901	593	606	TGCCCCTCTTGATG	2-10-2 MOE	31
346583	715	728	TGCCACATTGCCCT	3-8-3 MOE	32
346584	716	729	TTGCCACATTGCCC	3-8-3 MOE	33
346585	717	730	GTTGCCACATTGCC	3-8-3 MOE	34
346586	718	731	TGTTGCCACATTGC	3-8-3 MOE	35
346587	719	732	CTGTTGCCACATTG	3-8-3 MOE	36
346588	720	733	TCTGTTGCCACATT	3-8-3 MOE	37
346589	721	734	TTCTGTTGCCACAT	3-8-3 MOE	38
346590	722	735	TTTCTGTTGCCACA	3-8-3 MOE	39
346591	723	736	ATTTCTGTTGCCAC	3-8-3 MOE	40
372824	929	944	GTAGGAGAAAGGCAGG	3-10-3 MOE	41
372902	930	943	TAGGAGAAAGGCAG	2-10-2 MOE	42
372825	1256	1271	GGCTTGTAAAGTGATG	3-10-3 MOE	43
372903	1257	1270	GCTTGTAAAGTGAT	2-10-2 MOE	44
372826	1304	1319	CCACTGGAGGATGTGA	3-10-3 MOE	45
372904	1305	1318	CACTGGAGGATGTG	2-10-2 MOE	46
372829	2135	2150	TTTCAGCATGCTTTCT	3-10-3 MOE	47
372907	2136	2149	TTCAGCATGCTTTC	2-10-2 MOE	48
372832	2774	2789	CATATTTGTCACAAAC	3-10-3 MOE	49
372910	2775	2788	ATATTTGTCACAAA	2-10-2 MOE	50
372833	2779	2794	ATGCCCATATTTGTCA	3-10-3 MOE	51
372911	2780	2793	TGCCCATATTTGTC	2-10-2 MOE	52
372835	2961	2976	TTTTGGTGGTAGAGAC	3-10-3 MOE	53
372913	2962	2975	TTTGGTGGTAGAGA	2-10-2 MOE	54
346592	3248	3261	TCTGCTTCGCACCT	3-8-3 MOE	55
346593	3249	3262	GTCTGCTTCGCACC	3-8-3 MOE	56
346594	3250	3263	AGTCTGCTTCGCAC	3-8-3 MOE	57
346595	3251	3264	CAGTCTGCTTCGCA	3-8-3 MOE	58
346596	3252	3265	TCAGTCTGCTTCGC	3-8-3 MOE	59
346597	3253	3266	CTCAGTCTGCTTCG	3-8-3 MOE	60

346598	3254	3267	CCTCAGTCTGCTTC	3-8-3 MOE	61
346599	3255	3268	GCCTCAGTCTGCTT	3-8-3 MOE	62
346600	3256	3269	AGCCTCAGTCTGCT	3-8-3 MOE	63
372836	3350	3365	AACTCTGAGGATTGTT	3-10-3 MOE	64
372914	3351	3364	ACTCTGAGGATTGT	2-10-2 MOE	65
372837	3355	3370	TCATTAACTCTGAGGA	3-10-3 MOE	66
372915	3356	3369	CATTAACTCTGAGG	2-10-2 MOE	67
372838	3360	3375	ATTCATCATTAACTCT	3-10-3 MOE	68
372916	3361	3374	TTCATCATTAACTC	2-10-2 MOE	69
372839	3409	3424	TTGTTCTGAATGTCCA	3-10-3 MOE	70
387461	3409	3424	TTGTTCTGAATGTCCA	3-10-3 Methyleneoxy BNA Unmodified cytosines in gap	70
380147	3409	3424	TTGTTCTGAATGTCCA	3-10-3 Methyleneoxy BNA	70
372917	3410	3423	TGTTCTGAATGTCC	2-10-2 MOE	73
372840	3573	3588	CAGATGAGTCCATTTG	3-10-3 MOE	74
372918	3574	3587	AGATGAGTCCATTT	2-10-2 MOE	75
372841	3701	3716	ATCCACAGGGAAATTG	3-10-3 MOE	76
372919	3702	3715	TCCACAGGGAAATT	2-10-2 MOE	77
372843	4219	4234	CAGTTGTACAAGTTGC	3-10-3 MOE	78
372921	4220	4233	AGTTGTACAAGTTG	2-10-2 MOE	79
372844	4301	4316	CACAGAGTCAGCCTTC	3-10-3 MOE	80
372922	4302	4315	ACAGAGTCAGCCTT	2-10-2 MOE	81
372845	4308	4323	GGTCAACCACAGAGTC	3-10-3 MOE	82
372923	4309	4322	GTCAACCACAGAGT	2-10-2 MOE	83
346601	5588	5601	CAGCCACATGCAGC	3-8-3 MOE	84
346602	5589	5602	CCAGCCACATGCAG	3-8-3 MOE	85
346603	5590	5603	ACCAGCCACATGCA	3-8-3 MOE	86
346604	5591	5604	TACCAGCCACATGC	3-8-3 MOE	87
346605	5592	5605	TTACCAGCCACATG	3-8-3 MOE	88
346606	5593	5606	GTTACCAGCCACAT	3-8-3 MOE	89
346607	5594	5607	GGTTACCAGCCACA	3-8-3 MOE	90
346608	5595	5608	AGGTTACCAGCCAC	3-8-3 MOE	91
346609	5596	5609	TAGGTTACCAGCCA	3-8-3 MOE	92
372851	5924	5939	AGGTTCTGCTTTCAAC	3-10-3 MOE	93
372929	5925	5938	GGTTCTGCTTTCAA	2-10-2 MOE	94
372854	6664	6679	TACTGATCAAATTGTA	3-10-3 MOE	95
372932	6665	6678	ACTGATCAAATTGT	2-10-2 MOE	96
372855	6908	6923	TTTTTCTTGTATCTGG	3-10-3 MOE	97
372933	6909	6922	TTTTCTTGTATCTG	2-10-2 MOE	98
372856	7190	7205	ATCCATTAAAACCTGG	3-10-3 MOE	99
372934	7191	7204	TCCATTAAAACCTG	2-10-2 MOE	100
372858	7817	7832	ATATTGCTCTGCAAAG	3-10-3 MOE	101
372936	7818	7831	TATTGCTCTGCAAA	2-10-2 MOE	102
346610	7818	7831	TATTGCTCTGCAAA	3-8-3 MOE	102
346611	7819	7832	ATATTGCTCTGCAA	3-8-3 MOE	104
346612	7820	7833	AATATTGCTCTGCA	3-8-3 MOE	105
346613	7821	7834	GAATATTGCTCTGC	3-8-3 MOE	106
346614	7822	7835	AGAATATTGCTCTG	3-8-3 MOE	107

346615	7823	7836	TAGAATATTGCTCT	3-8-3 MOE	108
346616	7824	7837	ATAGAATATTGCTC	3-8-3 MOE	109
346617	7825	7838	GATAGAATATTGCT	3-8-3 MOE	110
346618	7826	7839	GGATAGAATATTGC	3-8-3 MOE	111
372859	7995	8010	ATGGAATCCTCAAATC	3-10-3 MOE	112
372937	7996	8009	TGGAATCCTCAAAT	2-10-2 MOE	113
372861	8336	8351	GAATTCTGGTATGTGA	3-10-3 MOE	114
372939	8337	8350	AATTCTGGTATGTG	2-10-2 MOE	115
372862	8341	8356	AGCTGGAATTCTGGTA	3-10-3 MOE	116
372940	8342	8355	GCTGGAATTCTGGT	2-10-2 MOE	117
372863	8539	8554	TGAAAATCAAAATTGA	3-10-3 MOE	118
372941	8540	8553	GAAAATCAAAATTG	2-10-2 MOE	119
372871	9344	9359	AAACAGTGCATAGTTA	3-10-3 MOE	120
372949	9345	9358	AACAGTGCATAGTT	2-10-2 MOE	121
372872	9515	9530	TTCAGGAATTGTTAAA	3-10-3 MOE	122
372950	9516	9529	TCAGGAATTGTTAA	2-10-2 MOE	123
372875	9794	9809	TTTTGTTTCATTATAG	3-10-3 MOE	124
372953	9795	9808	TTTGTTTCATTATA	2-10-2 MOE	125
372877	10157	10172	GATGACACTTGATTTA	3-10-3 MOE	126
372955	10158	10171	ATGACACTTGATTT	2-10-2 MOE	127
372878	10161	10176	GTGTGATGACACTTGA	3-10-3 MOE	128
372956	10162	10175	TGTGATGACACTTG	2-10-2 MOE	129
372879	10167	10182	TATTCAGTGTGATGAC	3-10-3 MOE	130
372957	10168	10181	ATTCAGTGTGATGA	2-10-2 MOE	131
372880	10172	10187	ATTGGTATTCAGTGTG	3-10-3 MOE	132
372958	10173	10186	TTGGTATTCAGTGT	2-10-2 MOE	133
346619	10838	10851	CCTCTAGCTGTAAG	3-8-3 MOE	134
346620	10839	10852	CCCTCTAGCTGTAA	3-8-3 MOE	135
346621	10840	10853	GCCCTCTAGCTGTA	3-8-3 MOE	136
346622	10841	10854	GGCCCTCTAGCTGT	3-8-3 MOE	137
346623	10842	10855	AGGCCCTCTAGCTG	3-8-3 MOE	138
346624	10843	10856	GAGGCCCTCTAGCT	3-8-3 MOE	139
346625	10844	10857	AGAGGCCCTCTAGC	3-8-3 MOE	140
346626	10845	10858	AAGAGGCCCTCTAG	3-8-3 MOE	141
346627	10846	10859	AAAGAGGCCCTCTA	3-8-3 MOE	142
372890	13689	13704	GAATGGACAGGTCAAT	3-10-3 MOE	143
372968	13690	13703	AATGGACAGGTCAA	2-10-2 MOE	144
372891	13694	13709	GTTTTGAATGGACAGG	3-10-3 MOE	145
372969	13695	13708	TTTTGAATGGACAG	2-10-2 MOE	146
372892	13699	13714	TGGTAGTTTTGAATGG	3-10-3 MOE	147
372970	13700	13713	GGTAGTTTTGAATG	2-10-2 MOE	148
346628	13907	13920	TCACTGTATGGTTT	3-8-3 MOE	149
346629	13908	13921	CTCACTGTATGGTT	3-8-3 MOE	150
346630	13909	13922	GCTCACTGTATGGT	3-8-3 MOE	151
346631	13910	13923	GGCTCACTGTATGG	3-8-3 MOE	152
346632	13911	13924	TGGCTCACTGTATG	3-8-3 MOE	153
346633	13912	13925	CTGGCTCACTGTAT	3-8-3 MOE	154
346634	13913	13926	GCTGGCTCACTGTA	3-8-3 MOE	155
346635	13914	13927	GGCTGGCTCACTGT	3-8-3 MOE	156
346636	13915	13928	AGGCTGGCTCACTG	3-8-3 MOE	157

346637	13963	13976	CAGGTCCAGTTCAT	3-8-3 MOE	158
346638	13964	13977	GCAGGTCCAGTTCA	3-8-3 MOE	159
346639	13965	13978	TGCAGGTCCAGTTC	3-8-3 MOE	160
346640	13966	13979	GTGCAGGTCCAGTT	3-8-3 MOE	161
346641	13967	13980	GGTGCAGGTCCAGT	3-8-3 MOE	162
346642	13968	13981	TGGTGCAGGTCCAG	3-8-3 MOE	163
346643	13969	13982	TTGGTGCAGGTCCA	3-8-3 MOE	164
346644	13970	13983	TTTGGTGCAGGTCC	3-8-3 MOE	165
346645	13971	13984	CTTTGGTGCAGGTC	3-8-3 MOE	166
346646	14051	14064	TAACTCAGATCCTG	3-8-3 MOE	167
346647	14052	14065	ATAACTCAGATCCT	3-8-3 MOE	168
346648	14053	14066	AATAACTCAGATCC	3-8-3 MOE	169
346649	14054	14067	AAATAACTCAGATC	3-8-3 MOE	170
346650	14055	14068	AAAATAACTCAGAT	3-8-3 MOE	171
346651	14056	14069	CAAAATAACTCAGA	3-8-3 MOE	172
346652	14057	14070	GCAAAATAACTCAG	3-8-3 MOE	173
346653	14058	14071	AGCAAAATAACTCA	3-8-3 MOE	174
346654	14059	14072	TAGCAAAATAACTC	3-8-3 MOE	175

Table 3: Short antisense compounds targeted to SEQ ID NO: 1 and having 1 or 2 mismatches

Isis NO.	5' Target Site	3' Target Site	Sequence (5'-3')	Gapmer Motif	SEQ ID NO
372894	771	784	CGGAGGTGCTTGAA	2-10-2 MOE	17
372905	1111	1124	CAGGGCCTGGAGAG	2-10-2 MOE	176
346628	1493	1506	TCACTGTATGGTTT	3-8-3 MOE	149
372828	2006	2021	TCTGAAGTCCATGATC	3-10-3 MOE	177
372906	2007	2020	CTGAAGTCCATGAT	2-10-2 MOE	178
372830	2382	2397	TGGGCATGATTCCATT	3-10-3 MOE	179
372908	2383	2396	GGGCATGATTCCAT	2-10-2 MOE	180
346616	3162	3175	ATAGAATATTGCTC	3-8-3 MOE	109
346617	3163	3176	GATAGAATATTGCT	3-8-3 MOE	110
372929	3513	3526	GGTTCTGCTTTCAA	2-10-2 MOE	94
372946	3800	3813	TGGAGCCCACGTGC	2-10-2 MOE	181
372904	4040	4053	CACTGGAGGATGTG	2-10-2 MOE	46
372842	4084	4099	TTGAAGTTGAGGGCTG	3-10-3 MOE	182
372920	4085	4098	TGAAGTTGAGGGCT	2-10-2 MOE	183
346586	4778	4791	TGTTGCCACATTGC	3-8-3 MOE	35
372847	5030	5045	ACCAGTATTAATTTTG	3-10-3 MOE	184
372925	5031	5044	CCAGTATTAATTTT	2-10-2 MOE	185
372848	5192	5207	GTGTTCTTTGAAGCGG	3-10-3 MOE	186
372926	5193	5206	TGTTCTTTGAAGCG	2-10-2 MOE	187
372953	5625	5638	TTTGTTTCATTATA	2-10-2 MOE	125
372935	7585	7598	AGTTACTTTGGTGT	2-10-2 MOE	188
372860	8255	8270	TGGTACATGGAAGTCT	3-10-3 MOE	189
372938	8256	8269	GGTACATGGAAGTC	2-10-2 MOE	190
391260	8256	8269	GGTACATGGAAGTC	2-10-2 MOE	190
392068	8256	8269	GGTACATGGAAGTC	2-10-2 MOE	190
387462	8256	8269	GGTACATGGAAGTC	2-10-2 Methyleneoxy	190

				BNA	
391872	8256	8269	GGTACATGGAAGTC	1-1-10-2 2'-(butylacetomido)-palmitamide Methyleneoxy BNA/Methyleneoxy BNA Unmodified cytosines in gap	190
380148	8256	8269	GGTACATGGAAGTC	2-10-2 Methyleneoxy BNA	190
391871	8256	8269	GGTACATGGAAGTC	1-1-10-2 2'-(butylacetomido)-palmitamide/MOE/MOE Unmodified cytosines in gap	190
391755	8256	8269	GGTACATGGAAGTC	2-10-2 ENA mC in wing only	190
398296	8256	8269	GGTACATGGAAGTC	2-10-2 (6'S)-6'-methyl-Methyleneoxy BNA Unmodified Cytosines	190
372942	8455	8468	TCCATGCCATATGT	2-10-2 MOE	200
372865	8888	8903	CCCTGAAGAAGTCCAT	3-10-3 MOE	201
372943	8889	8902	CCTGAAGAAGTCCA	2-10-2 MOE	202
372866	8908	8923	GCCCAGTTCCATGACC	3-10-3 MOE	203
372944	8909	8922	CCCAGTTCCATGAC	2-10-2 MOE	204
372867	9058	9073	TTGAGGAAGCCAGATT	3-10-3 MOE	205
372945	9059	9072	TGAGGAAGCCAGAT	2-10-2 MOE	206
372870	9261	9276	TGGATGCAGTAATCTC	3-10-3 MOE	207
372948	9262	9275	GGATGCAGTAATCT	2-10-2 MOE	208
372881	10185	10200	TATAAAGTCCAGCATT	3-10-3 MOE	209
372959	10186	10199	ATAAAGTCCAGCAT	2-10-2 MOE	210
372882	10445	10460	AAGTTCCTGCTTGAAG	3-10-3 MOE	211
372960	10446	10459	AGTTCCTGCTTGAA	2-10-2 MOE	212
372964	11451	11464	AATGGTGAAGTACT	2-10-2 MOE	213
346612	13459	13472	AATATTGCTCTGCA	3-8-3 MOE	105
346613	13460	13473	GAATATTGCTCTGC	3-8-3 MOE	106

In certain embodiments, a target region is nucleotides 263-278 of SEQ ID NO: 1. In certain such embodiments, short antisense compounds targeted to nucleotides 263-278 of SEQ ID NO: 1 comprise a nucleotide sequence selected from SEQ ID NO: 16 or 17. In certain such embodiments, a short antisense compound targeted to nucleotides 263-278 of SEQ ID NO: 1 is selected from Isis NO. 372816 or 372894.

In certain embodiments, a target region is nucleotides 428-483 of SEQ ID NO: 1. In certain such embodiments, a short antisense compound targeted to nucleotides 428-483 of SEQ ID NO: 1 comprises a nucleotide sequence selected from SEQ ID NO 18, 19, 20, 21, 22, 23, 24, 25, 26, or 27. In certain such embodiments, a short antisense compound targeted to nucleotides 428-483 of SEQ ID NO: 1 is selected from

Isis NO. 372817, 372895, 372818, 372896, 372819, 372897, 372820, 372898, 372821, or 372899.

In certain embodiments, a target region is nucleotides 428-458 of SEQ ID NO: 1. In certain such embodiments, a short antisense compound targeted to nucleotides 428-458 of SEQ ID NO: 1 comprises a nucleotide sequence selected from SEQ ID NO 18, 19, 20, 21, 22, 23, 24, or 25. In certain such embodiments, a short antisense compound targeted to nucleotides 428-458 of SEQ ID NO: 1 is selected from Isis NO. 372817, 372895, 372818, 372896, 372819, 372897, 372820, or 372898.

In certain embodiments, a target region is nucleotides 468-483 of SEQ ID NO: 1. In certain such embodiments, a short antisense compound targeted to nucleotides 468-483 of SEQ ID NO: 1 comprises a nucleotide sequence selected from SEQ ID NO 26 or 27. In certain such embodiments, a short antisense compound targeted to nucleotides 468-483 of SEQ ID NO: 1 is selected from Isis NO. 372821 or 372899.

In certain embodiments, a target region is nucleotides 587-607 of SEQ ID NO: 1. In certain such embodiments, a short antisense compound targeted to nucleotides 587-607 of SEQ ID NO: 1 comprises a nucleotide sequence selected from SEQ ID NO 28, 29, 30, or 31. In certain such embodiments, a short antisense compound targeted to nucleotides 587-607 of SEQ ID NO: 1 is selected from ISIS NO. 372822, 372900, 372823, or 372901.

In certain embodiments, a target region is nucleotides 715-736 of SEQ ID NO: 1. In certain such embodiments, a short antisense compound targeted to nucleotides 715-736 of SEQ ID NO: 1 comprises a nucleotide sequence selected from SEQ ID NO 32, 33, 34, 35, 36, 37, 38, 39, or 40. In certain such embodiments, a short antisense compound targeted to nucleotides 715-736 of SEQ ID NO: 1 is selected from Isis NO. 346583, 346584, 346585, 346586, 346587, 346588, 346589, 346590, or 346591.

In certain embodiments, a target region is nucleotides 929-944 of SEQ ID NO: 1. In certain such embodiments, a short antisense compound targeted to nucleotides 929-944 of SEQ ID NO: 1 comprises a nucleotide sequence selected from SEQ ID NO 41 or 42. In certain such embodiments, a short antisense compound targeted to nucleotides 929-944 of SEQ ID NO: 1 is selected from Isis NO. 372824 or 372902.

In certain embodiments, a target region is nucleotides 1256-1319 of SEQ ID NO: 1. In certain such embodiments, a short antisense compound targeted to nucleotides 1256-1319 of SEQ ID NO: 1 comprises a nucleotide sequence selected from SEQ ID NO 43, 44, 45, or 46. In certain such embodiments, a short antisense compound targeted to nucleotides 1256-1319 of SEQ ID NO: 1 is selected from Isis NO. 372825, 372903, 372826, or 372904.

In certain embodiments, a target region is nucleotides 1256-1271 of SEQ ID NO: 1. In certain such embodiments, a short antisense compound targeted to nucleotides 1256-1271 of SEQ ID NO: 1 comprises a nucleotide sequence selected from SEQ ID NO 43 or 44. In certain such embodiments, a short antisense compound targeted to nucleotides 1256-1271 of SEQ ID NO: 1 is selected from Isis NO. 372825 or 372903.

In certain embodiments, a target region is nucleotides 1304-1319 of SEQ ID NO: 1. In certain such embodiments, a short antisense compound targeted to nucleotides 1304-1319 of SEQ ID NO: 1 comprises a

nucleotide sequence selected from SEQ ID NO 45 or 46. In certain such embodiments, a short antisense compound targeted to nucleotides 1304-1319 of SEQ ID NO: 1 is selected from Isis NO. 372826 or 372904.

In certain embodiments, a target region is nucleotides 2135-2150 of SEQ ID NO: 1. In certain such embodiments, a short antisense compound targeted to nucleotides 2135-2150 of SEQ ID NO: 1 comprises a nucleotide sequence selected from SEQ ID NO 47 or 48. In certain such embodiments, a short antisense compound targeted to nucleotides 2135-2150 of SEQ ID NO: 1 is selected from ISIS NO. 372829 or 372907.

In certain embodiments, a target region is nucleotides 2774-2794 of SEQ ID NO: 1. In certain such embodiments, a short antisense compound targeted to nucleotides 2774-2794 of SEQ ID NO: 1 comprises a nucleotide sequence selected from SEQ ID NO 49, 50, 51, or 52. In certain such embodiments, a short antisense compound targeted to nucleotides 2774-2794 of SEQ ID NO: 1 is selected from ISIS NO. 372832, 372910, 372833, or 372911.

In certain embodiments, a target region is nucleotides 2961-2976 of SEQ ID NO: 1. In certain such embodiments, a short antisense compound targeted to nucleotides 2961-2976 of SEQ ID NO: 1 comprises a nucleotide sequence selected from SEQ ID NO 53 or 54. In certain such embodiments, a short antisense compound targeted to nucleotides 2961-2976 of SEQ ID NO: 1 is selected from ISIS NO. 372835 or 372913.

In certain embodiments, a target region is nucleotides 3248-3269 of SEQ ID NO: 1. In certain such embodiments, a short antisense compound targeted to nucleotides 3248-3269 of SEQ ID NO: 1 comprises a nucleotide sequence selected from SEQ ID NO 55, 56, 57, 58, 59, 60, 61, 62, or 63. In certain such embodiments, a short antisense compound targeted to nucleotides 3248-3269 of SEQ ID NO: 1 is selected from ISIS NO. 346592, 346593, 346594, 346595, 346596, 346597, 346598, 346599, or 346600.

In certain embodiments, a target region is nucleotides 3350-3375 of SEQ ID NO: 1. In certain such embodiments, a short antisense compound targeted to nucleotides 3350-3375 of SEQ ID NO: 1 comprises a nucleotide sequence selected from SEQ ID NO 64, 65, 66, 67, 68, or 69. In certain such embodiments, a short antisense compound targeted to nucleotides 3350-3375 of SEQ ID NO: 1 is selected from ISIS NO. 372836, 372914, 372837, 372915, 372838, or 372916.

In certain embodiments, a target region is nucleotides 3409-3424 of SEQ ID NO: 1. In certain such embodiments, a short antisense compound targeted to nucleotides 3409-3424 of SEQ ID NO: 1 comprises a nucleotide sequence selected from SEQ ID NO 70 or 73. In certain such embodiments, a short antisense compound targeted to nucleotides 3409-3424 of SEQ ID NO: 1 is selected from ISIS NO. 372839, 387461, 380147, or 372917.

In certain embodiments, a target region is nucleotides 3573-3588 of SEQ ID NO: 1. In certain such embodiments, a short antisense compound targeted to nucleotides 3573-3588 of SEQ ID NO: 1 comprises a nucleotide sequence selected from SEQ ID NO 74 or 75. In certain such embodiments, a short antisense compound targeted to nucleotides 3573-3588 of SEQ ID NO: 1 is selected from ISIS NO. 372840 or 372918.

In certain embodiments, a target region is nucleotides 3701-3716 of SEQ ID NO: 1. In certain such

embodiments, a short antisense compound targeted to nucleotides 3701-3716 of SEQ ID NO: 1 comprises a nucleotide sequence selected from SEQ ID NO 76 or 77. In certain such embodiments, a short antisense compound targeted to nucleotides 3701-3716 of SEQ ID NO: 1 is selected from ISIS NO. 372841 or 372919.

In certain embodiments, a target region is nucleotides 4219-4234 of SEQ ID NO: 1. In certain such embodiments, a short antisense compound targeted to nucleotides 4219-4234 of SEQ ID NO: 1 comprises a nucleotide sequence selected from SEQ ID NO 78 or 79. In certain such embodiments, a short antisense compound targeted to nucleotides 4219-4234 of SEQ ID NO: 1 is selected from ISIS NO. 372843 or 372921.

In certain embodiments, a target region is nucleotides 4301-4323 of SEQ ID NO: 1. In certain such embodiments, a short antisense compound targeted to nucleotides 4301-4323 of SEQ ID NO: 1 comprises a nucleotide sequence selected from SEQ ID NO 80, 81, 82, or 83. In certain embodiments, a short antisense compound targeted to nucleotides 4301-4323 of SEQ ID NO: 1 is selected from ISIS NO. 372844, 372922, 372845, or 372923.

In certain embodiments, a target region is nucleotides 5588-5609 of SEQ ID NO: 1. In certain such embodiments, a short antisense compound targeted to nucleotides 5588-5609 of SEQ ID NO: 1 comprises a nucleotide sequence selected from SEQ ID NO 84, 85, 86, 87, 88, 89, 90, 91, or 92. In certain such embodiments, a short antisense compound targeted to nucleotides 5588-5609 of SEQ ID NO: 1 is selected from ISIS NO. 346601, 346602, 346603, 346604, 346605, 346606, 346607, 346608, or 346609.

In certain embodiments, a target region is nucleotides 5924-5939 of SEQ ID NO: 1. In certain such embodiments, a short antisense compound targeted to nucleotides 5924-5939 of SEQ ID NO: 1 comprises a nucleotide sequence selected from SEQ ID NO 93 or 94. In certain such embodiments, a short antisense compound targeted to nucleotides 5924-5939 of SEQ ID NO: 1 is selected from ISIS NO. 372851 or 372929.

In certain embodiments, a target region is nucleotides 6664-6679 of SEQ ID NO: 1. In certain such embodiments, a short antisense compound targeted to nucleotides 6664-6679 of SEQ ID NO: 1 comprises a nucleotide sequence selected from SEQ ID NO 95 or 96. In certain such embodiments, a short antisense compound targeted to nucleotides 6664-6679 of SEQ ID NO: 1 is selected from ISIS NO. 372854 or 372932.

In certain embodiments, a target region is nucleotides 6908-6923 of SEQ ID NO: 1. In certain such embodiments, a short antisense compound targeted to nucleotides 6908-6923 of SEQ ID NO: 1 comprises a nucleotide sequence selected from SEQ ID NO 97 or 98. In certain such embodiments, a short antisense compound targeted to nucleotides 6908-6923 of SEQ ID NO: 1 is selected from ISIS NO. 372855 or 372933.

In certain embodiments, a target region is nucleotides 7190-7205 of SEQ ID NO: 1. In certain such embodiments, a short antisense compound targeted to nucleotides 7190-7205 of SEQ ID NO: 1 comprises a nucleotide sequence selected from SEQ ID NO 99 or 100. In certain such embodiments, a short antisense compound targeted to nucleotides 7190-7205 of SEQ ID NO: 1 is selected from ISIS NO. 372856 or 372934.

In certain embodiments, a target region is nucleotides 7817-7839 of SEQ ID NO: 1. In certain such embodiments, a short antisense compound targeted to nucleotides 7817-7839 of SEQ ID NO: 1 comprises a

nucleotide sequence selected from SEQ ID NO 101, 102, 104, 105, 106, 107, 108, 109, 110, or 111. In certain such embodiments, a short antisense compound targeted to nucleotides 7817-7839 of SEQ ID NO: 1 is selected from ISIS NO. 372858, 372936, 346610, 346611, 346612, 346613, 346614, 346615, 346616, 346617, or 346618.

In certain embodiments, a target region is nucleotides 7995-8010 of SEQ ID NO: 1. In certain such embodiments, a short antisense compound targeted to nucleotides 7995-8010 of SEQ ID NO: 1 comprises a nucleotide sequence selected from SEQ ID NO 112 or 113. In certain such embodiments, a short antisense compound targeted to nucleotides 7995-8010 of SEQ ID NO: 1 is selected from ISIS NO. 372859 or 372937.

In certain embodiments, a target region is nucleotides 8336-8356 of SEQ ID NO: 1. In certain such embodiments, a short antisense compound targeted to nucleotides 8336-8356 of SEQ ID NO: 1 comprises a nucleotide sequence selected from SEQ ID NO 114, 115, 116, or 117. In certain such embodiments, a short antisense compound targeted to nucleotides 8336-8356 of SEQ ID NO: 1 is selected from ISIS NO. 372861, 372939, 372862, or 372940.

In certain embodiments, a target region is nucleotides 8539-8554 of SEQ ID NO: 1. In certain such embodiments, a short antisense compound targeted to nucleotides 8539-8554 of SEQ ID NO: 1 comprises a nucleotide sequence selected from SEQ ID NO 118 or 119. In certain such embodiments, a short antisense compound targeted to nucleotides 8539-8554 of SEQ ID NO: 1 is selected from ISIS NO. 372863 or 372941.

In certain embodiments, a target region is nucleotides 9344-9359 of SEQ ID NO: 1. In certain such embodiments, a short antisense compound targeted to nucleotides 9344-9359 of SEQ ID NO: 1 comprises a nucleotide sequence selected from SEQ ID NO 120 or 121. In certain such embodiments, a short antisense compound targeted to nucleotides 9344-9359 of SEQ ID NO: 1 is selected from ISIS NO. 372871 or 372949.

In certain embodiments, a target region is nucleotides 9515-9530 of SEQ ID NO: 1. In certain such embodiments, a short antisense compound targeted to nucleotides 9515-9530 of SEQ ID NO: 1 comprises a nucleotide sequence selected from SEQ ID NO 122 or 123. In certain such embodiments, a short antisense compound targeted to nucleotides 9515-9530 of SEQ ID NO: 1 is selected from ISIS NO. 372872 or 372950.

In certain embodiments, a target region is nucleotides 9794-9809 of SEQ ID NO: 1. In certain such embodiments, a short antisense compound targeted to nucleotides 9794-9809 of SEQ ID NO: 1 comprises a nucleotide sequence selected from SEQ ID NO 124 or 125. In certain such embodiments, a short antisense compound targeted to nucleotides 9794-9809 of SEQ ID NO: 1 is selected from ISIS NO. 372875 or 372953.

In certain embodiments, a target region is nucleotides 10157-10187 of SEQ ID NO: 1. In certain such embodiments, a short antisense compound targeted to nucleotides 10157-10187 of SEQ ID NO: 1 comprises a nucleotide sequence selected from SEQ ID NO 126, 127, 128, 129, 130, 131, 132, or 133. In certain such embodiments, a short antisense compound targeted to nucleotides 10157-10187 of SEQ ID NO: 1 is selected from ISIS NO. 372877, 372955, 372878, 372956, 372879, 372957, 372880, or 372958.

In certain embodiments, a target region is nucleotides 10838-10859 of SEQ ID NO: 1. In certain such

embodiments, a short antisense compound targeted to nucleotides 10838-10859 of SEQ ID NO: 1 comprises a nucleotide sequence selected from SEQ ID NO 134, 135, 136, 137, 138, 139, 140, 141, or 142. In certain such embodiments, a short antisense compound targeted to nucleotides 10838-10859 of SEQ ID NO: 1 is selected from ISIS NO. 346619, 346620, 346621, 346622, 346623, 346624, 346625, 346626, or 346627.

In certain embodiments, a target region is nucleotides 13689-13714 of SEQ ID NO: 1. In certain such embodiments, a short antisense compound targeted to nucleotides 13689-13714 of SEQ ID NO: 1 comprises a nucleotide sequence selected from SEQ ID NO 143, 144, 145, 146, 147, or 148. In certain such embodiments, a short antisense compound targeted to nucleotides 13689-13714 of SEQ ID NO: 1 is selected from ISIS NO. 372890, 372968, 372891, 372969, 372892, or 372970.

In certain embodiments, a target region is nucleotides 13907-13928 of SEQ ID NO: 1. In certain such embodiments, a short antisense compound targeted to nucleotides 13907-13928 of SEQ ID NO: 1 comprises a nucleotide sequence selected from SEQ ID NO 149, 150, 151, 152, 153, 154, 155, 156, or 157. In certain such embodiments, a short antisense compound targeted to nucleotides 13907-13928 of SEQ ID NO: 1 is selected from ISIS NO. 346628, 346629, 346630, 346631, 346632, 346633, 346634, 346635, or 346636.

In certain embodiments, a target region is nucleotides 13963-13984 of SEQ ID NO: 1. In certain such embodiments, a short antisense compound targeted to nucleotides 13963-13984 of SEQ ID NO: 1 comprises a nucleotide sequence selected from SEQ ID NO 158, 159, 160, 161, 162, 163, 164, 165, or 166. In certain such embodiments, a short antisense compound targeted to nucleotides 13963-13984 of SEQ ID NO: 1 is selected from ISIS NO. 346637, 346638, 346639, 346640, 346641, 346642, 346643, 346644, or 346645.

In certain embodiments, a target region is nucleotides 14051-14072 of SEQ ID NO: 1. In certain such embodiments, a short antisense compound targeted to nucleotides 14051-14072 of SEQ ID NO: 1 comprises a nucleotide sequence selected from SEQ ID NO 167, 168, 169, 170, 171, 172, 173, 174, or 175. In certain such embodiments, a short antisense compound targeted to nucleotides 14051-14072 of SEQ ID NO: 1 is selected from ISIS NO. 346646, 346647, 346648, 346649, 346650, 346651, 346652, 346653, or 346654.

In certain embodiments, short antisense compounds targeted to an ApoB nucleic acid are 8 to 16, preferably 9 to 15, more preferably 9 to 14, more preferably 10 to 14 nucleotides in length. In certain embodiments, short antisense compounds targeted to an ApoB nucleic acid are 9 to 14 nucleotides in length. In certain embodiments, short antisense compounds targeted to an ApoB nucleic acid are 10 to 14 nucleotides in length. In certain embodiments, such short antisense compounds are short antisense oligonucleotides.

In certain embodiments, short antisense compounds targeted to an ApoB nucleic acid are short gapmers. In certain such embodiments, short gapmers targeted to an ApoB nucleic acid comprise at least one high affinity modification in one or more wings of the compound. In certain embodiments, short antisense compounds targeted to an ApoB nucleic acid comprise 1 to 3 high-affinity modifications in each wing. In certain such embodiments, the nucleosides or nucleotides of the wing comprise a 2' modification. In certain such embodiments, the monomers of the wing are BNA's. In certain such embodiments, the monomers of the wing are selected from α-L-Methyleneoxy (4'-CH_2-O-2') BNA , β-D-Methyleneoxy (4'-CH_2-O-2') BNA , Ethyleneoxy (4'-$(CH_2)_2$-O-2') BNA , Aminooxy (4'-CH_2-O-N(R)-2') BNA and Oxyamino (4'-CH_2-N(R)-O-2') BNA. In certain embodiments, the monomers of a wing comprise a substituent at the 2' position selected from allyl, amino, azido, thio, O-allyl, O-C_1-C_{10} alkyl, -OCF_3, O-$(CH_2)_2$-O-CH_3, 2'-O$(CH_2)_2SCH_3$, O-$(CH_2)_2$-O-N(R_m)(R_n), and O-CH_2-C(=O)-N(R_m)(R_n), where each R_m and R_n is, independently, H or substituted or unsubstituted C_1-C_{10} alkyl. In certain embodiments, the monomers of a wing are 2'MOE nucleotides.

In certain embodiments, short antisense compounds targeted to an ApoB nucleic acid comprise a gap between the 5' wing and the 3' wing. In certain embodiments the gap comprises five, six, seven, eight, nine, ten, eleven, twelve, thirteen, or fourteen monomers. In certain embodiments, the monomers of the gap are unmodified deoxyribonucleotides. In certain embodiments, the monomers of the gap are unmodified ribonucleotides. In certain embodiments, gap modifications (if any) gap result in an antisense compound that, when bound to its target nucleic acid, supports cleavage by an RNase, including, but not limited to, RNase H.

In certain embodiments, short antisense compounds targeted to an ApoB nucleic acid have uniform monomeric linkages. In certain such embodiments, those linkages are all phosphorothioate linkages. In certain embodiments, the linkages are all phosphodiester linkages. In certain embodiments, short antisense compounds targeted to an ApoB nucleic acid have mixed backbones.

In certain embodiments, short antisense compounds targeted to an ApoB nucleic acid are 8 monomers in length. In certain embodiments, short antisense compounds targeted to an ApoB nucleic acid are 9 monomers in length. In certain embodiments, short antisense compounds targeted to an ApoB nucleic acid are 10 monomers in length. In certain embodiments, short antisense compounds targeted to an ApoB nucleic acid are 11 monomers in length. In certain embodiments, short antisense compounds targeted to an ApoB nucleic acid are monomers in length. In certain embodiments, short antisense compounds targeted to an ApoB nucleic acid are 13 monomers in length. In certain embodiments, short antisense compounds targeted to an ApoB nucleic acid are 14 monomers in length. In certain embodiments, short antisense compounds targeted to an ApoB nucleic acid are 15 monomers in length. In certain embodiments, short antisense compounds targeted to an ApoB nucleic acid are 16 monomers in length. In certain embodiments, short antisense compounds targeted to an ApoB nucleic acid comprise 9 to 15 monomers. In certain embodiments, short antisense compounds targeted to an ApoB nucleic acid comprise 10 to 15 monomers. In certain embodiments, short antisense compounds targeted to an ApoB nucleic acid comprise 12 to 14 monomers. In certain embodiments, short antisense compounds targeted to an ApoB nucleic acid comprise 12 to 14 nucleotides or nucleosides.

In certain embodiments, the invention provides methods of modulating expression of ApoB. In certain embodiments, such methods comprise use of one or more short antisense compound targeted to an ApoB nucleic acid, wherein the short antisense compound targeted to an ApoB nucleic acid is from about 8 to about 16, preferably 9 to 15, more preferably 9 to 14, more preferably 10 to 14 monomers (i.e. from about 8 to about 16 linked monomers). One of ordinary skill in the art will appreciate that this comprehends methods of modulating expression of ApoB using one or more short antisense compounds targeted to an ApoB nucleic acid of 8, 9, 10, 11, 12, 13, 14, 15 or 16 monomers.

In certain embodiments, methods of modulating ApoB comprise use of a short antisense compound targeted to an ApoB nucleic acid that is 8 monomers in length. In certain embodiments, methods of modulating ApoB comprise use of a short antisense compound targeted to an ApoB nucleic acid that is 9 monomers in length. In certain embodiments, methods of modulating ApoB comprise use of a short antisense compound targeted to an ApoB nucleic acid that is 10 monomers in length. In certain embodiments, methods of modulating ApoB comprise use of a short antisense compound targeted to an ApoB nucleic acid that is 11 monomers in length. In certain embodiments, methods of modulating ApoB comprise use of a short antisense compound targeted to an ApoB nucleic acid that is 12 monomers in length. In certain embodiments, methods of modulating ApoB comprise use of a short antisense compound targeted to an ApoB nucleic acid that is 13 monomers in length. In certain embodiments, methods of modulating ApoB comprise use of a short antisense compound targeted to an ApoB nucleic acid that is 14 monomers in length. In certain embodiments, methods of modulating ApoB comprise use of a short antisense compound targeted to an ApoB nucleic acid that is 15 monomers in length. In certain embodiments, methods of modulating ApoB comprise use of a short antisense compound targeted to an ApoB nucleic acid that is 16 monomers in length.

In certain embodiments, methods of modulating expression of ApoB comprise use of a short antisense compound targeted to an ApoB nucleic acid comprising 9 to 15 monomers. In certain embodiments, methods of modulating expression of ApoB comprise use of a short antisense compound targeted to an ApoB nucleic acid comprising 10 to 15 monomers. In certain embodiments, methods of modulating expression of ApoB comprise use of a short antisense compound targeted to an ApoB nucleic acid comprising 12 to 14 monomers. In certain embodiments, methods of modulating expression of ApoB comprise use of a short antisense compound targeted to an ApoB nucleic acid comprising 12 or 14 nucleotides or nucleosides.

In certain embodiments, short antisense compounds targeting a ApoB nucleic acid may have any one or more properties or characteristics of the short antisense compounds generally described herein. In certain embodiments, short antisense compounds targeting a ApoB nucleic acid have a motif (wing – deoxy gap – wing) selected from 1-12-1, 1-1-10-2, 2-10-1-1, 3-10-3, 2-10-3, 2-10-2, 1-10-1,1-10-2, 3-8-3, 2-8-2, 1-8-1, 3-6-3 or 1-6-1, more preferably 1-10-1, 2-10-2, 3-10-3, and 1-9-2.

2. SGLT-2

Sodium dependent glucose transporter 2 (SGLT-2) is expressed in the kidney proximal tubule epithelial cells, and functions to reabsorb glucose preventing glucose loss in the urine. For the human genome SGLT-2 is a member of an 11-membered family of sodium substrate co-transporters. Many of these family members share sequence homology, for example SGLT-1 shares about 59% sequence identity with SGLT-2 and about 70% sequence identity with SGLT-3. SGLT-1 is a glucose transporter found in the heart and the CNS. SGLT-3 is a glucose sensing sodium channel in the small intestine. The separate localization patterns for these SGLTs is one point of distinction between the homologous family members. (Handlon, A.L., Expert Opin. Ther. Patents (2005) 15(11):1532-1540; Kanai et al., J. Clin. Invest., 1994, 93, 397-404; Wells et al., Am. J. Physiol. Endocrinol. Metab., 1992, 263, F459-465).

Studies of human SGLT2 injected into Xenopus oocytes demonstrated that this protein mediates sodium-dependent transport of D-glucose and .alpha.-methyl-D-glucopyranoside (.alpha.-MeGlc; a glucose analog) with a Km value of 1.6 mM for .alpha.-MeGlc and a sodium to glucose coupling ratio of 1:1 (Kanai et al., J. Clin. Invest., 1994, 93, 397-404; You et al., J. Biol. Chem., 1995, 270, 29365-29371). This transport activity was suppressed by phlorizin, a plant glycoside that binds to the glucose site of the SGLTs but is not transported and thus inhibits SGLT action (You et al., J. Biol. Chem., 1995, 270, 29365-29371).

Diabetes is a disorder characterized by hyperglycemia due to deficient insulin action. Chronic hyperglycemia is a major risk factor for diabetes-associated complications, including heart disease, retinopathy, nephropathy and neuropathy. As the kidneys play a major role in the regulation of plasma glucose levels, renal glucose transporters are becoming attractive drug targets (Wright, Am. J. Physiol. Renal Physiol., 2001, 280, F10-18). Diabetic nephropathy is the most common cause of end-stage renal disease that develops in many patients with diabetes. Glucotoxicity, which results from long-term hyperglycemia, induces tissue-dependent insulin resistance in diabetic patients (Nawano et al., Am. J. Physiol. Endocrinol. Metab., 2000, 278, E535-543).

Definitions

“Sodium dependent glucose transporter 2” is the gene product or protein of which expression is to be modulated by administration of a short antisense compound. Sodium dependent glucose transporter 2 is generally referred to as SGLT2 but may also be referred to as SLC5A2; sodium-glucose transporter 2; sodium-glucose cotransporter, kidney low affinity; sodium-glucose cotransporter, renal; solute carrier family 5 (sodium/glucose cotransporter), member 2; SL52.

“SGLT2 nucleic acid" means any nucleic acid encoding SGLT2. For example, in certain embodiments, a SGLT2 nucleic acid includes, without limitation, a DNA sequence encoding SGLT2, an RNA sequence transcribed from DNA encoding SGLT2, and an mRNA sequence encoding SGLT2. “SGLT2 mRNA” means an mRNA encoding a SGLT2 protein.

Therapeutic indications

In certain embodiments, short antisense compounds are used to modulate expression of SGLT-2 and related proteins. In certain embodiments, such modulation is accomplished by providing short antisense compounds that hybridize with one or more target nucleic acid molecules encoding SGLT-2, including, but is not limited to, SGLT2, SL52, SLC5A2, Sodium-Glucose Co-Transporter, Kidney Low Affinity Sodium-Glucose Co-Transporter, Renal Sodium-Glucose Co-Transporter 2 and Solute Carrier Family 5 Sodium/Glucose Co-Transporter Member 2. Also provided are methods of treating metabolic and/or cardiovascular disease and disorders as described herein. In particular embodiments, short antisense compounds that inhibit the expression of SGLT2 are used in methods of lowering blood glucose levels in an animal and methods of delaying or preventing the onset of type 2 diabetes. Such methods comprise administering a therapeutically or prophylactically effective amount of one or more of the compounds of the invention to the animal, which may be in need of treatment. The one or more compounds can be a short antisense compound targeting a nucleic acid encoding SGLT2. Provided herein are methods of enhancing inhibition of expression of SGLT2 in kidney cells or kidney tissues, comprising contacting the cells or tissues with one or more of the compounds of the invention, such as short antisense compounds targeting a nucleic acid encoding SGLT2.

While certain compounds, compositions and methods have been described with specificity in accordance with certain embodiments, the following examples serve only to illustrate the compounds of the invention and are not intended to limit the same.

In certain embodiments, short antisense compounds are chimeric oligomeric compounds having mixed phosphorothioate and phosphodiester backbones,. Certain mixed backbone short antisense compounds have a central gap comprising at least 5 contiguous 2'-deoxy nucleosides flanked by two wings each of which comprises at least one 2'-O-methoxyethyl nucleoside. In certain embodiments, the internucleoside linkages of the mixed backbone compounds are phosphorothioate linkages in the gap and phosphodiester linkages in the two wings. In certain embodiments, mixed backbone compounds have phosphorothioate linkages in the wings, except for one phosphodiester linkage at one or both of the extreme 5' and 3' ends of the oligonucleotide. In certain embodiments short antisense compounds targeted to SGLT2 have a motif (wing – deoxy gap –wing) selected from 3-10-3, 2-10-3, 2-10-2, 1-10-1,1-10-2, 2-8-2, 1-9-2, 1-8-1, 3-6-3 or 1-6-1. In certain embodiments short antisense compounds targeted to SGLT2 have a motif (wing – deoxy gap – wing) selected from 1-10-1, 1-10-2, 2-8-2, 1-9-2, 1-8-1, 3-6-3 or 1-6-1.

In certain embodiments, short antisense compounds targeted to an SGLT2 nucleic acid and having a mixed backbone are efficiently delivered to the kidney. In certain embodiments, administration of short antisense compounds targeted to an SGLT2 nucleic acid and having a mixed backbone results in modulation of target gene expression in the kidney. In certain such embodiments, there is little or no liver or kidney toxicity. In certain embodiments, short antisense compounds targeted to an SGLT2 nucleic acid and having a mixed backbone are more potent for reducing SGLT-2 mRNA and have a faster onset compared with a short antisense compound that does not have a mixed back-bone, but is otherwise identical. In certain such embodiments, such increase potency and/or reduced toxicity is in mouse and/or rat. In certain such embodiments, such increase potency and/or reduced toxicity is in a human.

By way of example, and only for illustrative purposes, ISIS 145733, which comprises uniform phosphorothioate linkages and ISIS 257016 which comprises phosphodiester linkage in the wings and phosphorothioate linkages in the gap, are otherwise identical. Both comprise the sequence GAAGTAGCCACCAACTGTGC (SEQ ID NO. 1572). Both of the oligonucleotides further comprise a gap consisting of ten 2'-deoxynucleotides, flanked on each side by five-nucleotide "2'-methoxyethyl (2'-MOE) nucleotides. All cytidine residues are 5-methylcytidines. The mixed back-bone compound, ISIS 257016, was about 50 times more potent for reducing SGLT-2 mRNA compared to the non-mixed parent compound, ISIS 145733 (see EXAMPLE 9).

Pharmacokinetic studies of certain mixed backbone compound ISIS 257016 indicate that in certain embodiments, the compound acts as a prodrug that is metabolized to a 12 nucleobase pharmacophore. Studies with ISIS 370717, a 12 nucleobase short antisense compound corresponding to ISIS 257016, show that the compound has a similar pharmacological profile to ISIS 257016 but with a faster onset of action. ISIS 370717 is a 12 nucleobase antisense oligonucleotide targeted to SGLT-2 comprising the sequence TAGCCACCAACT (SEQ ID NO. 1554), further comprising a gap consisting of ten 2'-deoxynucleotides, flanked on both sides by one-nucleotide wings. The wings are composed of 2'-methoxyethyl (2'-MOE) nucleotides. All cytidine residues are 5-methylcytidines. The internucleoside linkages are phosphorothioate (P=S) throughout the oligonucleotide. The similarity in pharmacological activity of ISIS 257016 and ISIS 370717 supports the pharmacokinetic studies indicating ISIS 257016 was a prodrug having a 12 nucleotide pharmacophore (see EXAMPLE 10). Further, studies with stabilized (end-capped) versions of ISIS 257016 show dramatic loss of activity.

In certain embodiments, short antisense compounds comprising 2' MOE monomers in the wings are efficiently delivered to the kidney and treatment with such compounds results in efficient modulation of target gene expression in the kidney without liver or kidney toxicity. It is further shown herein that in certain embodiments, short antisense compounds are more potent for reducing SGLT-2 mRNA and have a faster onset compared with parent oligonucleotides targeted to SGLT-2 mRNA in mouse and rat. 2' MOE gap shortmers are shown herein to improve potency and bioavailability over parent compounds.

By way of example, and only for illustrative purposes studies with ISIS 370717 reveal significantly higher accumulation of the short antisense compound in the kidney tissue (approximately 500 micro grams per gram of tissue) compared to the longer parent. Moreover, SGLT-2 mRNA was reduced by more than 80% over the controls (see EXAMPLE 11). ISIS 370717 1-10-1 gapmer was used as a template to make sequence related oligos with varying motifs. Studies evaluating wing, gap and total length variations around the ISIS 370717 12 mer oligonucleotide can be seen in EXAMPLE 12. Certain motifs evaluated included 1-10-1, 2-8-2, 1-8-1, 3-6-3, and 1-6-1 (see Table 60 in EXAMPLE 12). The compounds were analyzed for their effect on SGLT2 mRNA levels. All the motifs inhibited the expression of SGLT2 in vivo in a dose-dependent manner. The 1-10-1, 2-8-2 and 1-8-1 gapmers were found to be particularly potent. SGLT-2 mRNA was reduced by more than 80% over the controls using these motifs.

In certain embodiments, the invention provides short antisense compounds targeted to an SGLT2 nucleic acid and having a motif selected from: 1-10-1 and 1-10-2 MOE gapmer. (see Table 62 in EXAMPLE 13). Certain such compounds were analyzed for their effect on rat SGLT2 mRNA. Results in Table 63 illustrate that both the 1-10-1 and 1-10-2 MOE gapmers inhibit the expression of SGLT2 in vivo in a dose-dependent manner and over 80% reduction of SGLT-2 mRNA could be achieved.

Certain additional 1-10-1 and 2-8-2 MOE gapmers were evaluated in both mouse and rat in vivo models (see, e.g., EXAMPLE 14 and 15). Greater than 80% reduction in SGLT-2 mRNA was achieved with many of the 1-10-1 and 2-8-2 MOE gapmers at relatively low concentrations of oligo and in the absence of any toxicity effects.

In another non-limiting example, the effect of ISIS 388625 on dog SGLT2 mRNA levels was also analyzed. Dog studies illustrate that greater than 80% inhibition of the expression of SGLT2 can be achieved at a 1 mg/kg/wk dose. Even greater inhibition can be achieved at slightly higher doses. Administration of ISIS 388625 in dog was also shown to improved glucose tolerance. Peak plasma glucose levels were decreased by over 50% on average and the subsequent drop in glucose was lessened compared to saline controls in a standard glucose tolerance test (See EXAMPLE 17). Also, in a rat model of diabetes, short antisense compounds were shown to significantly decrease plasma glucose levels and HbA1C over time compared to PBS and control treated animals (See Example 16).

The animals in all studies were further evaluated for toxicity. For example, total body weight, liver, spleen and kidney weight were evaluated. Significant changes in spleen, liver or body weight can indicate that a particular compound causes toxic effects. All changes were found to be within the margin of error. No significant changes in body weight were observed during the treatment or at study termination. No significant changes in liver or spleen weights were observed.

Certain Short Antisense Compounds Targeted to an SGLT2 nucleic acid

In certain embodiments, short antisense compounds are targeted to an SGLT2 nucleic acid having the sequence of GENBANK® Accession No. NM_003041.1, incorporated herein as SEQ ID NO: 2. In certain such embodiments, a short antisense compound targeted to SEQ ID NO: 3 is at least 90% complementary to SEQ ID NO: 3. In certain such embodiments, a short antisense compound targeted to SEQ ID NO: 3 is at least 95% complementary to SEQ ID NO: 3. In certain such embodiments, a short antisense compound targeted to SEQ ID NO: 3 is 100% complementary to SEQ ID NO: 1. In certain embodiments, a short antisense compound targeted to SEQ ID NO: 3 comprises a nucleotide sequence selected from the nucleotide sequences set forth in Table 4 and 5.

The nucleotide sequence set forth in each SEQ ID NO set forth in Tables 4 and 5 is independent of any modification to a sugar moiety, a monomeric linkage, or a nucleobase. As such, short antisense compounds defined by a SEQ ID NO may comprise, independently, one or more modifications to a sugar moiety, an internucleoside linkage, or a nucleobase. Antisense compounds described by Isis Number (Isis NO.) indicate a combination of nucleobase sequence and one or more modifications to a sugar moiety, an internucleoside linkage, or a nucleobase.

Tables 4 and 5 illustrate examples of short antisense compounds targeted to SEQ ID NO: 3. Table 4 illustrates short antisense compounds that are 100% complementary to SEQ ID NO: 3. Table 5 illustrates short antisense compounds that have one or two mismatches with respect to SEQ ID NO: 3. The column labeled 'gapmer motif' indicates the wing-gap-wing motif of each short antisense compounds. The gap segment comprises 2'-deoxynucleotides and each nucleotide of each wing segment comprises a 2'-modified sugar. The particular 2'-modified sugar is also indicated in the 'gapmer motif' column. For example, '2-10-2 MOE' means a 2-10-2 gapmer motif, where a gap segment of ten 2'-deoxynucleotides is flanked by wing segments of two nucleotides, where the nucleotides of the wing segments are 2'-MOE nucleotides. Internucleoside linkages are phosphorothioate. The short antisense compounds comprise 5-methylcytidine in place of unmodified cytosine, unless "unmodified cytosine" is listed in the gapmer motif column, in which case the indicated cytosines are unmodified cytosines. For example, "5-mC in gap only" indicates that the gap segment has 5-methylcytosines, while the wing segments have unmodified cytosines.

Table 4: Short Antisense Compounds Targeted to SEQ ID NO: 3

ISIS No	5' Target Site	3' Target Site	Sequence (5'-3')	Gapmer Motif	SEQ ID NO
379684	84	95	TGTCAGCAGGAT	1-10-1 MOE	214
405193	113	124	CAGCAGGAAATA	2-8-2 MOE	215
405194	114	125	CCAGCAGGAAAT	2-8-2 MOE	216
405195	115	126	ACCAGCAGGAAA	2-8-2 MOE	217
405196	116	127	GACCAGCAGGAA	2-8-2 MOE	218
405197	117	128	TGACCAGCAGGA	2-8-2 MOE	219
379685	117	128	TGACCAGCAGGA	1-10-1 MOE	219
405198	118	129	ATGACCAGCAGG	2-8-2 MOE	221
405199	119	130	AATGACCAGCAG	2-8-2 MOE	222
405200	120	131	CAATGACCAGCA	2-8-2 MOE	223
405201	121	132	CCAATGACCAGC	2-8-2 MOE	224
379686	135	146	ACCACAAGCCAA	1-10-1 MOE	225
379711	172	183	TAGCCGCCCACA	1-10-1 MOE	226
388628	172	183	TAGCCGCCCACA	2-8-2 MOE	226

405202	207	218	CCGGCCACCACA	2-8-2 MOE	228
405203	208	219	ACCGGCCACCAC	2-8-2 MOE	229
405204	236	247	GATGTTGCTGGC	2-8-2 MOE	230
379687	236	247	GATGTTGCTGGC	1-10-1 MOE	230
405205	237	248	CGATGTTGCTGG	2-8-2 MOE	232
405206	238	249	CCGATGTTGCTG	2-8-2 MOE	233
405207	239	250	GCCGATGTTGCT	2-8-2 MOE	234
405208	240	251	TGCCGATGTTGC	2-8-2 MOE	235
405209	241	252	CTGCCGATGTTG	2-8-2 MOE	236
405210	260	271	CAGGCCCACAAA	2-8-2 MOE	237
405211	261	272	CCAGGCCCACAA	2-8-2 MOE	238
405212	262	273	GCCAGGCCCACA	2-8-2 MOE	239
379688	288	299	CCAAGCCACTTG	1-10-1 MOE	240
379689	318	329	AGAGCGCATTCC	1-10-1 MOE	241
379690	435	446	ACAGGTAGAGGC	1-10-1 MOE	242
405248	474	485	AGATCTTGGTGA	2-8-2 MOE	243
379691	474	485	AGATCTTGGTGA	1-10-1 MOE	243
382676	527	539	TGTTCCAGCCCAG	1-10-2 MOE	245
388625	528	539	TGTTCCAGCCCA	2-8-2 MOE	246
389780	528	539	TGTTCCAGCCCA	1-9-2 MOE	246
379692	528	539	TGTTCCAGCCCA	1-10-1 MOE	246
392170	528	539	TGTTCCAGCCCA	1-10-1 Methyleneoxy BNA	246
392173	528	539	TGTTCCAGCCCA	2-8-2 Methyleneoxy BNA	246
405213	529	540	ATGTTCCAGCCC	2-8-2 MOE	251
405214	564	575	TGGTGATGCCCA	2-8-2 MOE	252
405215	565	576	ATGGTGATGCCC	2-8-2 MOE	253
405216	566	577	CATGGTGATGCC	2-8-2 MOE	254
379693	566	577	CATGGTGATGCC	1-10-1 MOE	254
405217	567	578	TCATGGTGATGC	2-8-2 MOE	256
405218	568	579	ATCATGGTGATG	2-8-2 MOE	257
405219	587	598	CCCTCCTGTCAC	2-8-2 MOE	258
405220	588	599	GCCCTCCTGTCA	2-8-2 MOE	259
405221	589	600	AGCCCTCCTGTC	2-8-2 MOE	260
405222	590	601	CAGCCCTCCTGT	2-8-2 MOE	261
405223	591	602	CCAGCCCTCCTG	2-8-2 MOE	262
405224	592	603	GCCAGCCCTCCT	2-8-2 MOE	263
379694	629	640	GACGAAGGTCTG	1-10-1 MOE	264
405225	707	718	GTATTTGTCGAA	2-8-2 MOE	265
379695	737	748	GGACACCGTCAG	1-10-1 MOE	266
379696	974	985	CAGCTTCAGGTA	1-10-1 MOE	267
405226	998	1009	CATGACCATGAG	2-8-2 MOE	268
405227	999	1010	GCATGACCATGA	2-8-2 MOE	269
405228	1000	1011	GGCATGACCATG	2-8-2 MOE	270
405229	1001	1012	TGGCATGACCAT	2-8-2 MOE	271
405230	1002	1013	CTGGCATGACCA	2-8-2 MOE	272
379697	1002	1013	CTGGCATGACCA	1-10-1 MOE	272

405231	1003	1014	CCTGGCATGACC	2-8-2 MOE	274
379698	1091	1102	GCAGCCCACCTC	1-10-1 MOE	275
405232	1092	1103	AGCAGCCCACCT	2-8-2 MOE	276
405233	1093	1104	GAGCAGCCCACC	2-8-2 MOE	277
405234	1130	1141	CATGAGCTTCAC	2-8-2 MOE	278
405235	1131	1142	GCATGAGCTTCA	2-8-2 MOE	279
382677	1131	1143	GGCATGAGCTTCA	1-10-2 MOE	280
388626	1132	1143	GGCATGAGCTTC	2-8-2 MOE	281
379699	1132	1143	GGCATGAGCTTC	1-10-1 MOE	281
405236	1133	1144	GGGCATGAGCTT	2-8-2 MOE	283
405237	1157	1168	CAGCATGAGTCC	2-8-2 MOE	284
405238	1158	1169	CCAGCATGAGTC	2-8-2 MOE	285
379700	1158	1169	CCAGCATGAGTC	1-10-1 MOE	285
405239	1159	1170	GCCAGCATGAGT	2-8-2 MOE	287
379701	1230	1241	CCATGGTGAAGA	1-10-1 MOE	288
405240	1542	1553	CACAGCTGCCCG	2-8-2 MOE	289
405241	1543	1554	ACACAGCTGCCC	2-8-2 MOE	290
405242	1544	1555	CACACAGCTGCC	2-8-2 MOE	291
382678	1544	1556	GCACACAGCTGCC	1-10-2 MOE	292
388627	1545	1556	GCACACAGCTGC	2-8-2 MOE	293
379702	1545	1556	GCACACAGCTGC	1-10-1 MOE	293
379703	1701	1712	GCCGGAGACTGA	1-10-1 MOE	295
405243	1976	1987	ATTGAGGTTGAC	2-8-2 MOE	296
405244	1977	1988	CATTGAGGTTGA	2-8-2 MOE	297
405245	1978	1989	GCATTGAGGTTG	2-8-2 MOE	298
405246	1979	1990	GGCATTGAGGTT	2-8-2 MOE	299
405247	1980	1991	GGGCATTGAGGT	2-8-2 MOE	300

Table 5: Short antisense compounds targeted to SEQ ID NO: 3 and having 1 or 2 mismatches

ISIS No	5' Target Site	3' Target Site	Sequence (5'-3')	Gapmer Motif	SEQ ID NO
405200	96	107	CAATGACCAGCA	2-8-2 MOE	223
405215	382	393	ATGGTGATGCCC	2-8-2 MOE	253
405216	383	394	CATGGTGATGCC	2-8-2 MOE	254
379693	383	394	CATGGTGATGCC	1-10-1 MOE	254
379701	471	482	CCATGGTGAAGA	1-10-1 MOE	288
405218	472	483	ATCATGGTGATG	2-8-2 MOE	257
405246	536	547	GGCATTGAGGTT	2-8-2 MOE	299
405248	570	581	AGATCTTGGTGA	2-8-2 MOE	243
379691	570	581	AGATCTTGGTGA	1-10-1 MOE	243
379698	683	694	GCAGCCCACCTC	1-10-1 MOE	275
405232	684	695	AGCAGCCCACCT	2-8-2 MOE	276
379711	685	696	TAGCCGCCCACA	1-10-1 MOE	226
388628	685	696	TAGCCGCCCACA	2-8-2 MOE	226
379698	950	961	GCAGCCCACCTC	1-10-1 MOE	275
405232	951	962	AGCAGCCCACCT	2-8-2 MOE	276
405235	978	989	GCATGAGCTTCA	2-8-2 MOE	279
382677	978	990	GGCATGAGCTTCA	1-10-2 MOE	280

388626	979	990	GGCATGAGCTTC	2-8-2 MOE	281
379699	979	990	GGCATGAGCTTC	1-10-1 MOE	281
405236	980	991	GGGCATGAGCTT	2-8-2 MOE	283
379698	1043	1054	GCAGCCCACCTC	1-10-1 MOE	275
405239	1171	1182	GCCAGCATGAGT	2-8-2 MOE	287
405209	1213	1224	CTGCCGATGTTG	2-8-2 MOE	236
405233	1364	1375	GAGCAGCCCACC	2-8-2 MOE	277
405240	1366	1377	CACAGCTGCCCG	2-8-2 MOE	289
405211	1500	1511	CCAGGCCCACAA	2-8-2 MOE	238
405212	1501	1512	GCCAGGCCCACA	2-8-2 MOE	239
379695	1643	1654	GGACACCGTCAG	1-10-1 MOE	266
379698	1875	1886	GCAGCCCACCTC	1-10-1 MOE	275
405239	1993	2004	GCCAGCATGAGT	2-8-2 MOE	287
405211	2210	2221	CCAGGCCCACAA	2-8-2 MOE	238
405212	2211	2222	GCCAGGCCCACA	2-8-2 MOE	239

In certain embodiments, a target region is nucleotides 85-184 of SEQ ID NO: 3. In certain embodiments, a short antisense compound is targeted to nucleotides 85-184 of SEQ ID NO: 3. In certain such embodiments, a short antisense compound targeted to nucleotides 85-184 comprises a nucleotide sequence selected from SEQ ID NO 214, 215, 216, 217, 218, 219, 221, 222, 223, 224, 225, or 227. In certain such embodiments, a short antisense compound targeted to nucleotides 85-184 of SEQ ID NO: 3 is selected from Isis No 379684, 405193, 405194, 405195, 405196, 405197, 379685, 405198, 405199, 405200, 405201, 379686, 379711 or 388628.

In certain embodiments, a target region is nucleotides 113-132 of SEQ ID NO: 3. In certain embodiments, a short antisense compound is targeted to nucleotides 113-132 of SEQ ID NO: 3. In certain such embodiments, a short antisense compound targeted to nucleotides 113-132 comprises a nucleotide sequence selected from SEQ ID NO 215, 216, 217, 218, 219, 221, 222, 223, or 224. In certain such embodiments, a short antisense compound targeted to nucleotides 113-132 of SEQ ID NO: 3 is selected from Isis No 405193, 405194, 405195, 405196, 405197, 379685, 405198, 405199, 405200, or 405201.

In certain embodiments, a target region is nucleotides 207-329 of SEQ ID NO: 3. In certain embodiments, a short antisense compound is targeted to nucleotides 207-329 of SEQ ID NO: 3. In certain such embodiments, a short antisense compound targeted to nucleotides 207-329 comprises a nucleotide sequence selected from SEQ ID NO 228, 229, 230, 232, 233, 234, 235, 236, 237, 238, 239, 240, or 241. In certain such embodiments, a short antisense compound targeted to nucleotides 207-329 of SEQ ID NO: 3 is selected from Isis No 405202, 405203, 405204, 379687, 405205, 405206, 405207, 405208, 405209, 405210, 405211, 405212, 379688, or 379689.

In certain embodiments, a target region is nucleotides 207-273 of SEQ ID NO: 3. In certain embodiments, a short antisense compound is targeted to nucleotides 207-273 of SEQ ID NO: 3. In certain such embodiments, a short antisense compound targeted to nucleotides 207-273 comprises a nucleotide

sequence selected from SEQ ID NO 228, 229, 230, 232, 233, 234, 235, 236, 237, 238, or 239. In certain such embodiments, a short antisense compound targeted to nucleotides 207-273 of SEQ ID NO: 3 is selected from Isis No 405202, 405203, 405204, 379687, 405205, 405206, 405207, 405208, 405209, 405210, 405211, or 405212.

In certain embodiments, a target region is nucleotides 207-219 of SEQ ID NO: 3. In certain embodiments, a short antisense compound is targeted to nucleotides 207-219 of SEQ ID NO: 3. In certain such embodiments, a short antisense compound targeted to nucleotides 207-219 comprises a nucleotide sequence selected from SEQ ID NO 228 or 229. In certain such embodiments, a short antisense compound targeted to nucleotides 207-219 of SEQ ID NO: 3 is selected from Isis NO.. 405202 or 405203.

In certain embodiments, a target region is nucleotides 236-252 of SEQ ID NO: 3. In certain embodiments, a short antisense compound is targeted to nucleotides 236-252 of SEQ ID NO: 3. In certain such embodiments, a short antisense compound targeted to nucleotides 236-252 comprises a nucleotide sequence selected from SEQ ID NO 230, 232, 233, 234, 235, or 236. In certain such embodiments, a short antisense compound targeted to nucleotides 236-252 of SEQ ID NO: 3 is selected from Isis NO. 405204, 379687, 405205, 405206, 405207, 405208, or 405209.

In certain embodiments, a target region is nucleotides 260-273 of SEQ ID NO: 3. In certain embodiments, a short antisense compound is targeted to nucleotides 260-273 of SEQ ID NO: 3. In certain such embodiments, a short antisense compound targeted to nucleotides 260-273 comprises a nucleotide sequence selected from SEQ ID NO 237, 238, or 239. In certain such embodiments, a short antisense compound targeted to nucleotides 260-273 of SEQ ID NO: 3 is selected from Isis NO. 405210, 405211, or 405212.

In certain embodiments, a target region is nucleotides 435-640 of SEQ ID NO: 3. In certain embodiments, a short antisense compound is targeted to nucleotides 435-640 of SEQ ID NO: 3. In certain such embodiments, a short antisense compound targeted to nucleotides 435-640 comprises a nucleotide sequence selected from SEQ ID NO 242, 243, 245, 246, 251, 252, 253, 254, 256, 257, 258, 259, 260, 261, 262, 263, or 264. In certain such embodiments, a short antisense compound targeted to nucleotides 435-640 of SEQ ID NO: 3 is selected from Isis NO. 379690, 405248, 379691, 389780, 379692, 382676, 388625, 392170, 392173, 405213, 405214, 405215, 405216, 379693, 405217, 405218, 405219, 405220, 405221, 405222, 405223, 405224, or 379694.

In certain embodiments, a target region is nucleotides 527-540 of SEQ ID NO: 3. In certain embodiments, a short antisense compound is targeted to nucleotides 527-540 of SEQ ID NO: 3. In certain such embodiments, a short antisense compound targeted to nucleotides 527-540 comprises a nucleotide sequence selected from SEQ ID NO 245, 246, or 251. In certain such embodiments, a short antisense compound targeted to nucleotides 527-540 of SEQ ID NO: 3 is selected from Isis NO. 389780, 379692, 382676, 388626, 392170, 392173, or 405213.

In certain embodiments, a target region is nucleotides 564-603 of SEQ ID NO: 3. In certain embodiments, a short antisense compound is targeted to nucleotides 564-603 of SEQ ID NO: 3. In certain such embodiments, a short antisense compound targeted to nucleotides 564-603 comprises a nucleotide sequence selected from SEQ ID NO 252, 253, 254, 256, 257, 258, 259, 260, 261, 262, or 263. In certain such embodiments, a short antisense compound targeted to nucleotides 564-603 of SEQ ID NO: 3 is selected from Isis NO. 405214, 405215, 405216, 379693, 405217, 405218, 405219, 405220, 405221, 405222, 405223, or 405224.

In certain embodiments, a target region is nucleotides 564-579 of SEQ ID NO: 3. In certain embodiments, a short antisense compound is targeted to nucleotides 564-579 of SEQ ID NO: 3. In certain such embodiments, a short antisense compound targeted to nucleotides 564-579 comprises a nucleotide sequence selected from SEQ ID NO 252, 253, 254, 256, or 257. In certain such embodiments, a short antisense compound targeted to nucleotides 564-579 of SEQ ID NO: 3 is selected from Isis NO. 405214, 405215, 405216, 379693, 405217, or 405218.

In certain embodiments, a target region is nucleotides 587-603 of SEQ ID NO: 3. In certain embodiments, a short antisense compound is targeted to nucleotides 587-603 of SEQ ID NO: 3. In certain such embodiments, a short antisense compound targeted to nucleotides 587-603 comprises a nucleotide sequence selected from SEQ ID NO 258, 259, 260, 261, 262, or 263. In certain such embodiments, a short antisense compound targeted to nucleotides 587-603 of SEQ ID NO: 3 is selected from Isis NO. 405219, 405220, 405221, 405222, 405223, or 405224.

In certain embodiments, a target region is nucleotides 974-1014 of SEQ ID NO: 3. In certain embodiments, a short antisense compound is targeted to nucleotides 974-1014 of SEQ ID NO: 3. In certain such embodiments, a short antisense compound targeted to nucleotides 974-1014 comprises a nucleotide sequence selected from SEQ ID NO 267, 268, 269, 270, 271, 272, or 274. In certain such embodiments, a short antisense compound targeted to nucleotides 974-1014 of SEQ ID NO: 3 is selected from Isis NO. 379696, 405226, 405227, 405228, 405229, 405230, 379697, or 405231.

In certain embodiments, a target region is nucleotides 998-1014 of SEQ ID NO: 3. In certain embodiments, a short antisense compound is targeted to nucleotides 998-1014 of SEQ ID NO: 3. In certain such embodiments, a short antisense compound targeted to nucleotides 998-1014 comprises a nucleotide sequence selected from SEQ ID NO 268, 269, 270, 271, 272, or 274. In certain such embodiments, a short antisense compound targeted to nucleotides 998-1014 of SEQ ID NO: 3 is selected from Isis NO. 405226, 405227, 405228, 405229, 405230, 379697, or 405231.

In certain embodiments, a target region is nucleotides 1091-1170 of SEQ ID NO: 3. In certain embodiments, a short antisense compound is targeted to nucleotides 1091-1170 of SEQ ID NO: 3. In certain such embodiments, a short antisense compound targeted to nucleotides 1091-1170 comprises a nucleotide sequence selected from SEQ ID NO 275, 276, 277, 278, 279, 280, 281, 283, 284, 285, 286, or 287. In certain such embodiments, a short antisense compound targeted to nucleotides 1091-1170 of SEQ ID NO: 3 is selected from Isis NO. 379698, 405232, 405233, 405234, 405235, 388626, 379699, 382677, 405236, 405237, 405238, 379700, or 405239.

In certain embodiments, a target region is nucleotides 1091-1104 of SEQ ID NO: 3. In certain embodiments, a short antisense compound is targeted to nucleotides 1091-1104 of SEQ ID NO: 3. In certain such embodiments, a short antisense compound targeted to nucleotides 1091-1104 comprises a nucleotide sequence selected from SEQ ID NO 275, 276, or 277. In certain such embodiments, an short antisense compound targeted to nucleotides 1091-1104 of SEQ ID NO: 3 is selected from Isis NO. 379698, 405232, or 405233.

In certain embodiments, a target region is nucleotides 1130-1144 of SEQ ID NO: 3. In certain embodiments, a short antisense compound is targeted to nucleotides 1130-1144 of SEQ ID NO: 3. In certain such embodiments, a short antisense compound targeted to nucleotides 1130-1144 comprises a nucleotide sequence selected from SEQ ID NO 278, 279, 280, 281, or 283. In certain such embodiments, a short antisense compound targeted to nucleotides 1130-1144 of SEQ ID NO: 3 is selected from Isis NO. 405234, 405235, 388626, 379699, 382677, or 405236.

In certain embodiments, a target region is nucleotides 1157-1170 of SEQ ID NO: 3. In certain embodiments, a short antisense compound is targeted to nucleotides 1157-1170 of SEQ ID NO: 3. In certain such embodiments, a short antisense compound targeted to nucleotides 1157-1170 comprises a nucleotide sequence selected from SEQ ID NO 284, 285, or 287. In certain such embodiments, a short antisense compound targeted to nucleotides 1157-1170 of SEQ ID NO: 3 is selected from Isis NO. 405237, 405238, 379700, or 405239.

In certain embodiments, a target region is nucleotides 1542-1556 of SEQ ID NO: 3. In certain embodiments, a short antisense compound is targeted to nucleotides 1542-1556 of SEQ ID NO: 3. In certain such embodiments, a short antisense compound targeted to nucleotides 1542-1556 comprises a nucleotide sequence selected from SEQ ID NO 289, 290, 291, 292, or 293. In certain such embodiments, a short antisense compound targeted to nucleotides 1542-1556 of SEQ ID NO: 3 is selected from Isis NO. 405240, 405241, 405242, 388629, 379702, or 382678.

In certain embodiments, a target region is nucleotides 1976-1991 of SEQ ID NO: 3. In certain embodiments, a short antisense compound is targeted to nucleotides 1976-1991 of SEQ ID NO: 3. In certain such embodiments, a short antisense compound targeted to nucleotides 1976-1991 comprises a nucleotide sequence selected from SEQ ID NO 296, 297, 298, 299, or 300. In certain such embodiments, a short antisense compound targeted to nucleotides 1976-1991 of SEQ ID NO: 3 is selected from Isis NO. 405243, 405244, 405245, 405246, or 405247.

In certain embodiments, short antisense compounds targeted to an SGLT2 nucleic acid are 8 to 16, preferably 9 to 15, more preferably 9 to 14, more preferably 10 to 14 nucleotides in length. In certain embodiments, short antisense compounds targeted to an SGLT2 nucleic acid are 9 to 14 nucleotides in length. In certain embodiments, short antisense compounds targeted to an SGLT2 nucleic acid are 10 to 14 nucleotides in length. In certain embodiments, such short antisense compounds are short antisense oligonucleotides.

In certain embodiments, short antisense compounds targeted to an SGLT2 nucleic acid are short gapmers. In certain such embodiments, short gapmers targeted to an SGLT2 nucleic acid comprise at least one high affinity modification in one or more wings of the compound. In certain embodiments, short antisense compounds targeted to an SGLT2 nucleic acid comprise 1 to 3 high-affinity modifications in each wing. In certain such embodiments, the nucleosides or nucleotides of the wing comprise a 2' modification. In certain such embodiments, the monomers of the wing are BNA's. In certain such embodiments, the monomers of the wing are selected from α-L-Methyleneoxy (4'-CH_2-O-2') BNA , β-D-Methyleneoxy (4'-CH_2-O-2') BNA , Ethyleneoxy (4'-$(CH_2)_2$-O-2') BNA , Aminooxy (4'-CH_2-O-N(R)-2') BNA and Oxyamino (4'-CH_2-N(R)-O-2') BNA. In certain embodiments, the monomers of a wing comprise a substituent at the 2' position selected from allyl, amino, azido, thio, O-allyl, O-C_1-C_{10} alkyl, -OCF_3, O-$(CH_2)_2$-O-CH_3, 2'-O$(CH_2)_2SCH_3$, O-$(CH_2)_2$-O-N(R_m)(R_n), and O-CH_2-C(=O)-N(R_m)(R_n), where each R_m and R_n is, independently, H or substituted or unsubstituted C_1-C_{10} alkyl. In certain embodiments, the monomers of a wing are 2'MOE nucleotides.

In certain embodiments, short antisense compounds targeted to an SGLT2 nucleic acid comprise a gap between the 5' wing and the 3' wing. In certain embodiments the gap comprises five, six, seven, eight, nine, ten, eleven, twelve, thirteen, or fourteen monomers. In certain embodiments, the monomers of the gap are unmodified deoxyribonucleotides. In certain embodiments, the monomers of the gap are unmodified ribonucleotides. In certain embodiments, gap modifications (if any) gap result in an antisense compound that, when bound to its target nucleic acid, supports cleavage by an RNase, including, but not limited to, RNase H.

In certain embodiments, short antisense compounds targeted to an SGLT2 nucleic acid have uniform monomeric linkages. In certain such embodiments, those linkages are all phosphorothioate linkages. In certain embodiments, the linkages are all phosphodiester linkages. In certain embodiments, short antisense compounds targeted to an SGLT2 nucleic acid have mixed backbones.

In certain embodiments, short antisense compounds targeted to an SGLT2 nucleic acid are 8 monomers in length. In certain embodiments, short antisense compounds targeted to an SGLT2 nucleic acid are 9 monomers in length. In certain embodiments, short antisense compounds targeted to an SGLT2 nucleic acid are 10 monomers in length. In certain embodiments, short antisense compounds targeted to an SGLT2 nucleic acid are 11 monomers in length. In certain embodiments, short antisense compounds targeted to an SGLT2 nucleic acid are monomers in length. In certain embodiments, short antisense compounds targeted to an SGLT2 nucleic acid are 13 monomers in length. In certain embodiments, short antisense compounds targeted to an SGLT2 nucleic acid are 14 monomers in length. In certain embodiments, short antisense compounds targeted to an SGLT2 nucleic acid are 15 monomers in length. In certain embodiments, short antisense compounds targeted to an SGLT2 nucleic acid are 16 monomers in length. In certain embodiments, short antisense compounds targeted to an SGLT2 nucleic acid comprise 9 to 15 monomers. In certain embodiments, short antisense compounds targeted to an SGLT2 nucleic acid comprise 10 to 15 monomers. In certain embodiments, short antisense compounds targeted to an SGLT2 nucleic acid comprise 12 to 14 monomers. In certain embodiments, short antisense compounds targeted to an SGLT2 nucleic acid comprise 12 to 14 nucleotides or nucleosides.

In certain embodiments, the invention provides methods of modulating expression of SGLT2. In certain embodiments, such methods comprise use of one or more short antisense compound targeted to an SGLT2 nucleic acid, wherein the short antisense compound targeted to an SGLT2 nucleic acid is from about 8 to about 16, preferably 9 to 15, more preferably 9 to 14, more preferably 10 to 14 monomers (i.e. from about 8 to about 16 linked monomers). One of ordinary skill in the art will appreciate that this comprehends methods of modulating expression of SGLT2 using one or more short antisense compounds targeted to an SGLT2 nucleic acid of 8, 9, 10, 11, 12, 13, 14, 15 or 16 monomers.

In certain embodiments, methods of modulating SGLT2 comprise use of a short antisense compound targeted to an SGLT2 nucleic acid that is 8 monomers in length. In certain embodiments, methods of modulating SGLT2 comprise use of a short antisense compound targeted to an SGLT2 nucleic acid that is 9 monomers in length. In certain embodiments, methods of modulating SGLT2 comprise use of a short antisense compound targeted to an SGLT2 nucleic acid that is 10 monomers in length. In certain embodiments, methods of modulating SGLT2 comprise use of a short antisense compound targeted to an SGLT2 nucleic acid that is 11 monomers in length. In certain embodiments, methods of modulating SGLT2 comprise use of a short antisense compound targeted to an SGLT2 nucleic acid that is 12 monomers in length. In certain embodiments, methods of modulating SGLT2 comprise use of a short antisense compound targeted to an SGLT2 nucleic acid that is 13 monomers in length. In certain embodiments, methods of modulating SGLT2 comprise use of a short antisense compound targeted to an SGLT2 nucleic acid that is 14 monomers in length. In certain embodiments, methods of modulating SGLT2 comprise use of a short antisense compound targeted to an SGLT2 nucleic acid that is 15 monomers in length. In certain embodiments, methods of modulating SGLT2 comprise use of a short antisense compound targeted to an SGLT2 nucleic acid that is 16 monomers in length.

In certain embodiments, methods of modulating expression of SGLT2 comprise use of a short antisense compound targeted to an SGLT2 nucleic acid comprising 9 to 15 monomers. In certain embodiments, methods of modulating expression of SGLT2 comprise use of a short antisense compound targeted to an SGLT2 nucleic acid comprising 10 to 15 monomers. In certain embodiments, methods of modulating expression of SGLT2 comprise use of a short antisense compound targeted to an SGLT2 nucleic acid comprising 12 to 14 monomers. In certain embodiments, methods of modulating expression of SGLT2 comprise use of a short antisense compound targeted to an SGLT2 nucleic acid comprising 12 or 14 nucleotides or nucleosides.

3. PCSK9

In individuals with autosomal dominant hypercholesterolemia (ADH), elevated LDL-C levels have been linked to mutations in the genes encoding LDL-receptor (LDL-R), apolipoprotein B (apoB), or proprotein convertase subtilisin/kexin type 9 (PCSK9) (Abifadel et al., Nat. Genet., 2003, 34:154-156). PCSK9 was identified as a third locus associated with ADH when gain-of-function mutations in PCSK9 were found to be linked to elevated LDL-C levels. ApoB participates in the intracellular assembly and secretion of triglyceride-rich lipoproteins and is a ligand for the LDL-R. PCSK9 is proposed to reduce LDL-R expression levels in the liver. Reduced LDL-R expression results in reduced hepatic uptake of circulating ApoB-containing lipoproteins, which in turn leads to elevated cholesterol.

Definitions

"PCSK9" is the gene product or protein of which expression is to be modulated by administration of a short antisense compound.

"PCSK9 nucleic acid" means any nucleic acid encoding PCSK9. For example, in certain embodiments, a PCSK9nucleic acid includes, without limitation, a DNA sequence encoding PCSK9, an RNA sequence transcribed from DNA encoding PCSK9, and an mRNA sequence encoding PCSK9.

"PCSK9 mRNA" means an mRNA encoding PCSK9.

PCSK9 Therapeutic Indications

In certain embodiments, the invention provides methods of modulating the expression of PCSK9 in an individual comprising administering a short antisense compound targeted to a PCSK9 nucleic acid. In certain embodiments, the invention provides methods of treating an individual comprising administering one or more pharmaceutical compositions of the present invention. In certain embodiments, the individual has hypercholesterolemia, mixed dyslipidemia, atherosclerosis, a risk of developing atherosclerosis, coronary heart disease, a history of coronary heart disease, early onset coronary heart disease, one or more risk factors for coronary heart disease, type II diabetes, type II diabetes with dyslipidemia, dyslipidemia, hypertriglyceridemia, hyperlipidemia, hyperfattyacidemia, hepatic steatosis, non-alcoholic steatohepatitis, or non-alcoholic fatty liver disease.

Guidelines for lipid-lowering therapy were established in 2001 by Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP), and updated in 2004 (Grundy et al., Circulation, 2004, 110, 227-239). The guidelines include obtaining a complete lipoprotein profile, typically after a 9 to 12 hour fast, for determination of LDL-C, total cholesterol, and HDL-C levels. According to the most recently established guidelines, LDL-C levels of 130-159 mg/dL, 160-189 mg/dL, and greater than or equal to 190 mg/dL are considered borderline high, high, and very high, respectively. Total cholesterol levels of 200-239 and greater than or equal to 240 mg/dL are considered borderline high and high, respectively. HDL-C levels of less than 40 mg/dL are considered low.

In certain embodiments, the individual has been identified as in need of lipid-lowering therapy. In certain such embodiments, the individual has been identified as in need of lipid-lowering therapy according to the guidelines established in 2001 by Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP), and updated in 2004 (Grundy et al., Circulation, 2004, 110, 227-239). In certain such embodiments, the individual in need of lipid-lowering therapy has LDL-C above 190 mg/dL. In certain such embodiments, the individual in need of lipid-lowering therapy has LDL-C above 160 mg/dL. In certain such embodiments, the individual in need of lipid-lowering therapy has LDL-C above 130 mg/dL. In certain such embodiments the individual in need of lipid-lowering therapy has LDL-C above 100 mg/dL. In certain such embodiments the individual in need of lipid-lowering therapy should maintain LDL-C below 160 mg/dL. In certain such embodiments the individual in need of lipid-lowering therapy should maintain LDL-C below 130 mg/dL. In certain such embodiments the individual in need of lipid-lowering therapy should maintain LDL-C below 100 mg/dL. In certain such embodiments the individual should maintain LDL-C below 70 mg/dL.

In certain embodiments the invention provides methods for reducing ApoB in an individual. In certain embodiments the invention provides methods for reducing ApoB-containing lipoprotein in an individual. In certain embodiments the invention provides methods for reducing LDL-C in an individual. In certain embodiments the invention provides methods for reducing VLDL-C in an individual. In certain embodiments the invention provides methods for reducing IDL-C in an individual. In certain embodiments the invention provides methods for reducing non-HDL-C in an individual. In certain embodiments the invention provides methods for reducing Lp(a) in an individual. In certain embodiments the invention provides methods for reducing serum triglyceride in an individual. In certain embodiments the invention provides methods for reducing liver triglyceride in an individual. In certain embodiments the invention provides methods for reducing Ox-LDL-C in an individual. In certain embodiments the invention provides methods for reducing small LDL particles in an individual. In certain embodiments the invention provides methods for reducing small VLDL particles in an individual. In certain embodiments the invention provides methods for reducing phospholipids in an individual. In certain embodiments the invention provides methods for reducing oxidized phospholipids in an individual.

In certain embodiments, the methods provided by the present invention do not lower HDL-C. In certain embodiments, the methods provided by the present invention do not result in accumulation of lipids in the liver.

In certain embodiments a pharmaceutical composition comprising a short antisense compound targeted to a PCSK9 nucleic acid is for use in therapy. In certain embodiments, the therapy is the reduction of LDL-C, ApoB, VLDL-C, IDL-C, non-HDL-C, Lp(a) , serum triglyceride, liver triglyceride, Ox-LDL-C, small LDL particles, small VLDL, phospholipids, or oxidized phospholipids in an individual. In certain embodiments, the therapy is the treatment of hypercholesterolemia, mixed dyslipidemia, atherosclerosis, a risk of developing atherosclerosis, coronary heart disease, a history of coronary heart disease, early onset coronary heart disease, one or more risk factors for coronary heart disease, type II diabetes, type II diabetes with dyslipidemia, dyslipidemia, hypertriglyceridemia, hyperlipidemia, hyperfattyacidemia, hepatic steatosis, non-alcoholic steatohepatitis, or non-alcoholic fatty liver disease. In additional embodiments, the therapy is the reduction of CHD risk. In certain the therapy is prevention of atherosclerosis. In certain embodiments, the therapy is the prevention of coronary heart disease.

In certain embodiments a pharmaceutical composition comprising a short antisense compound targeted to a PCSK9 nucleic acid is used for the preparation of a medicament for reducing LDL-C, ApoB, VLDL-C, IDL-C, non-HDL-C, Lp(a) , serum triglyceride, liver triglyceride, Ox-LDL-C, small LDL particles, small VLDL, phospholipids, or oxidized phospholipids in an individual. In certain embodiments pharmaceutical composition comprising a short antisense compound targeted to PCKS9 is used for the preparation of a medicament for reducing coronary heart disease risk. In certain embodiments a short antisense compound targeted to a PCSK9 nucleic acid is used for the preparation of a medicament for the treatment of hypercholesterolemia, mixed dyslipidemia, atherosclerosis, a risk of developing atherosclerosis, coronary heart disease, a history of coronary heart disease, early onset coronary heart disease, one or more risk factors for coronary heart disease, type II diabetes, type II diabetes with dyslipidemia, dyslipidemia, hypertriglyceridemia, hyperlipidemia, hyperfattyacidemia, hepatic steatosis, non-alcoholic steatohepatitis, or non-alcoholic fatty liver disease.

PCSK9 Combination Therapies

In certain embodiments, one or more pharmaceutical compositions of the present invention are co-administered with one or more other pharmaceutical agents. In certain embodiments, such one or more other pharmaceutical agents are designed to treat the same disease or condition as the one or more pharmaceutical compositions of the present invention. In certain embodiments, such one or more other pharmaceutical agents are designed to treat a different disease or condition as the one or more pharmaceutical compositions of the present invention. In certain embodiments, such one or more other pharmaceutical agents are designed to treat an undesired effect of one or more pharmaceutical compositions of the present invention. In certain embodiments, one or more pharmaceutical compositions of the present invention are co-administered with another pharmaceutical agent to treat an undesired effect of that other pharmaceutical agent. In certain embodiments, one or more pharmaceutical compositions of the present invention and one or more other pharmaceutical agents are administered at the same time. In certain embodiments, one or more pharmaceutical compositions of the present invention and one or more other pharmaceutical agents are administered at different times. In certain embodiments, one or more pharmaceutical compositions of the present invention and one or more other pharmaceutical agents are prepared together in a single formulation. In certain embodiments, one or more pharmaceutical compositions of the present invention and one or more other pharmaceutical agents are prepared separately.

In certain embodiments, pharmaceutical agents that may be co-administered with a pharmaceutical composition of the present invention include lipid-lowering agents. In certain such embodiments, pharmaceutical agents that may be co-administered with a pharmaceutical composition of the present invention include, but are not limited to atorvastatin, simvastatin, rosuvastatin, and ezetimibe. In certain such embodiments, the lipid-lowering agent is administered prior to administration of a pharmaceutical composition of the present invention. In certain such embodiments, the lipid-lowering agent is administered following administration of a pharmaceutical composition of the present invention. In certain such embodiments the lipid-lowering agent is administered at the same time as a pharmaceutical composition of the present invention. In certain such embodiments the dose of a co-administered lipid-lowering agent is the same as the dose that would be administered if the lipid-lowering agent was administered alone. In certain such embodiments the dose of a co-administered lipid-lowering agent is lower than the dose that would be administered if the lipid-lowering agent was administered alone. In certain such embodiments the dose of a co-administered lipid-lowering agent is greater than the dose that would be administered if the lipid-lowering agent was administered alone.

In certain embodiments, a co-administered lipid-lowering agent is a HMG-CoA reductase inhibitor. In certain such embodiments the HMG-CoA reductase inhibitor is a statin. In certain such embodiments the statin is selected from atorvastatin, simvastatin, pravastatin, fluvastatin, and rosuvastatin.

In certain embodiments, a co-administered lipid-lowering agent is a cholesterol absorption inhibitor. In certain such embodiments, cholesterol absorption inhibitor is ezetimibe.

In certain embodiments, a co-administered lipid-lowering agent is a co-formulated HMG-CoA reductase inhibitor and cholesterol absorption inhibitor. In certain such embodiments the co-formulated lipid-lowering agent is ezetimibe/simvastatin.

In certain embodiments, a co-administered lipid-lowering agent is a microsomal triglyceride transfer protein inhibitor (MTP inhibitor).

In certain embodiments, a co-administered lipid-lowering agent is an oligonucleotide targeted to an ApoB nucleic acid.

In certain embodiments, a co-administered pharmaceutical agent is a bile acid sequestrant. In certain such embodiments, the bile acid sequestrant is selected from cholestyramine, colestipol, and colesevelam.

In certain embodiments, a co-administered pharmaceutical agent is a nicotinic acid. In certain such embodiments, the nicotinic acid is selected from immediate release nicotinic acid, extended release nicotinic acid, and sustained release nicotinic acid.

In certain embodiments, a co-administered pharmaceutical agent is a fibric acid. In certain such embodiments, a fibric acid is selected from gemfibrozil, fenofibrate, clofibrate, bezafibrate, and ciprofibrate.

Further examples of pharmaceutical agents that may be co-administered with a pharmaceutical composition of the present invention include, but are not limited to, corticosteroids, including but not limited to prednisone; immunoglobulins, including, but not limited to intravenous immunoglobulin (IVIg); analgesics (e.g., acetaminophen); anti-inflammatory agents, including, but not limited to non-steroidal anti-inflammatory drugs (e.g., ibuprofen, COX-1 inhibitors, and COX-2, inhibitors); salicylates; antibiotics; antivirals; antifungal agents; antidiabetic agents (e.g., biguanides, glucosidase inhibitors, insulins, sulfonylureas, and thiazolidenediones); adrenergic modifiers; diuretics; hormones (e.g., anabolic steroids, androgen, estrogen, calcitonin, progestin, somatostan, and thyroid hormones); immunomodulators; muscle relaxants; antihistamines; osteoporosis agents (e.g., biphosphonates, calcitonin, and estrogens); prostaglandins, antineoplastic agents; psychotherapeutic agents; sedatives; poison oak or poison sumac products; antibodies; and vaccines.

In certain embodiments, the pharmaceutical compositions of the present invention may be administered in conjuction with a lipid-lowering therapy. In certain such embodiments, a lipid-lowering therapy is therapeutic lifestyle change. In certain such embodiments, a lipid-lowering therapy is LDL apheresis.

Certain Short Antisense Compounds Targeted to a PCSK9 Nucleic Acid

In certain embodiments, short antisense compounds are targeted to a PCSK9 nucleic acid having the sequence of GENBANK® Accession No. NM_174936.2, incorporated herein as SEQ ID NO: 4. In certain such embodiments, a short antisense compound targeted to SEQ ID NO: 4 is at least 90% complementary to SEQ ID NO: 4. In certain such embodiments, a short antisense compound targeted to SEQ ID NO: 4 is at least 95% complementary to SEQ ID NO: 4. In certain such embodiments, a short antisense compound targeted to SEQ ID NO: 4 is 100% complementary to SEQ ID NO: 4. In certain embodiments, a short antisense compound targeted to SEQ ID NO: 4 comprises a nucleotide sequence selected from the nucleotide sequences set forth in Table 6 or Table 7.

The nucleotide sequence set forth in each SEQ ID NO in Tables 6 and 7 is independent of any modification to a sugar moiety, an internucleoside linkage, or a nucleobase. As such, short antisense compounds defined by a SEQ ID NO may comprise, independently, one or more modifications to a sugar moiety, an internucleoside linkage, or a nucleobase. Short antisense compounds described by Isis Number (Isis NO.) indicate a combination of nucleobase sequence and one or more modifications to a sugar moiety, an internucleoside linkage, or a nucleobase.

Tables 6 and 7 illustrate examples of short antisense compounds targeted to SEQ ID NO: 4. Table 6 illustrates short antisense compounds that are 100% complementary to SEQ ID NO: 4. Table 7 illustrates short antisense compounds that have one or two mismatches with respect to SEQ ID NO: 4. The column labeled 'gapmer motif' indicates the wing-gap-wing motif of each short antisense compounds. The gap segment comprises 2'-deoxynucleotides and each nucleotide of each wing segment comprises a 2'-modified sugar. The particular 2'-modified sugar is also indicated in the 'gapmer motif' column. For example, '2-10-2 MOE' means a 2-10-2 gapmer motif, where a gap segment of ten 2'-deoxynucleotides is flanked by wing segments of two nucleotides, where the nucleotides of the wing segments are 2'-MOE nucleotides. Internucleoside linkages are phosphorothioate. The short antisense compounds comprise 5-methylcytidine in place of unmodified cytosine, unless "unmodified cytosine" is listed in the gapmer motif column, in which case the indicated cytosines are unmodified cytosines. For example, "5-mC in gap only" indicates that the gap segment has 5-methylcytosines, while the wing segments have unmodified cytosines.

Table 6: Short Antisense Compounds targeted to SEQ ID NO: 4

ISIS NO.	5' Target Site	3' Target Site	Sequence (5'-3')	Gapmer Motif	SEQ ID NO
400297	695	708	ATGGGGCAACTTCA	2-10-2 MOE	329
400298	696	709	CATGGGGCAACTTC	2-10-2 MOE	330
400299	697	710	ACATGGGGCAACTT	2-10-2 MOE	331
400300	742	755	GGGATGCTCTGGGC	2-10-2 MOE	332
400301	757	770	CGCTCCAGGTTCCA	2-10-2 MOE	333
400302	828	841	GATACACCTCCACC	2-10-2 MOE	334
400303	829	842	AGATACACCTCCAC	2-10-2 MOE	335
400304	830	843	GAGATACACCTCCA	2-10-2 MOE	336
400305	937	950	GCCTGTCTGTGGAA	2-10-2 MOE	337
400306	952	965	CTGTCACACTTGCT	2-10-2 MOE	338
400307	988	1001	CGGCCGCTGACCAC	2-10-2 MOE	339
400308	989	1002	CCGGCCGCTGACCA	2-10-2 MOE	340
400309	990	1003	CCCGGCCGCTGACC	2-10-2 MOE	341
400310	991	1004	TCCCGGCCGCTGAC	2-10-2 MOE	342
400311	992	1005	ATCCCGGCCGCTGA	2-10-2 MOE	343
400312	993	1006	CATCCCGGCCGCTG	2-10-2 MOE	344
400313	994	1007	GCATCCCGGCCGCT	2-10-2 MOE	345
400314	1057	1070	GTGCCCTTCCCTTG	2-10-2 MOE	346
400315	1075	1088	ATGAGGGTGCCGCT	2-10-2 MOE	347
400316	1076	1089	TATGAGGGTGCCGC	2-10-2 MOE	348
400317	1077	1090	CTATGAGGGTGCCG	2-10-2 MOE	349
400318	1078	1091	CCTATGAGGGTGCC	2-10-2 MOE	350
400319	1093	1106	CGAATAAACTCCAG	2-10-2 MOE	351
400320	1094	1107	CCGAATAAACTCCA	2-10-2 MOE	352
400321	1095	1108	TCCGAATAAACTCC	2-10-2 MOE	353
400322	1096	1109	TTCCGAATAAACTC	2-10-2 MOE	354
400323	1147	1160	GCCAGGGGCAGCAG	2-10-2 MOE	355

400324	1255	1268	GAGTAGAGGCAGGC	2-10-2 MOE	356
400325	1334	1347	CCCCAAAGTCCCCA	2-10-2 MOE	357
400326	1335	1348	TCCCCAAAGTCCCC	2-10-2 MOE	358
400327	1336	1349	GTCCCCAAAGTCCC	2-10-2 MOE	359
400328	1453	1466	ACGTGGGCAGCAGC	2-10-2 MOE	360
400329	1454	1467	CACGTGGGCAGCAG	2-10-2 MOE	361
400330	1455	1468	CCACGTGGGCAGCA	2-10-2 MOE	362
400331	1456	1469	GCCACGTGGGCAGC	2-10-2 MOE	363
400332	1569	1582	CAGGGAACCAGGCC	2-10-2 MOE	364
400333	1570	1583	TCAGGGAACCAGGC	2-10-2 MOE	365
400334	1571	1584	CTCAGGGAACCAGG	2-10-2 MOE	366
400335	1572	1585	CCTCAGGGAACCAG	2-10-2 MOE	367
400336	1573	1586	TCCTCAGGGAACCA	2-10-2 MOE	368
400337	1574	1587	GTCCTCAGGGAACC	2-10-2 MOE	369
400338	1575	1588	GGTCCTCAGGGAAC	2-10-2 MOE	370
400339	1576	1589	TGGTCCTCAGGGAA	2-10-2 MOE	371
400340	1577	1590	CTGGTCCTCAGGGA	2-10-2 MOE	372
400341	1578	1591	GCTGGTCCTCAGGG	2-10-2 MOE	373
400342	1621	1634	GTGCTGGGGGGCAG	2-10-2 MOE	374
400343	1622	1635	GGTGCTGGGGGGCA	2-10-2 MOE	375
400344	1623	1636	GGGTGCTGGGGGGC	2-10-2 MOE	376
400345	1624	1637	TGGGTGCTGGGGGG	2-10-2 MOE	377
400346	1738	1751	GAGCAGCTCAGCAG	2-10-2 MOE	378
400347	1739	1752	GGAGCAGCTCAGCA	2-10-2 MOE	379
400348	1740	1753	TGGAGCAGCTCAGC	2-10-2 MOE	380
400349	1741	1754	CTGGAGCAGCTCAG	2-10-2 MOE	381
400350	1834	1847	CCCTCACCCCCAAA	2-10-2 MOE	382
400351	1835	1848	ACCCTCACCCCCAA	2-10-2 MOE	383
400352	1836	1849	CACCCTCACCCCCA	2-10-2 MOE	384
400353	1837	1850	ACACCCTCACCCCC	2-10-2 MOE	385
400354	1838	1851	GACACCCTCACCCC	2-10-2 MOE	386
400355	1839	1852	AGACACCCTCACCC	2-10-2 MOE	387
400356	1840	1853	TAGACACCCTCACC	2-10-2 MOE	388
400357	2083	2096	TGGCAGCAGGAAGC	2-10-2 MOE	389
400358	2084	2097	ATGGCAGCAGGAAG	2-10-2 MOE	390
400359	2085	2098	CATGGCAGCAGGAA	2-10-2 MOE	391
400360	2086	2099	GCATGGCAGCAGGA	2-10-2 MOE	392
400361	2316	2329	GGCAGCAGATGGCA	2-10-2 MOE	393
400362	2317	2330	CGGCAGCAGATGGC	2-10-2 MOE	394
400363	2318	2331	CCGGCAGCAGATGG	2-10-2 MOE	395
400364	2319	2332	TCCGGCAGCAGATG	2-10-2 MOE	396
400365	2320	2333	CTCCGGCAGCAGAT	2-10-2 MOE	397
400366	2321	2334	GCTCCGGCAGCAGA	2-10-2 MOE	398
400367	2322	2335	GGCTCCGGCAGCAG	2-10-2 MOE	399
400368	2323	2336	CGGCTCCGGCAGCA	2-10-2 MOE	400
400369	2324	2337	CCGGCTCCGGCAGC	2-10-2 MOE	401
400370	2325	2338	GCCGGCTCCGGCAG	2-10-2 MOE	402
400371	3543	3556	AGTTACAAAAGCAA	2-10-2 MOE	403
403739	988	1001	CGGCCGCTGACCAC	2-10-2 (6'S)-6'-methyl-	339

				Methyleneoxy BNA	
403740	1455	1468	CCACGTGGGCAGCA	2-10-2 (6'S)-6'-methyl-Methyleneoxy BNA	362

Table 7: Short antisense compounds targeted to SEQ ID NO: 4 and having 1 or 2 mismatches

ISIS NO.	5' Target Site	3' Target Site	Sequence (5'-3')	Gapmer Motif	SEQ ID NO
400323	349	362	GCCAGGGGCAGCAG	2-10-2 MOE	355
400370	679	692	GCCGGCTCCGGCAG	2-10-2 MOE	402
400361	1860	1873	GGCAGCAGATGGCA	2-10-2 MOE	393
400323	1873	1886	GCCAGGGGCAGCAG	2-10-2 MOE	355
400310	2257	2270	TCCCGGCCGCTGAC	2-10-2 MOE	342
400361	2653	2666	GGCAGCAGATGGCA	2-10-2 MOE	393
400350	2811	2824	CCCTCACCCCCAAA	2-10-2 MOE	382
400351	2812	2825	ACCCTCACCCCCAA	2-10-2 MOE	383
400352	2813	2826	CACCCTCACCCCCA	2-10-2 MOE	384
400353	2814	2827	ACACCCTCACCCCC	2-10-2 MOE	385
400334	2966	2979	CTCAGGGAACCAGG	2-10-2 MOE	366
400332	3379	3392	CAGGGAACCAGGCC	2-10-2 MOE	364
400340	3448	3461	CTGGTCCTCAGGGA	2-10-2 MOE	372
400341	3449	3462	GCTGGTCCTCAGGG	2-10-2 MOE	373

In certain embodiments, a target region is nucleotides 695-710 of SEQ ID NO: 4. In certain such embodiments, short antisense compounds targeted to nucleotides 695-710 of SEQ ID NO: 4 comprise a nucleotide sequence selected from SEQ ID NO: 329, 330, or 331. In certain such embodiments, a short antisense compound targeted to nucleotides 695-710 of SEQ ID NO: 4 is selected from Isis NO. 400297, 400298, or 400299.

In certain embodiments, a target region is nucleotides 742-770 of SEQ ID NO: 4. In certain such embodiments, a short antisense compound targeted to nucleotides 742-770 of SEQ ID NO: 4 comprises a nucleotide sequence selected from SEQ ID NO 332 or 333. In certain such embodiments, a short antisense compound targeted to nucleotides 742-770 of SEQ ID NO: 4 is selected from Isis NO. 400300 or 400301.

In certain embodiments, a target region is nucleotides 828-843 of SEQ ID NO: 4. In certain such embodiments, a short antisense compound targeted to nucleotides 828-843 of SEQ ID NO: 4 comprises a nucleotide sequence selected from SEQ ID NO 334, 335, or 336. In certain such embodiments, a short antisense compound targeted to nucleotides 828-843 of SEQ ID NO: 4 is selected from ISIS No. 400302, 400303, or 400304.

In certain embodiments, a target region is nucleotides 937-1007 of SEQ ID NO: 4. In certain such embodiments, a short antisense compound targeted to nucleotides 937-1007 of SEQ ID NO: 4 comprises a nucleotide sequence selected from SEQ ID NO 337, 338, 339, 340, 341, 342, 343, 344, or 345. In certain such embodiments, a short antisense compound targeted to nucleotides 937-1007 of SEQ ID NO: 4 is selected from Isis NO. 400305, 400306, 400307, 400308, 400309, 400310, 400311, 400312, 400313, or 403739.

In certain embodiments, a target region is nucleotides 937-965 of SEQ ID NO: 4. In certain such embodiments, a short antisense compound targeted to nucleotides 937-965 of SEQ ID NO: 4 comprises a nucleotide sequence selected from SEQ ID NO 337 or 338. In certain such embodiments, a short antisense compound targeted to nucleotides 937-965 of SEQ ID NO: 4 is selected from Isis NO. 400305 or 400306.

In certain embodiments, a target region is nucleotides 988-1007 of SEQ ID NO: 4. In certain such embodiments, a short antisense compound targeted to nucleotides 988-1007 of SEQ ID NO: 4 comprises a nucleotide sequence selected from SEQ ID NO 339, 340, 341, 342, 343, 344, or 345. In certain such embodiments, a short antisense compound targeted to nucleotides 937-1007 of SEQ ID NO: 4 is selected from Isis NO. 400307, 400308, 400309, 400310, 400311, 400312, 4003313, or 403739.

In certain embodiments, a target region is nucleotides 1057-1160 of SEQ ID NO: 4. In certain such embodiments, a short antisense compound targeted to nucleotides 1057-1160 of SEQ ID NO: 4 comprises a nucleotide sequence selected from SEQ ID NO 346, 347, 348, 349, 350, 351, 352, 353, 354, or 355. In certain such embodiments, a short antisense compound targeted to nucleotides 1057-1160 of SEQ ID NO: 4 is selected from ISIS NO. 400314, 400315, 400316, 400317, 400318, 400319, 400320, 400321, 400322, or 400323.

In certain embodiments, a target region is nucleotides 1057-1109 of SEQ ID NO: 4. In certain such embodiments, a short antisense compound targeted to nucleotides 1057-1109 of SEQ ID NO: 4 comprises a nucleotide sequence selected from SEQ ID NO 346, 347, 348, 349, 350, 351, 352, 353, or 354. In certain such embodiments, a short antisense compound targeted to nucleotides 1057-1109 of SEQ ID NO: 4 is selected from ISIS NO. 400314, 400315, 400316, 400317, 400318, 400319, 400320, 400321, or 400322.

In certain embodiments, a target region is nucleotides 1057-1091 of SEQ ID NO: 4. In certain such embodiments, a short antisense compound targeted to nucleotides 1057-1091 of SEQ ID NO: 4 comprises a nucleotide sequence selected from SEQ ID NO 346, 347, 348, 349, or 350. In certain such embodiments, a short antisense compound targeted to nucleotides 1057-1091 of SEQ ID NO: 4 is selected from ISIS NO. 400314, 400315, 400316, 400317, or 400318.

In certain embodiments, a target region is nucleotides 1093-1109 of SEQ ID NO: 4. In certain such embodiments, a short antisense compound targeted to nucleotides 1093-1109 of SEQ ID NO: 4 comprises a nucleotide sequence selected from SEQ ID NO 351, 352, 353, or 354. In certain such embodiments, a short antisense compound targeted to nucleotides 1057-1109 of SEQ ID NO: 4 is selected from ISIS NO. 400319, 400320, 400321, or 400322.

In certain embodiments, a target region is nucleotides 1334-1349 of SEQ ID NO: 4. In certain such embodiments, a short antisense compound targeted to nucleotides 1334-1349 of SEQ ID NO: 4 comprises a

nucleotide sequence selected from SEQ ID NO 357, 358, or 359. In certain such embodiments, a short antisense compound targeted to nucleotides 1334-1349 of SEQ ID NO: 4 is selected from ISIS NO 400325, 400326, or 400327.

In certain embodiments, a target region is nucleotides 1453-1469 of SEQ ID NO: 4. In certain such embodiments, a short antisense compound targeted to nucleotides 1453-1469 of SEQ ID NO: 4 comprises a nucleotide sequence selected from SEQ ID NO 360, 361, 362, or 363. In certain such embodiments, a short antisense compound targeted to nucleotides 1453-1469 of SEQ ID NO: 4 is selected from ISIS NO 400328, 400329, 400330, 400331, or 403470.

In certain embodiments, a target region is nucleotides 1569-1591 of SEQ ID NO: 4. In certain such embodiments, a short antisense compound targeted to nucleotides 1569-1591 of SEQ ID NO: 4 comprises a nucleotide sequence selected from SEQ ID NO 364, 365, 366, 367, 368, 369, 370, 371, 372, or 373. In certain such embodiments, a short antisense compound targeted to nucleotides 1569-1591 of SEQ ID NO: 4 is selected from ISIS NO 400332, 400333, 400334, 400335, 400336, 400337, 400338, 400339, 400340, or 400341.

In certain embodiments, a target region is nucleotides 1621-1637 of SEQ ID NO: 4. In certain such embodiments, a short antisense compound targeted to nucleotides 1621-1637 of SEQ ID NO: 4 comprises a nucleotide sequence selected from SEQ ID NO 374, 375, 376, or 377. In certain such embodiments, a short antisense compound targeted to nucleotides 1621-1637 of SEQ ID NO: 4 is selected from ISIS NO 400342, 400343, 400344, or 400345.

In certain embodiments, a target region is nucleotides 1738-1754 of SEQ ID NO: 4. In certain such embodiments, a short antisense compound targeted to nucleotides 1738-1754 of SEQ ID NO: 4 comprises a nucleotide sequence selected from SEQ ID NO 378, 379, 380, or 381. In certain such embodiments, a short antisense compound targeted to nucleotides 1738-1754 of SEQ ID NO: 4 is selected from ISIS NO 400346, 400347, 400348, or 400349.

In certain embodiments, a target region is nucleotides 1834-1853 of SEQ ID NO: 4. In certain such embodiments, a short antisense compound targeted to nucleotides 1834-1853 of SEQ ID NO: 4 comprises a nucleotide sequence selected from SEQ ID NO 382, 383, 384, 385, 386, 387, or 388. In certain embodiments, a short antisense compound targeted to nucleotides 1834-1853 of SEQ ID NO: 4 is selected from ISIS NO 400350, 400351, 400352, 400353, 400354, 400355, or 400356.

In certain embodiments, a target region is nucleotides 2083-2099 of SEQ ID NO: 4. In certain such embodiments, a short antisense compound targeted to nucleotides 2083-2099 of SEQ ID NO: 4 comprises a nucleotide sequence selected from SEQ ID NO 389, 390, 391, or 392. In certain such embodiments, a short antisense compound targeted to nucleotides 2083-2099 of SEQ ID NO: 4 is selected from ISIS NO 400357, 400358, 400359, or 400360.

In certain embodiments, a target region is nucleotides 2316-2338 of SEQ ID NO: 4. In certain such

embodiments, a short antisense compound targeted to nucleotides 2316-2338 of SEQ ID NO: 4 comprises a nucleotide sequence selected from SEQ ID NO 393, 394, 395, 396, 397, 398, 399, 400, 401, or 402. In certain such embodiments, a short antisense compound targeted to nucleotides 2316-2338 of SEQ ID NO: 4 is selected from ISIS NO 400361, 400362, 400363, 400364, 400365, 400366, 400367, 400368, 400369, or 400370.

In certain embodiments, short antisense compounds targeted to a PCSK9 nucleic acid are 8 to 16, preferably 9 to 15, more preferably 9 to 14, more preferably 10 to 14 nucleotides in length. In certain embodiments, short antisense compounds targeted to a PCSK9 nucleic acid are 9 to 14 nucleotides in length. In certain embodiments, short antisense compounds targeted to a PCSK9 nucleic acid are 10 to 14 nucleotides in length. In certain embodiments, such short antisense compounds are short antisense oligonucleotides.

In certain embodiments, short antisense compounds targeted to a PCSK9 nucleic acid are short gapmers. In certain such embodiments, short gapmers targeted to a PCSK9 nucleic acid comprise at least one high affinity modification in one or more wings of the compound. In certain embodiments, short antisense compounds targeted to a PCSK9 nucleic acid comprise 1 to 3 high-affinity modifications in each wing. In certain such embodiments, the nucleosides or nucleotides of the wing comprise a 2' modification. In certain such embodiments, the monomers of the wing are BNA's. In certain such embodiments, the monomers of the wing are selected from α-L-Methyleneoxy (4'-CH_2-O-2') BNA , β-D-Methyleneoxy (4'-CH_2-O-2') BNA , Ethyleneoxy (4'-$(CH_2)_2$-O-2') BNA , Aminooxy (4'-CH_2-O-N(R)-2') BNA and Oxyamino (4'-CH_2-N(R)-O-2') BNA. In certain embodiments, the monomers of a wing comprise a substituent at the 2' position selected from allyl, amino, azido, thio, O-allyl, O-C_1-C_{10} alkyl, -OCF_3, O-$(CH_2)_2$-O-CH_3, 2'-O$(CH_2)_2SCH_3$, O-$(CH_2)_2$-O-N(R_m)(R_n), and O-CH_2-C(=O)-N(R_m)(R_n), where each R_m and R_n is, independently, H or substituted or unsubstituted C_1-C_{10} alkyl. In certain embodiments, the monomers of a wing are 2'MOE nucleotides.

In certain embodiments, short antisense compounds targeted to a PCSK9 nucleic acid comprise a gap between the 5' wing and the 3' wing. In certain embodiments the gap comprises five, six, seven, eight, nine, ten, eleven, twelve, thirteen, or fourteen monomers. In certain embodiments, the monomers of the gap are unmodified deoxyribonucleotides. In certain embodiments, the monomers of the gap are unmodified ribonucleotides. In certain embodiments, gap modifications (if any) gap result in an antisense compound that, when bound to its target nucleic acid, supports cleavage by an RNase, including, but not limited to, RNase H.

In certain embodiments, short antisense compounds targeting a PCSK9 nucleic acid may have any one or more properties or characteristics of the short antisense compounds generally described herein. In certain embodiments, short antisense compounds targeting a PCSK9 nucleic acid have a motif (wing – deoxy gap –wing) selected from 1-12-1, 1-1-10-2, 2-10-1-1, 3-10-3, 2-10-3, 2-10-2, 1-10-1,1-10-2, 3-8-3, 2-8-2, 1-8-1, 3-6-3 or 1-6-1, more preferably 1-10-1, 2-10-2, 3-10-3, and 1-9-2.

In certain embodiments, short antisense compounds targeted to a PCSK9 nucleic acid have uniform monomeric linkages. In certain such embodiments, those linkages are all phosphorothioate linkages. In certain embodiments, the linkages are all phosphodiester linkages. In certain embodiments, short antisense compounds targeted to a PCSK9 nucleic acid have mixed backbones.

In certain embodiments, short antisense compounds targeted to a PCSK9 nucleic acid are 8 monomers in length. In certain embodiments, short antisense compounds targeted to a PCSK9 nucleic acid are 9 monomers in length. In certain embodiments, short antisense compounds targeted to a PCSK9 nucleic acid are 10 monomers in length. In certain embodiments, short antisense compounds targeted to a PCSK9 nucleic acid are 11 monomers in length. In certain embodiments, short antisense compounds targeted to a PCSK9 nucleic acid are monomers in length. In certain embodiments, short antisense compounds targeted to a PCSK9 nucleic acid are 13 monomers in length. In certain embodiments, short antisense compounds targeted to a PCSK9 nucleic acid are 14 monomers in length. In certain embodiments, short antisense compounds targeted to a PCSK9 nucleic acid are 15 monomers in length. In certain embodiments, short antisense compounds targeted to a PCSK9 nucleic acid are 16 monomers in length. In certain embodiments, short antisense compounds targeted to a PCSK9 nucleic acid comprise 9 to 15 monomers. In certain embodiments, short antisense compounds targeted to a PCSK9 nucleic acid comprise 10 to 15 monomers. In certain embodiments, short antisense compounds targeted to a PCSK9 nucleic acid comprise 12 to 14 monomers. In certain embodiments, short antisense compounds targeted to a PCSK9 nucleic acid comprise 12 to 14 nucleotides or nucleosides.

In certain embodiments, the invention provides methods of modulating expression of PCSK9. In certain embodiments, such methods comprise use of one or more short antisense compound targeted to a PCSK9 nucleic acid, wherein the short antisense compound targeted to a PCSK9 nucleic acid is from about 8 to about 16, preferably 9 to 15, more preferably 9 to 14, more preferably 10 to 14 monomers (i.e. from about 8 to about 16 linked monomers). One of ordinary skill in the art will appreciate that this comprehends methods of modulating expression of PCSK9 using one or more short antisense compounds targeted to a PCSK9 nucleic acid of 8, 9, 10, 11, 12, 13, 14, 15 or 16 monomers.

In certain embodiments, methods of modulating PCSK9 comprise use of a short antisense compound targeted to a PCSK9 nucleic acid that is 8 monomers in length. In certain embodiments, methods of modulating PCSK9 comprise use of a short antisense compound targeted to a PCSK9 nucleic acid that is 9 monomers in length. In certain embodiments, methods of modulating PCSK9 comprise use of a short antisense compound targeted to a PCSK9 nucleic acid that is 10 monomers in length. In certain embodiments, methods of modulating PCSK9 comprise use of a short antisense compound targeted to a PCSK9 nucleic acid that is 11 monomers in length. In certain embodiments, methods of modulating PCSK9 comprise use of a short antisense compound targeted to a PCSK9 nucleic acid that is 12 monomers in length. In certain embodiments, methods of modulating PCSK9 comprise use of a short antisense compound targeted to a PCSK9 nucleic acid that is 13 monomers in length. In certain embodiments, methods of modulating PCSK9 comprise use of a short antisense compound targeted to a PCSK9 nucleic acid that is 14 monomers in length. In certain embodiments, methods of modulating PCSK9 comprise use of a short antisense compound targeted to a PCSK9 nucleic acid that is 15 monomers in length. In certain embodiments, methods of modulating PCSK9 comprise use of a short antisense compound targeted to a PCSK9 nucleic acid that is 16 monomers in length.

In certain embodiments, methods of modulating expression of PCSK9 comprise use of a short antisense compound targeted to a PCSK9 nucleic acid comprising 9 to 15 monomers. In certain embodiments, methods of modulating expression of PCSK9 comprise use of a short antisense compound targeted to a PCSK9 nucleic acid comprising 10 to 15 monomers. In certain embodiments, methods of modulating expression of PCSK9 comprise use of a short antisense compound targeted to a PCSK9 nucleic acid comprising 12 to 14 monomers. In certain embodiments, methods of modulating expression of PCSK9 comprise use of a short antisense compound targeted to a PCSK9 nucleic acid comprising 12 or 14 nucleotides or nucleosides.

4. Superoxide Dismutase 1 Enzyme (SOD1)

The enzymes known as the superoxide dismutases (SODs) provide defense against oxidative damage of biomolecules by catalyzing the dismutation of superoxide to hydrogen peroxide (H_2O_2) (Fridovich, *Annu. Rev. Biochem.*, **1995**, *64*, 97-112). Two major classes of superoxide dismutases exist. One consists of a group of enzymes with active sites containing copper and zinc while the other class has either manganese or iron at the active site (Fridovich, *Annu. Rev. Biochem.*, **1995**, *64*, 97-112).

Mutations in the superoxide dismutase 1 gene are associated with a dominantly-inherited form of amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's disease) a disorder characterized by a selective degeneration of upper and lower motor neurons (Cleveland and Liu, *Nat. Med.*, **2000**, *6*, 1320-1321). The deleterious effects of various mutations on superoxide dismutase 1 are most likely mediated through a gain of toxic function rather than a loss of superoxide dismutase 1 activity, as the complete absence of superoxide dismutase 1 in mice neither diminishes life nor provokes overt disease (Al-Chalabi and Leigh, *Curr. Opin. Neurol.*, **2000**, *13*, 397-405; Alisky and Davidson, *Hum. Gene Ther.*, **2000**, *11*, 2315-2329).

Over 100 mutations of the human SOD1 gene have been identified, and altogether account for approximately 20% of familial amyotrophic lateral sclerosis (ALS) cases. Some mutations, such as the A4V mutation most commonly found in the United States, are highly lethal and result in survival only nine months from the onset of disease symptoms. Other mutations of SOD1 manifest in a slower disease course.

Definitions

"SOD1" means the gene product or protein of which expression is to be modulated by administration of a short antisense compound.

"SOD1 nucleic acid" means any nucleic acid encoding SOD1. For example, in certain embodiments, a SOD1 nucleic acid includes, without limitations, a DNA sequence encoding SOD1, an RNA sequence transcribed from DNA encoding SOD1, and an mRNA sequence encoding SOD1.

"SOD1 mRNA" means an mRNA encoding SOD1.

SOD1 Therapeutic Indications

It has been discovered that antisense inhibition of superoxide dismutase 1 (SOD1) in an animal model of familial ALS reduces both SOD1 mRNA and protein, and further results in a slowing of disease progression and, importantly, increased survival time. Accordingly, in certain embodiments, the invention provides methods for the slowing of disease progression in an individual suffering from familial ALS by administering to such an individual a short antisense compound targeted to an SOD1 nucleic acid. In certain such embodiments, a short antisense compound targeted to SOD1 are delivered directly to the cerebrospinal fluid of the individual. In certain such embodiments, methods further comprise increasing survival time of an individual suffering from familial ALS. Slowing of disease progression is indicated by an improvement in one or more indicators of ALS disease progression, including, without limitation, the revised ALS functional rating scale, pulmonary function tests, and muscle strength measurements.

SOD1 Combination Therapies

In certain embodiments, one or more pharmaceutical compositions comprising a short antisense compound targeted to an SOD1 nucleic acid is co-administered with one or more other pharmaceutical agents. In certain embodiments, such one or more other pharmaceutical agents are designed to treat the same disease or condition as the one or more pharmaceutical compositions of the present invention. In certain embodiments, such one or more other pharmaceutical agents are designed to treat a different disease or condition as the one or more pharmaceutical compositions of the present invention. In certain embodiments, such one or more other pharmaceutical agents are designed to treat an undesired effect of one or more pharmaceutical compositions of the present invention. In certain embodiments, one or more pharmaceutical compositions of the present invention are co-administered with another pharmaceutical agent to treat an undesired effect of that other pharmaceutical agent. In certain embodiments, one or more pharmaceutical compositions of the present invention and one or more other pharmaceutical agents are administered at the same time. In certain embodiments, one or more pharmaceutical compositions of the present invention and one or more other pharmaceutical agents are administered at different times. In certain embodiments, one or more pharmaceutical compositions of the present invention and one or more other pharmaceutical agents are prepared together in a single formulation. In certain embodiments, one or more pharmaceutical compositions of the present invention and one or more other pharmaceutical agents are prepared separately.

In certain embodiments, a co-administered pharmaceutical agent is a nicotinic acid. In certain such embodiments, the nicotinic acid is selected from immediate release nicotinic acid, extended release nicotinic acid, and sustained release nicotinic acid.

In certain embodiments, a co-administered pharmaceutical agent is a fibric acid. In certain such embodiments, a fibric acid is selected from gemfibrozil, fenofibrate, clofibrate, bezafibrate, and ciprofibrate.

Further examples of pharmaceutical agents that may be co-administered with a pharmaceutical composition comprising a short antisense compound targeted to SOD1 include, but are not limited to, corticosteroids, including but not limited to prednisone; immunoglobulins, including, but not limited to intravenous immunoglobulin (IVIg); analgesics (e.g., acetaminophen); anti-inflammatory agents, including, but not limited to non-steroidal anti-inflammatory drugs (e.g., ibuprofen, COX-1 inhibitors, and COX-2, inhibitors); salicylates; antibiotics; antivirals; antifungal agents; antidiabetic agents (e.g., biguanides, glucosidase inhibitors, insulins, sulfonylureas, and thiazolidenediones); adrenergic modifiers; diuretics; hormones (e.g., anabolic steroids, androgen, estrogen, calcitonin, progestin, somatostan, and thyroid hormones); immunomodulators; muscle relaxants; antihistamines; osteoporosis agents (e.g., biphosphonates, calcitonin, and estrogens); prostaglandins, antineoplastic agents; psychotherapeutic agents; sedatives; poison oak or poison sumac products; antibodies; and vaccines.

Certain Short Antisense Compounds Targeted to a SOD1 Nucleic Acid

In certain embodiments, short antisense compounds are targeted to a SOD1 nucleic acid having the sequence of GENBANK® Accession No. NM_X02317.1, incorporated herein as SEQ ID NO: 5. In certain such embodiments, a short antisense compound targeted to SEQ ID NO: 5 is at least 90% complementary to SEQ ID NO: 5. In certain such embodiments, a short antisense compound targeted to SEQ ID NO: 5 is at least 95% complementary to SEQ ID NO: 5. In certain such embodiments, a short antisense compound targeted to SEQ ID NO: 5 is 100% complementary to SEQ ID NO: 5. In certain embodiments, a short antisense compound targeted to SEQ ID NO: 5 comprises a nucleotide sequence selected from the nucleotide sequences set forth in Table 8 or Table 9.

The nucleotide sequence set forth in each SEQ ID NO in Tables 8 and 9 is independent of any modification to a sugar moiety, an internucleoside linkage, or a nucleobase. As such, short antisense compounds defined by a SEQ ID NO may comprise, independently, one or more modifications to a sugar moiety, an internucleoside linkage, or a nucleobase. Short antisense compounds described by Isis Number (Isis NO.) indicate a combination of nucleobase sequence and one or more modifications to a sugar moiety, an internucleoside linkage, or a nucleobase.

Table 8 illustrates examples of short antisense compounds targeted to SEQ ID NO: 5. Table 8 illustrates short antisense compounds that are 100% complementary to SEQ ID NO: 5. The column labeled 'gapmer motif' indicates the wing-gap-wing motif of each short antisense compounds. The gap segment comprises 2'-deoxynucleotides and each nucleotide of each wing segment comprises a 2'-modified sugar. The particular 2'-modified sugar is also indicated in the 'gapmer motif' column. For example, '2-10-2 MOE' means a 2-10-2 gapmer motif, where a gap segment of ten 2'-deoxynucleotides is flanked by wing segments of two nucleotides, where the nucleotides of the wing segments are 2'-MOE nucleotides. Internucleoside linkages are phosphorothioate. The short antisense compounds comprise 5-methylcytidine in place of unmodified cytosine, unless "unmodified cytosine" is listed in the gapmer motif column, in which case the indicated cytosines are unmodified cytosines. For example, "5-mC in gap only" indicates that the gap segment has 5-methylcytosines, while the wing segments have unmodified cytosines.

In certain embodiments, short antisense compounds targeting a SOD1 nucleic acid may have any one or more properties or characteristics of the short antisense compounds generally described herein. In certain embodiments, short antisense compounds targeting a SOD1 nucleic acid have a motif (wing – deoxy gap – wing) selected from 1-12-1, 1-1-10-2, 2-10-1-1, 3-10-3, 2-10-3, 2-10-2, 1-10-1,1-10-2, 3-8-3, 2-8-2, 1-8-1, 3-6-3 or 1-6-1, more preferably 1-10-1, 2-10-2, 3-10-3, and 1-9-2.

Table 8: Short Antisense Compounds targeted to SEQ ID NO: 5

ISIS NO.	5' Target Site	3' Target Site	Sequence (5'-3')	Gapmer Motif	SEQ ID NO
387541	85	100	GTCGCCCTTCAGCACG	3-10-3 MOE	406
387540	86	99	TCGCCCTTCAGCAC	2-10-2 MOE	407
387539	87	98	CGCCCTTCAGCA	1-10-1 MOE	408

In certain embodiments, a target region is nucleotides 85-100 of SEQ ID NO: 5. In certain such embodiments, short antisense compounds targeted to nucleotides 85-100 of SEQ ID NO: 5 comprise a nucleotide sequence selected from SEQ ID NO: 406, 407, or 408. In certain such embodiments, a short antisense compound targeted to nucleotides 85-100 of SEQ ID NO: 5 is selected from Isis No. 387541, 387540, or 387539.

In certain embodiments, short antisense compounds targeted to a SOD1 nucleic acid are 8 to 16, preferably 9 to 15, more preferably 9 to 14, more preferably 10 to 14 nucleotides in length. In certain embodiments, short antisense compounds targeted to a SOD1 nucleic acid are 9 to 14 nucleotides in length. In certain embodiments, short antisense compounds targeted to a SOD1 nucleic acid are 10 to 14 nucleotides in length. In certain embodiments, such short antisense compounds are short antisense oligonucleotides.

In certain embodiments, short antisense compounds targeted to a SOD1 nucleic acid are short gapmers. In certain such embodiments, short gapmers targeted to a SOD1 nucleic acid comprise at least one high affinity modification in one or more wings of the compound. In certain embodiments, short antisense compounds targeted to a SOD1 nucleic acid comprise 1 to 3 high-affinity modifications in each wing. In certain such embodiments, the nucleosides or nucleotides of the wing comprise a 2' modification. In certain such embodiments, the monomers of the wing are BNA's. In certain such embodiments, the monomers of the wing are selected from α-L-Methyleneoxy (4'-CH_2-O-2') BNA , β-D-Methyleneoxy (4'-CH_2-O-2') BNA , Ethyleneoxy (4'-$(CH_2)_2$-O-2') BNA , Aminooxy (4'-CH_2-O-N(R)-2') BNA and Oxyamino (4'-CH_2-N(R)-O-2') BNA. In certain embodiments, the monomers of a wing comprise a substituent at the 2' position selected from allyl, amino, azido, thio, O-allyl, O-C_1-C_{10} alkyl, -OCF_3, O-$(CH_2)_2$-O-CH_3, 2'-O$(CH_2)_2$$SCH_3$, O-$(CH_2)_2$-O-N($R_m$)($R_n$), and O-$CH_2$-C(=O)-N($R_m$)($R_n$), where each R_m and R_n is, independently, H or substituted or unsubstituted C_1-C_{10} alkyl. In certain embodiments, the monomers of a wing are 2'MOE nucleotides.

In certain embodiments, short antisense compounds targeted to a SOD1 nucleic acid comprise a gap between the 5' wing and the 3' wing. In certain embodiments the gap comprises five, six, seven, eight, nine, ten, eleven, twelve, thirteen, or fourteen monomers. In certain embodiments, the monomers of the gap are unmodified deoxyribonucleotides. In certain embodiments, the monomers of the gap are unmodified ribonucleotides. In certain embodiments, gap modifications (if any) gap result in an antisense compound that, when bound to its target nucleic acid, supports cleavage by an RNase, including, but not limited to, RNase H.

In certain embodiments, short antisense compounds targeted to a SOD1 nucleic acid have uniform monomeric linkages. In certain such embodiments, those linkages are all phosphorothioate linkages. In certain embodiments, the linkages are all phosphodiester linkages. In certain embodiments, short antisense compounds targeted to a SOD1 nucleic acid have mixed backbones.

In certain embodiments, short antisense compounds targeted to a SOD1 nucleic acid are 8 monomers in length. In certain embodiments, short antisense compounds targeted to a SOD1 nucleic acid are 9 monomers in length. In certain embodiments, short antisense compounds targeted to a SOD1 nucleic acid are 10 monomers in length. In certain embodiments, short antisense compounds targeted to a SOD1 nucleic acid are 11 monomers in length. In certain embodiments, short antisense compounds targeted to a SOD1 nucleic acid are monomers in length. In certain embodiments, short antisense compounds targeted to a SOD1 nucleic acid are 13 monomers in length. In certain embodiments, short antisense compounds targeted to a SOD1 nucleic acid are 14 monomers in length. In certain embodiments, short antisense compounds targeted to a SOD1 nucleic acid are 15 monomers in length. In certain embodiments, short antisense compounds targeted to a SOD1 nucleic acid are 16 monomers in length. In certain embodiments, short antisense compounds targeted to a SOD1 nucleic acid comprise 9 to 15 monomers. In certain embodiments, short antisense compounds targeted to a SOD1 nucleic acid comprise 10 to 15 monomers. In certain embodiments, short antisense compounds targeted to a SOD1 nucleic acid comprise 12 to 14 monomers. In certain embodiments, short antisense compounds targeted to a SOD1 nucleic acid comprise 12 to 14 nucleotides or nucleosides.

In certain embodiments, the invention provides methods of modulating expression of SOD1. In certain embodiments, such methods comprise use of one or more short antisense compound targeted to a SOD1 nucleic acid, wherein the short antisense compound targeted to a SOD1 nucleic acid is from about 8 to about 16, preferably 9 to 15, more preferably 9 to 14, more preferably 10 to 14 monomers (i.e. from about 8 to about 16 linked monomers). One of ordinary skill in the art will appreciate that this comprehends methods of modulating expression of SOD1 using one or more short antisense compounds targeted to a SOD1 nucleic acid of 8, 9, 10, 11, 12, 13, 14, 15 or 16 monomers.

In certain embodiments, methods of modulating SOD1 comprise use of a short antisense compound targeted to a SOD1 nucleic acid that is 8 monomers in length. In certain embodiments, methods of modulating SOD1 comprise use of a short antisense compound targeted to a SOD1 nucleic acid that is 9 monomers in length. In certain embodiments, methods of modulating SOD1 comprise use of a short antisense compound targeted to a SOD1 nucleic acid that is 10 monomers in length. In certain embodiments, methods of modulating SOD1 comprise use of a short antisense compound targeted to a SOD1 nucleic acid that is 11 monomers in length. In certain embodiments, methods of modulating SOD1 comprise use of a short antisense compound targeted to a SOD1 nucleic acid that is 12 monomers in length. In certain embodiments, methods of modulating SOD1 comprise use of a short antisense compound targeted to a SOD1 nucleic acid that is 13 monomers in length. In certain embodiments, methods of modulating SOD1 comprise use of a short antisense compound targeted to a SOD1 nucleic acid that is 14 monomers in length. In certain embodiments, methods of modulating SOD1 comprise use of a short antisense compound targeted to a SOD1 nucleic acid that is 15 monomers in length. In certain embodiments, methods of modulating SOD1 comprise use of a short antisense compound targeted to a SOD1 nucleic acid that is 16 monomers in length.

In certain embodiments, methods of modulating expression of SOD1 comprise use of a short antisense compound targeted to a SOD1 nucleic acid comprising 9 to 15 monomers. In certain embodiments, methods of modulating expression of SOD1 comprise use of a short antisense compound targeted to a SOD1 nucleic acid comprising 10 to 15 monomers. In certain embodiments, methods of modulating expression of SOD1 comprise use of a short antisense compound targeted to a SOD1 nucleic acid comprising 12 to 14 monomers. In certain embodiments, methods of modulating expression of SOD1 comprise use of a short antisense compound targeted to a SOD1 nucleic acid comprising 12 or 14 nucleotides or nucleosides.

5. <u>CRP</u>

CRP (also known as C-reactive protein and PTX1) is an essential human acute-phase reactant produced in the liver in response to a variety of inflammatory cytokines. The protein, first identified in 1930, is highly conserved and considered to be an early indicator of infectious or inflammatory conditions. Plasma CRP levels increase 1,000-fold in response to infection, ischemia, trauma, burns, and inflammatory conditions. In clinical trials where patients receive lipid-lowering therapy, such as statin therapy, it has been demonstrated that patients having reductions in both LDL-C and CRP have a reduced risk of future coronary events relative to patients experiencing only reductions in LDL-C.

Definitions

"CRP" means the gene product or protein of which expression is to be modulated by a short antisense compound.

"CRP nucleic acid" means any nucleic acid encoding CRP. For example, in certain embodiments, a CRP nucleic acid includes, without limitations, a DNA sequence encoding CRP, an RNA sequence transcribed from DNA encoding CRP, and an mRNA sequence encoding CRP.

"CRP mRNA" means an mRNA encoding CRP.

CRP Therapeutic Indications

In certain embodiments, the invention provides methods of modulating CRP expression in an individual comprising administering to the individual a short antisense compound targeted to a CRP nucleic acid. In certain embodiments, the invention provides methods of treating an individual comprising administering one or more pharmaceutical compositions comprising a short antisense compound targeted to a CRP nucleic acid. In certain embodiments, the individual has hypercholesterolemia, non-familial hypercholesterolemia, familial hypercholesterolemia, heterozygous familial hypercholesterolemia, homozygous familial hypercholesterolemia, mixed dyslipidemia, atherosclerosis, a risk of developing atherosclerosis, coronary heart disease, a history of coronary heart disease, early onset coronary heart disease, one or more risk factors for coronary heart disease. In certain embodiments, the individual has acute coronary syndrome, vascular injury, arterial occlusion, unstable angina, post peripheral vascular disease, post myocardial infarction (MI), thrombosis, deep vein thrombus, end-stage renal disease (ESRD), chronic renal failure, complement activation, congestive heart failure, or systemic vasculitis. In certain embodiments, the individual has had a stroke.

In certain embodiments, the individual has undergone a procedure selected from elective stent placement, angioplasty, post percutaneous transluminal angioplasty (PTCA), cardiac transplantation, renal dialysis or cardiopulmonary bypass.

In certain embodiments, the individual has an inflammatory disease. In certain such embodiments, the inflammatory disease is selected from inflammatory bowel disease, ulcerative colitis, rheumatoid arthritis, or osteoarthritis.

Guidelines for lipid-lowering therapy were established in 2001 by Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP), and updated in 2004 (Grundy et al., Circulation, 2004, 110, 227-239). The guidelines include obtaining a complete lipoprotein profile, typically after a 9 to 12 hour fast, for determination of LDL-C, total cholesterol, and HDL-C levels. According to the most recently established guidelines, LDL-C levels of 130-159 mg/dL, 160-189 mg/dL, and greater than or equal to 190 mg/dL are considered borderline high, high, and very high, respectively. Total cholesterol levels of 200-239 and greater than or equal to 240 mg/dL are considered borderline high and high, respectively. HDL-C levels of less than 40 mg/dL are considered low.

In certain embodiments, the individual has been identified as in need of lipid-lowering therapy. In certain such embodiments, the individual has been identified as in need of lipid-lowering therapy according to the guidelines established in 2001 by Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP), and updated in 2004 (Grundy et al., Circulation, 2004, 110, 227-239). In certain such embodiments, the individual in need of lipid-lowering therapy has LDL-C above 190 mg/dL. In certain such embodiments, the individual in need of lipid-lowering therapy has LDL-C above 160 mg/dL. In certain such embodiments, the individual in need of lipid-lowering therapy has LDL-C above 130 mg/dL. In certain such embodiments the individual in need of lipid-lowering therapy has LDL-C above 100 mg/dL. In certain such embodiments the individual in need of lipid-lowering therapy should maintain LDL-C below 160 mg/dL. In certain such embodiments the individual in need of lipid-lowering therapy should maintain LDL-C below 130 mg/dL. In certain such embodiments the individual in need of lipid-lowering therapy should maintain LDL-C below 100 mg/dL. In certain such embodiments the individual should maintain LDL-C below 70 mg/dL.

In certain embodiments the invention provides methods for reducing CRP in an individual. In certain such embodiments, the reduction in CRP is at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, and at least 100%.

In certain embodiments, the methods provided by the present invention do not lower HDL-C. In certain embodiments, the methods provided by the present invention do not result in accumulation of lipids in the liver. In certain embodiments, the methods provided by the present invention do not cause hepatic steatosis.

In certain embodiments, the invention provides methods for lowering CRP concentration in a subject while reducing side effects associated with treatment. In certain such embodiments, a side effect is liver toxicity. In certain such embodiments, a side effect is abnormal liver function. In certain such embodiments, a side effect is elevated alanine aminotransferase (ALT). In certain such embodiments, a side effect is elevated aspartate aminotransferase (AST).

In certain embodiments, the invention provides methods for lowering CRP concentration in a subject who is not reaching target LDL-C levels as a result of lipid-lowering therapy. In certain such embodiments, a short antisense compound targeted to a CRP nucleic acid is the only pharmaceutical agent administered to the subject. In certain such embodiments, the subject has not complied with recommended lipid-lowering therapy. In certain such embodiments, a pharmaceutical composition of the invention is co-administered with an additional different lipid-lowering therapy. In certain such embodiments, an additional lipid-lowering therapy is LDL-apheresis. In certain such embodiments, an additional lipid-lowering therapy is a statin. In certain such embodiments, an additional lipid-lowering therapy is ezetimibe.

In certain embodiments, the invention provides methods for lowering CRP concentration in a statin-intolerant subject. In certain such embodiments, the subject has creatine kinase concentration increases as a result of statin administration. In certain such embodiments, the subject has liver function abnormalities as a result of statin administration. In certain such embodiments the subject has muscle aches as a result of statin administration. In certain such embodiments the subject has central nervous system side effects as a result of statin administration. In certain embodiments, the subject has not complied with recommended statin administration.

In certain embodiments, the invention provides methods for reducing coronary heart disease risk in a subject. In certain embodiments the invention provides methods for slowing the progression of atherosclerosis in a subject. In certain such embodiments the invention provides methods for stopping the progression of atherosclerosis in a subject. In certain such embodiments the invention provides methods for reducing the size and/or prevalence of atherosclerotic plaques in a subject. In certain embodiments the methods provided reduce a subject's risk of developing atherosclerosis.

In certain embodiments the methods provided improve the cardiovascular outcome in a subject. In certain such embodiments improved cardiovascular outcome is the reduction of the risk of developing coronary heart disease. In certain such embodiments, improved cardiovascular outcome is a reduction in the occurance of one or more major cardiovascular events, which include, but are not limited to, death, myocardial infarction, reinfarction, stroke, cardiogenic shock, pulmonary edema, cardiac arrest, and atrial dysrhythmia. In certain such embodiments, the improved cardiovascular outcome is evidenced by improved carotid intimal media thickness. In certain such embodiments, improved carotid intimal media thickness is a decrease in thickness. In certain such embodiments, improved carotid intimal media thickness is a prevention an increase of intimal media thickness.

In certain embodiments a pharmaceutical composition comprising a short antisense compound targeted to a CRP nucleic acid is for use in therapy. In certain embodiments, the therapy is the reduction of CRP in an individual. In certain embodiments, the therapy is the treatment of hypercholesterolemia, non-familial hypercholesterolemia, familial hypercholesterolemia, heterozygous familial hypercholesterolemia, homozygous familial hypercholesterolemia, mixed dyslipidemia, atherosclerosis, a risk of developing atherosclerosis, coronary heart disease, a history of coronary heart disease, or early onset coronary heart disease. In additional embodiments, the therapy is the reduction of CHD risk. In certain the therapy is prevention of atherosclerosis. In certain embodiments, the therapy is the prevention of coronary heart disease. In certain embodiments, the therapy is the treatment of acute coronary syndrome, chronic renal failure, vascular injury, arterial occlusion, atherothrombosis, unstable angina, post peripheral vascular disease, post myocardial infarction (MI), thrombosis, deep vein thrombus, end-stage renal disease (ESRD), complement activation, congestive heart failure, or systemic vasculitis. In certain embodiments the therapy is the treatment of an individual who has undergone a procedure selected from elective stent placement, angioplasty, post percutaneous transluminal angioplasty (PTCA), cardiac transplantation, renal dialysis or cardiopulmonary bypass. In certain embodiments, the therapy is the treatment of an inflammatory disorder.

In certain embodiments a pharmaceutical composition comprising a short antisense compound targeted to a CRP nucleic acid is used for the preparation of a medicament for reducing CRP in an individual. In certain embodiments pharmaceutical composition comprising a short antisense compound targeted to a CRP nucleic acid is used for the preparation of a medicament for reducing coronary heart disease risk. In certain embodiments a short antisense compound targeted to a CRP nucleic acid is used for the preparation of a medicament for the treatment of hypercholesterolemia, non-familial hypercholesterolemia, familial hypercholesterolemia, heterozygous familial hypercholesterolemia, homozygous familial hypercholesterolemia, mixed dyslipidemia, atherosclerosis, a risk of developing atherosclerosis, coronary heart disease, a history of coronary heart disease, early onset coronary heart disease, or one or more risk factors for coronary heart disease.

In certain embodiments, a short antisense compound targeted to a CRP nucleic acid is used for the preparation of a medicament for the treatment of acute coronary syndrome, chronic renal failure, vascular injury, arterial occlusion, atherothrombosis, unstable angina, post peripheral vascular disease, post myocardial infarction (MI), thrombosis, deep vein thrombus, end-stage renal disease (ESRD), complement activation, congestive heart failure, or systemic vasculitis. In certain embodiments, a short antisense compound targeted to a CRP nucleic acid is used for the preparation of a medicament for the treatment of an individual who has had a stroke.

In certain embodiments, a short antisense compound targeted to a CRP nucleic acid is used for the preparation of a medicament for the treatment in an individual who has undergone a procedure selected from elective stent placement, angioplasty, post percutaneous transluminal angioplasty (PTCA), cardiac transplantation, renal dialysis or cardiopulmonary bypass.

In certain embodiments, a short antisense compound targeted to a CRP nucleic acid is used for the preparation of a medicament for the treatment of an inflammatory disease. In certain such embodiments, a short antisense compound targeted to a CRP nucleic acid is used for the preparation of a medicament for the treatment of inflammatory bowel disease, ulcerative colitis, rheumatoid arthritis, or osteoarthritis.

CRP Combination Therapies

In certain embodiments, one or more pharmaceutical compositions comprising a short antisense compound targeted to a CRP nucleic acid are co-administered with one or more other pharmaceutical agents. In certain embodiments, the one or more other pharmaceutical agents is a lipid-lowering agent. In certain embodiments, such one or more other pharmaceutical agents are designed to treat the same disease or condition as the one or more pharmaceutical compositions of the present invention. In certain embodiments, such one or more other pharmaceutical agents are designed to treat a different disease or condition as the one or more pharmaceutical compositions of the present invention. In certain embodiments, such one or more other pharmaceutical agents are designed to treat an undesired effect of one or more pharmaceutical compositions of the present invention. In certain embodiments, one or more pharmaceutical compositions of the present invention are co-administered with another pharmaceutical agent to treat an undesired effect of that other pharmaceutical agent. In certain embodiments, one or more pharmaceutical compositions of the present invention and one or more other pharmaceutical agents are administered at the same time. In certain embodiments, one or more pharmaceutical compositions of the present invention and one or more other pharmaceutical agents are administered at different times. In certain embodiments, one or more pharmaceutical compositions of the present invention and one or more other pharmaceutical agents are prepared together in a single formulation. In certain embodiments, one or more pharmaceutical compositions of the present invention and one or more other pharmaceutical agents are prepared separately.

In certain embodiments, pharmaceutical agents that may be co-administered with a pharmaceutical composition comprising a short antisense compound targeted to a CRP nucleic acid include lipid-lowering agents. In certain such embodiments, pharmaceutical agents that may be co-administered with a pharmaceutical composition of the present invention include, but are not limited to atorvastatin, simvastatin, rosuvastatin, and ezetimibe. In certain such embodiments, the lipid-lowering agent is administered prior to administration of a pharmaceutical composition of the present invention. In certain such embodiments, the lipid-lowering agent is administered following administration of a pharmaceutical composition of the present invention. In certain such embodiments the lipid-lowering agent is administered at the same time as a pharmaceutical composition of the present invention. In certain such embodiments the dose of a co-administered lipid-lowering agent is the same as the dose that would be administered if the lipid-lowering agent was administered alone. In certain such embodiments the dose of a co-administered lipid-lowering agent is lower than the dose that would be administered if the lipid-lowering agent was administered alone. In certain such embodiments the dose of a co-administered lipid-lowering agent is greater than the dose that would be administered if the lipid-lowering agent was administered alone.

In certain embodiments, a co-administered lipid-lowering agent is a HMG-CoA reductase inhibitor. In certain such embodiments the HMG-CoA reductase inhibitor is a statin. In certain such embodiments the statin is selected from atorvastatin, simvastatin, pravastatin, fluvastatin, and rosuvastatin.

In certain embodiments, a co-administered lipid-lowering agent is ISIS 301012.

In certain embodiments, a co-administered lipid-lowering agent is a cholesterol absorption inhibitor. In certain such embodiments, cholesterol absorption inhibitor is ezetimibe.

In certain embodiments, a co-administered lipid-lowering agent is a co-formulated HMG-CoA reductase inhibitor and cholesterol absorption inhibitor. In certain such embodiments the co-formulated lipid-lowering agent is ezetimibe/simvastatin.

In certain embodiments, a co-administered lipid-lowering agent is a microsomal triglyceride transfer protein inhibitor (MTP inhibitor).

In certain embodiments, a co-administered pharmaceutical agent is a bile acid sequestrant. In certain such embodiments, the bile acid sequestrant is selected from cholestyramine, colestipol, and colesevelam.

In certain embodiments, a co-administered pharmaceutical agent is a nicotinic acid. In certain such embodiments, the nicotinic acid is selected from immediate release nicotinic acid, extended release nicotinic acid, and sustained release nicotinic acid.

In certain embodiments, a co-administered pharmaceutical agent is a fibric acid. In certain such embodiments, a fibric acid is selected from gemfibrozil, fenofibrate, clofibrate, bezafibrate, and ciprofibrate.

Further examples of pharmaceutical agents that may be co-administered with a pharmaceutical composition comprising a short antisense compound targeted to a CRP nucleic acid include, but are not limited to, corticosteroids, including but not limited to prednisone; immunoglobulins, including, but not limited to intravenous immunoglobulin (IVIg); analgesics (e.g., acetaminophen); anti-inflammatory agents, including, but not limited to non-steroidal anti-inflammatory drugs (e.g., ibuprofen, COX-1 inhibitors, and COX-2, inhibitors); salicylates; antibiotics; antivirals; antifungal agents; antidiabetic agents (e.g., biguanides, glucosidase inhibitors, insulins, sulfonylureas, and thiazolidenediones); adrenergic modifiers; diuretics; hormones (e.g., anabolic steroids, androgen, estrogen, calcitonin, progestin, somatostan, and thyroid hormones); immunomodulators; muscle relaxants; antihistamines; osteoporosis agents (e.g., biphosphonates, calcitonin, and estrogens); prostaglandins, antineoplastic agents; psychotherapeutic agents; sedatives; poison oak or poison sumac products; antibodies; and vaccines.

In certain embodiments, a pharmaceutical composition comprising a short antisense compound targeted to a CRP nucleic acid may be administered in conjuction with a lipid-lowering therapy. In certain such embodiments, a lipid-lowering therapy is therapeutic lifestyle change. In certain such embodiments, a lipid-lowering therapy is LDL apheresis.

Certain Short Antisense Compounds Targeted to a CRP nucleic acid

In certain embodiments, short antisense compounds are targeted to a CRP nucleic acid having the sequence of GENBANK® Accession No. NM_000567.1, incorporated herein as SEQ ID NO: 6. In certain such embodiments, a short antisense compound targeted to SEQ ID NO: 6 is at least 90% complementary to SEQ ID NO: 6. In certain such embodiments, a short antisense compound targeted to SEQ ID NO: 6 is at least 95% complementary to SEQ ID NO: 6. In certain such embodiments, a short antisense compound targeted to SEQ ID NO: 6 is 100% complementary to SEQ ID NO: 6. In certain embodiments, a short antisense compound targeted to SEQ ID NO: 6 comprises a nucleotide sequence selected from the nucleotide sequences set forth in Table 9.

The nucleotide sequence set forth in each SEQ ID NO in Table 9 is independent of any modification to a sugar moiety, an internucleoside linkage, or a nucleobase. As such, short antisense compounds defined by a SEQ ID NO may comprise, independently, one or more modifications to a sugar moiety, an internucleoside linkage, or a nucleobase. Short antisense compounds described by Isis Number (Isis NO.) indicate a combination of nucleobase sequence and one or more modifications to a sugar moiety, an internucleoside linkage, or a nucleobase.

Table 9 illustrates examples of short antisense compounds targeted to SEQ ID NO: 6. Table 9 illustrates short antisense compounds that are 100% complementary to SEQ ID NO: 6. The column labeled 'gapmer motif' indicates the wing-gap-wing motif of each short antisense compounds. The gap segment comprises 2'-deoxynucleotides and each nucleotide of each wing segment comprises a 2'-modified sugar. The particular 2'-modified sugar is also indicated in the 'gapmer motif' column. For example, '2-10-2 MOE' means a 2-10-2 gapmer motif, where a gap segment of ten 2'-deoxynucleotides is flanked by wing segments of two nucleotides, where the nucleotides of the wing segments are 2'-MOE nucleotides. Internucleoside linkages are phosphorothioate. The short antisense compounds comprise 5-methylcytidine in place of unmodified cytosine, unless "unmodified cytosine" is listed in the gapmer motif column, in which case the indicated cytosines are unmodified cytosines. For example, "5-mC in gap only" indicates that the gap segment has 5-methylcytosines, while the wing segments have unmodified cytosines.

In certain embodiments, short antisense compounds targeting a CRP nucleic acid may have any one or more properties or characteristics of the short antisense compounds generally described herein. In certain embodiments, short antisense compounds targeting a CRP nucleic acid have a motif (wing – deoxy gap – wing) selected from 1-12-1, 1-1-10-2, 2-10-1-1, 3-10-3, 2-10-3, 2-10-2, 1-10-1,1-10-2, 3-8-3, 2-8-2, 1-8-1, 3-6-3 or 1-6-1, more preferably 1-10-1, 2-10-2, 3-10-3, and 1-9-2.

Table 9: Short Antisense Compounds targeted to SEQ ID NO: 6

ISIS NO.	5' Target Site	3' Target Site	Sequence (5'-3')	Gapmer Motif	Seq ID NO
353506	1257	1272	ACTCTGGACCCAAACC	3-10-3 MOE	409
353507	1258	1271	CTCTGGACCCAAAC	2-10-2 MOE	410
353484	1305	1320	CCATTTCAGGAGACCT	3-10-3 MOE	411
353485	1306	1319	CATTTCAGGAGACC	2-10-2 MOE	412

In certain embodiments, a target region is nucleotides 1305-1320 of NM_000567.1. In certain such embodiments, short antisense compounds targeted to nucleotides 1305-1320 of NM_000567.1 comprise a nucleotide sequence selected from SEQ ID NO: 1305 or 1306. In certain such embodiments, a short antisense compound targeted to nucleotides 263-278 of NM_000567.1 is selected from Isis NO. 353484 or 353485.

In certain embodiments, a target region is nucleotides 1257-1272 of NM_000567.1. In certain such embodiments, a short antisense compound targeted to nucleotides 1257-1272 of NM_000567.1 comprises a nucleotide sequence selected from SEQ ID NO 1257 or 1258. In certain such embodiments, a short antisense compound targeted to nucleotides 428-483 of NM_000567.1 is selected from Isis NO. 353506 or 353507.

In certain embodiments, short antisense compounds targeted to a CRP nucleic acid are 8 to 16, preferably 9 to 15, more preferably 9 to 14, more preferably 10 to 14 nucleotides in length. In certain embodiments, short antisense compounds targeted to a CRP nucleic acid are 9 to 14 nucleotides in length. In certain embodiments, short antisense compounds targeted to a CRP nucleic acid are 10 to 14 nucleotides in length. In certain embodiments, such short antisense compounds are short antisense oligonucleotides.

In certain embodiments, short antisense compounds targeted to a CRP nucleic acid are short gapmers. In certain such embodiments, short gapmers targeted to a CRP nucleic acid comprise at least one high affinity modification in one or more wings of the compound. In certain embodiments, short antisense compounds targeted to a CRP nucleic acid comprise 1 to 3 high-affinity modifications in each wing. In certain such embodiments, the nucleosides or nucleotides of the wing comprise a 2' modification. In certain such embodiments, the monomers of the wing are BNA's. In certain such embodiments, the monomers of the wing are selected from α-L-Methyleneoxy (4'-CH_2-O-2') BNA , β-D-Methyleneoxy (4'-CH_2-O-2') BNA , Ethyleneoxy (4'-$(CH_2)_2$-O-2') BNA , Aminooxy (4'-CH_2-O-N(R)-2') BNA and Oxyamino (4'-CH_2-N(R)-O-2') BNA. In certain embodiments, the monomers of a wing comprise a substituent at the 2' position selected from allyl, amino, azido, thio, O-allyl, O-C_1-C_{10} alkyl, -OCF_3, O-$(CH_2)_2$-O-CH_3, 2'-O$(CH_2)_2SCH_3$, O-$(CH_2)_2$-O-N(R_m)(R_n), and O-CH_2-C(=O)-N(R_m)(R_n), where each R_m and R_n is, independently, H or substituted or unsubstituted C_1-C_{10} alkyl. In certain embodiments, the monomers of a wing are 2'MOE nucleotides.

In certain embodiments, short antisense compounds targeted to a CRP nucleic acid comprise a gap between the 5' wing and the 3' wing. In certain embodiments the gap comprises five, six, seven, eight, nine, ten, eleven, twelve, thirteen, or fourteen monomers. In certain embodiments, the monomers of the gap are unmodified deoxyribonucleotides. In certain embodiments, the monomers of the gap are unmodified ribonucleotides. In certain embodiments, gap modifications (if any) gap result in an antisense compound that, when bound to its target nucleic acid, supports cleavage by an RNase, including, but not limited to, RNase H.

In certain embodiments, short antisense compounds targeted to a CRP nucleic acid have uniform monomeric linkages. In certain such embodiments, those linkages are all phosphorothioate linkages. In certain embodiments, the linkages are all phosphodiester linkages. In certain embodiments, short antisense compounds targeted to a CRP nucleic acid have mixed backbones.

In certain embodiments, short antisense compounds targeted to a CRP nucleic acid are 8 monomers in length. In certain embodiments, short antisense compounds targeted to a CRP nucleic acid are 9 monomers in length. In certain embodiments, short antisense compounds targeted to a CRP nucleic acid are 10 monomers in length. In certain embodiments, short antisense compounds targeted to a CRP nucleic acid are 11 monomers in length. In certain embodiments, short antisense compounds targeted to a CRP nucleic acid are monomers in length. In certain embodiments, short antisense compounds targeted to a CRP nucleic acid are 13 monomers in length. In certain embodiments, short antisense compounds targeted to a CRP nucleic acid are 14 monomers in length. In certain embodiments, short antisense compounds targeted to a CRP nucleic acid are 15 monomers in length. In certain embodiments, short antisense compounds targeted to a CRP nucleic acid are 16 monomers in length. In certain embodiments, short antisense compounds targeted to a CRP nucleic acid comprise 9 to 15 monomers. In certain embodiments, short antisense compounds targeted to a CRP nucleic acid comprise 10 to 15 monomers. In certain embodiments, short antisense compounds targeted to a CRP nucleic acid comprise 12 to 14 monomers. In certain embodiments, short antisense compounds targeted to a CRP nucleic acid comprise 12 to 14 nucleotides or nucleosides.

In certain embodiments, the invention provides methods of modulating expression of CRP. In certain embodiments, such methods comprise use of one or more short antisense compound targeted to a CRP nucleic acid, wherein the short antisense compound targeted to a CRP nucleic acid is from about 8 to about 16, preferably 9 to 15, more preferably 9 to 14, more preferably 10 to 14 monomers (i.e. from about 8 to about 16 linked monomers). One of ordinary skill in the art will appreciate that this comprehends methods of modulating expression of CRP using one or more short antisense compounds targeted to a CRP nucleic acid of 8, 9, 10, 11, 12, 13, 14, 15 or 16 monomers.

In certain embodiments, methods of modulating CRP comprise use of a short antisense compound targeted to a CRP nucleic acid that is 8 monomers in length. In certain embodiments, methods of modulating CRP comprise use of a short antisense compound targeted to a CRP nucleic acid that is 9 monomers in length. In certain embodiments, methods of modulating CRP comprise use of a short antisense compound targeted to a CRP nucleic acid that is 10 monomers in length. In certain embodiments, methods of modulating CRP comprise use of a short antisense compound targeted to a CRP nucleic acid that is 11 monomers in length. In certain embodiments, methods of modulating CRP comprise use of a short antisense compound targeted to a CRP nucleic acid that is 12 monomers in length. In certain embodiments, methods of modulating CRP comprise use of a short antisense compound targeted to a CRP nucleic acid that is 13 monomers in length. In certain embodiments, methods of modulating CRP comprise use of a short antisense compound targeted to a CRP nucleic acid that is 14 monomers in length. In certain embodiments, methods of modulating CRP comprise use of a short antisense compound targeted to a CRP nucleic acid that is 15 monomers in length. In certain embodiments, methods of modulating CRP comprise use of a short antisense compound targeted to a CRP nucleic acid that is 16 monomers in length.

In certain embodiments, methods of modulating expression of CRP comprise use of a short antisense compound targeted to a CRP nucleic acid comprising 9 to 15 monomers. In certain embodiments, methods of modulating expression of CRP comprise use of a short antisense compound targeted to a CRP nucleic acid comprising 10 to 15 monomers. In certain embodiments, methods of modulating expression of CRP comprise use of a short antisense compound targeted to a CRP nucleic acid comprising 12 to 14 monomers. In certain embodiments, methods of modulating expression of CRP comprise use of a short antisense compound targeted to a CRP nucleic acid comprising 12 or 14 nucleotides or nucleosides.

6. Glucocorticoid Receptor (GCCR)

Glucocorticoids were among the first steroid hormones to be identified and are responsible for a multitude of physiological functions, including the stimulation of gluconeogenesis, decreased glucose uptake and utilization in peripheral tissues, increased glycogen deposition, suppression of immune and inflammatory responses, inhibition of cytokine synthesis and acceleration of various developmental events. Glucocorticoids are also especially important for combating stress. Stress-induced elevation of glucocorticoid synthesis and release leads to, among other responses, increased ventricular workload, inhibition of inflammatory mediators, inhibition of cytokine synthesis and increased glucose production (Karin, *Cell,* 1998, *93*, 487-490).

Both natural glucocorticoids and their synthetic derivatives exert their action through the glucocorticoid receptor, a ubiquitously expressed cytoplasmic member of the nuclear hormone superfamily of receptors. Human glucocorticoid receptor is also known as nuclear receptor subfamily 3, group C, member 1; NR3C1; GCCR; GCR; GRL; Glucocorticoid receptor, lymphocyte. The gene is located on human chromosome 5q11-q13 and consists of 9 exons (Encio and Detera-Wadleigh, *J Biol Chem,* 1991, *266*, 7182-7188; Gehring et al., *Proc Natl Acad Sci U S A,* 1985, *82*, 3751-3755). Multiple forms of human glucocorticoid receptor mRNA exist: a 5.5 kb human glucocorticoid receptor α cDNA containing exons 1-8 and exon 9α; a 4.3 kb human glucocorticoid receptor β cDNA containing exons 1-8 and exon 9β; and a 7.0 kb human glucocorticoid receptor α cDNA containing exons 1-8 and the entire exon 9, which includes exon 9α, exon 9β and the 'J region', which is flanked by exons 9α and 9β (Hollenberg et al., *Nature,* 1985, *318*, 635-641; Oakley et al., *J Biol Chem,* 1996, *271*, 9550-9559). Human glucocorticoid receptor α is the predominant isoform of the receptor and the one that exhibits steroid binding activity (Hollenberg et al., *Nature,* 1985, *318*, 635-641). Additionally, through usage of three different promoters three different exon 1 variants can be transcribed, and alternative splicing of one exon 1 variant can result in three different versions of this exon. Thus, human glucocorticoid receptor mRNA may contain 5 different versions of exon 1 (Breslin et al., *Mol Endocrinol,* 2001, *15*, 1381-1395).

Examination of the expression patterns of the α and β isoforms of human glucocorticoid receptor mRNA reveals that the α isoform is more abundantly expressed. Both isoforms are expressed in similar tissues and cell types, including lung, kidney, heart, liver, skeletal muscle, macrophages, neutrophils and peripheral blood mononuclear cells. Only human glucocorticoid receptor α is expressed in colon. At the level of protein, while the α isoform is detected in all tissues examined, the β isoform is undetectable, suggesting that under physiological conditions, the default splicing pathway is the one that produces the α isoform (Pujols et al., *Am J Physiol Cell Physiol,* 2002, *283*, C1324-1331). The β isoform of glucocorticoid receptor binds neither a glucocorticoid agonist nor an antagonist. Furthermore, the β isoform is localized primarily in the nucleus in transfected cells, independent of hormone stimulation. When both isoforms are expressed in the same cell, the glucocorticoid receptor β inhibits the hormone-induced, glucocorticoid receptor α-mediated stimulation of gene expression, suggesting that the β isoform functions as an inhibitor of glucocorticoid receptor α activity (Oakley et al., *J Biol Chem,* 1996, *271*, 9550-9559). Unless otherwise noted, the human glucocorticoid receptor described herein is defined as the ubiquitous product(s) of the gene located on chromosome 5q11-q13.

Cell lines transfected with a complementary glucocorticoid receptor antisense RNA strand exhibited a reduction in glucocorticoid receptor mRNA levels and a decreased response to the glucocorticoid receptor agonist dexamethasone (Pepin and Barden, *Mol Cell Biol,* 1991, *11*, 1647-1653). Transgenic mice bearing an antisense glucocorticoid receptor gene construct were used to study the glucocorticoid feedback effect on the hypothalamus-pituitary-adrenal axis (Pepin et al., *Nature,* 1992, *355*, 725-728). In another study of similarly genetically engineered mice, energy intake and expenditure, heart and vastus lateralis muscle lipoprotein lipase activity, and heart and brown adipose tissue norepinephrine were lower than in control animals. Conversely, fat content and total body energy were significantly higher than in control animals. These results suggest that a defective glucocorticoid receptor system may affect energy balance through increasing energetic efficiency, and they emphasize the modulatory effects of hypothalamic-pituitary-adrenal axis changes on muscle lipoprotein lipase activity (Richard et al., *Am J Physiol,* 1993, *265*, R146-150).

Behavorial effects of glucocorticoid receptor antagonists have been measured in animal models designed to assess anxiety, learning and memory. Reduced expression of glucocorticoid receptor in rats long-term intracerebroventricularly infused with antisense oligodeoxynucleotides targeting glucocorticoid receptor mRNA did not interfere with spatial navigation in the Morris water maze test (Engelmann et al., *Eur J Pharmacol,* 1998, *361*, 17-26). Bilateral infusion of an antisense oligodeoxynucleotide targeting the glucocorticoid receptor mRNA into the dentate gyrus of the rat hippocampus reduced the immobility of rats in the Porsolt forced swim test (Korte et al., *Eur J Pharmacol,* 1996, *301*, 19-25).

Glucocorticoids are frequently used for their immunosuppressive, anti-inflammatory effects in the treatment of diseases such as allergies, athsma, rheumatoid arthritis, AIDS, systemic lupus erythematosus and degenerative osteoarthritis. Negative regulation of gene expression, such as that caused by the interaction of glucocorticoid receptor with NF-kB, is proposed to be at least partly responsible for the anti-inflammatory action of glucocorticoids in vivo. Interleukin-6, tumor necrosis factor α and interleukin-1 are the three cytokines that account for most of the hypothalamic-pituitary-adrenal (HPA) axis stimulation during the stress of inflammation. The HPA axis and the systemic sympathetic and adrenomedullary system are the peripheral components of the stress system, responsible for maintaining basal and stress-related homeostasis. Glucocorticoids, the end products of the HPA axis, inhibit the production of all three inflammatory cytokines and also inhibit their effects on target tissues, with the exception of interleukin-6, which acts synergistically with glucocorticoids to stimulate the production of acute-phase reactants. Glucocorticoid treatment decreases the activity of the HPA axis (Chrousos, N Engl J Med, 1995, 332, 1351-1362).

In some cases, patients are refractory to glucocorticoid treatment. One reason for this resistance to steroids lies with mutations or polymorphisms present in the glucocorticoid receptor gene. A total of 15 missense, three nonsense, three frameshift, one splice site, and two alternative spliced mutations, as well as 16 polymorphisms, have been reported in the NR3C1 gene in association with glucocorticoid resistance (Bray and Cotton, Hum Mutat, 2003, 21, 557-568). Additional studies in humans have suggested a positive association between metabolic syndrome incidence and progression, with alleles at the glucocorticoid receptor (GR) gene (Rosmond, Obes Res, 2002, 10, 1078-1086).

Other cases of glucocorticoid insensitivity are associated with altered expression of glucocorticoid receptor isoforms. A study of human glucocorticoid receptor β isoform mRNA expression in glucocorticoid-resistant ulcerative colitis patients revealed the presence of this mRNA was significantly higher than in the glucocorticoid-sensitive patients, suggesting that the expression of human glucocorticoid receptor β mRNA in the peripheral blood mononuclear cells may serve as a predictor of glucocorticoid response in ulcerative colitis (Honda et al., Gastroenterology, 2000, 118, 859-866). Increased expression of glucocorticoid receptor β is also observed in a significantly high number of glucocorticoid-insensitive asthmatics. Additionally, cytokine-induced abnormalities in the DNA binding capacity of the glucocorticoid receptor were found in peripheral blood mononuclear cells from glucocorticoid-insensitive patients transfection, and HepG2 cells with the glucocorticoid receptor β gene resulted in a significant reduction of glucocorticoid receptor α DNA-binding capacity (Leung et al., J Exp Med, 1997, 186, 1567-1574). Dexamethasone binding studies demonstrate that human glucocorticoid receptor β does not alter the affinity of glucocorticoid receptor α for hormonal ligands, but rather its ability to bind to the GRE (Bamberger et al., J Clin Invest, 1995, 95, 2435-2441). Taken together, these results illustrate that glucocorticoid receptor β, through competition with glucocorticoid receptor α for GRE target sites, may function as a physiologically and pathophysiologically relevant endogenous inhibitor of glucocorticoid action.

In the liver, glucocorticoid agonists increase hepatic glucose production by activating the glucocorticoid receptor, which subsequently leads to increased expression of the gluconeogenic enzymes phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase. Through gluconeogenesis, glucose is formed through non-hexose precursors, such as lactate, pyruvate and alanine (Link, Curr Opin Investig Drugs, 2003, 4, 421-429). Steroidal glucocorticoid receptor antagonists such as RU 486 have been tested in rodent models of diabetes. Mice deficient in the leptin receptor gene, termed db/db mice, are genetically obese, diabetic and hyperinsulinemic. Treatment of hyperglycemic db/db mice with RU 486 decreased blood glucose levels by approximately 49%, without affecting plasma insulin levels. Additionally, RU 486 treatment reduced the expression of glucocorticoid receptor responsive genes PEPCK, glucose-6-phosphatase, glucose transporter type 2 and tyrosine aminotransferase in db/db mice as compared to untreated animals (Friedman et al., J Biol Chem, 1997, 272, 31475-31481). RU 486 also ameliorates diabetes in the ob/ob mouse model of diabetes, obesity and hyperinsulinemia, through a reduction in serum insulin and blood glucose levels (Gettys et al., Int J Obes Relat Metab Disord, 1997, 21, 865-873).

As increased gluconeogenesis is considered to be the major source of increased glucose production in diabetes, a number of therapeutic targets for the inhibition of hepatic glucose production have been investigated. Due to the ability of antagonists of the glucocorticoid receptor to ameliorate diabetes in animal models, such compounds are among the potential therapies being explored. However, there are detrimental systemic effects of glucocorticoid receptor antagonists, including activation of the HPA axis (Link, Curr Opin Investig Drugs, 2003, 4, 421-429). Increased HPA axis activity is associated with suppression of immune-related inflammatory action, which can increase susceptibility to infectious agents and neoplasms. Conditions associated with suppression of immune-mediated inflammation through defects in the HPA axis, or its target tissues, include Cushing's syndrome, chronic stress, chronic alcoholism and melancholic depression (Chrousos, N Engl J Med, 1995, 332, 1351-1362). Thus, it is of great value to develop liver-specific glucocorticoid receptor antagonists. Steroidal glucocorticoid receptor antagonists have been conjugated to bile acids for the purpose of targeting them to the liver (Apelqvist et al., 2000). Currently, there are no known therapeutic agents that target the glucocorticoid receptor without undesired peripheral effects (Link, Curr Opin Investig Drugs, 2003, 4, 421-429). Consequently, there remains a long felt need for agents capable of effectively inhibiting hepatic glucocorticoid receptor.

Definitions

"Glucocorticoid receptor" is the gene product or protein of which expression is to be modulated by administration of a short antisense compound. Glucocorticoid receptor is generally referred to as GCCR.

"GCCR nucleic acid" means any nucleic acid encoding GCCR. For example, in certain embodiments, a GCCR nucleic acid includes, without limitation, a DNA sequence encoding GCCR, an RNA sequence transcribed from DNA encoding GCCR, and an mRNA sequence encoding GCCR. "GCCR mRNA" means an mRNA encoding GCCR.

Therapeutic indications

Antisense technology is an effective means of reducing the expression of specific gene products and therefore is useful in a number of therapeutic, diagnostic and research applications for the modulation of glucocorticoid receptor expression. Furthermore, in certain embodiments, liver is one of the tissues in which the highest concentrations of antisense oligonucleotides are found following administration (Geary et al., *Curr. Opin. Investig. Drugs,* 2001, *2,* 562-573). Therefore, in such embodiments, antisense technology represents an attractive method for the liver-specific inhibition of glucocorticoid receptor.

In certain embodiments, short antisense compounds targeted to a nucleic acid encoding glucocorticoid receptor are preferentially distributed to the liver. In certain embodiments, short antisense compounds have increased potency in the liver when compared to a longer parent compound. In certain embodiments, target RNA is predominantly expressed in the liver.

For therapeutics, a subject, suspected of having a disease or disorder which can be treated by modulating the expression of GCCR is treated by administering one or more short antisense compound. In a non-limiting example, the methods comprise the step of administering to an animal a therapeutically effective amount of a short antisense compound. Certain short antisense compounds inhibit the activity of GCCR and/ or inhibit expression of GCCR. In certain embodiments, the activity or expression of GCCR in a subject is inhibited by at least 10%, by at least 20%, by at least 25%, by at least 30%, by at least 40%, by at least 50%, by at least 60%, by at least 70%, by at least 75%, by at least 80%, by at least 85%, by at least 90%, by at least 95%, by at least 98%, by at least 99%, or by 100%. In certain embodiments, the activity or expression of GCCR in a subject is inhibited by at least 30%. In certain embodiments, the activity or expression of GCCR in a subject is inhibited by at least 50% or more.

The reduction of the expression of GCCR may be measured, for example, in blood, plasma, serum, adipose tissue, liver or any other body fluid, tissue or organ of the animal. In certain embodiments, cells contained within such fluids, tissues or organs being analyzed comprise nucleic acids encoding GCCR and/or they contain the GCCR protein itself.

Certain pharmaceutical and other compositions comprising short antisense compounds are also provided. In certain embodiments, short antisense compounds are be utilized in pharmaceutical compositions by adding to them an effective amount of a compound to a suitable pharmaceutically acceptable diluent or carrier.

In certain embodiments, short antisense compounds targeting a GCCR nucleic acid have any one or more properties or characteristics of the short antisense compounds generally described herein. In certain embodiments, short antisense compounds targeting a GCCR nucleic acid have a motif (wing – deoxy gap – wing) selected from 1-12-1, 1-1-10-2, 2-10-1-1, 3-10-3, 2-10-3, 2-10-2, 1-10-1,1-10-2, 3-8-3, 2-8-2, 1-8-1, 3-6-3 or 1-6-1, . In certain embodiments, short antisense compounds targeting a GCCR nucleic acid have a motif (wing – deoxy gap –wing) selected from 1-10-1, 2-10-2, 3-10-3, and 1-9-2. . In certain embodiments, short antisense compounds targeting a GCCR nucleic acid have a motif (wing – deoxy gap –wing) selected from 3-10-3, 2-10-3, 2-10-2, 1-10-1,1-10-2, 2-8-2, 1-8-1, 3-6-3 or 1-6-1, more preferably 2-10-2 and 2-8-2.

In certain embodiments, provided herein are methods of treating an individual by administering one or more short antisense compound targeted to a GCCR nucleic acid or a pharmaceutical composition comprising such compound. Further provided are methods of treating a subject having a disease or conditions associated with GCCR activity by administering a short antisense compound targeted to a GCCR nucleic acid. In addition to diabetes, particularly type 2 diabetes, diseases and conditions associated with GCCR include but are not limited to, obesity, Metabolic syndrome X, Cushing's Syndrome, Addison's disease, inflammatory diseases such as asthma, rhinitis and arthritis, allergy, autoimmune disease, immunodeficiency, anorexia, cachexia, bone loss or bone frailty, and wound healing. Metabolic syndrome, metabolic syndrome X or simply Syndrome X refers to a cluster of risk factors that include obesity, dyslipidemia, particularly high blood triglycerides, glucose intolerance, high blood sugar and high blood pressure. In certain embodiments, short antisense compounds targeted to GCCR are used for amelioration of hyperglycemia induced by systemic steroid therapy. Moreover, antisense technology provides a means of inhibiting the expression of the glucocorticoid receptor β isoform, demonstrated to be overexpressed in patients refractory to glucocorticoid treatment.

In certain embodiments, the invention provides short antisense compounds targeted to a nucleic acid encoding GCGR, and which modulate the expression of glucocorticoid receptor. Pharmaceutical and other compositions comprising the compounds of the invention are also provided. Further provided are methods of screening for modulators of glucocorticoid receptor and methods of modulating the expression of glucocorticoid receptor in cells, tissues or animals comprising contacting said cells, tissues or animals with one or more of the compounds or compositions of the invention. Methods of treating an animal, particularly a human, suspected of having or being prone to a disease or condition associated with expression of glucocorticoid receptor are also set forth herein. Such methods comprise administering a therapeutically or prophylactically effective amount of one or more of the compounds or compositions of the invention to the person in need of treatment.

Certain Short Antisense Compounds Targeted to a GCCR nucleic acid

In certain embodiments, short antisense compounds are targeted to a GCCR nucleic acid having the sequence of nucleotides 1 to 106000 of GENBANK® Accession No. AC012634, incorporated herein as SEQ ID NO: 8. In certain such embodiments, a short antisense compound targeted to SEQ ID NO: 8 is at least 90% complementary to SEQ ID NO: 8. In certain such embodiments, a short antisense compound targeted to SEQ ID NO: 8 is at least 95% complementary to SEQ ID NO: 8. In certain such embodiments, a short antisense compound targeted to SEQ ID NO: 8 is 100% complementary to SEQ ID NO: 8. In certain embodiments, a short antisense compound targeted to SEQ ID NO: 8 includes a nucleotide sequence selected from the nucleotide sequences set forth in Tables 10 and 11.

The nucleotide sequence set forth in each SEQ ID NO in Tables 10 and 11 is independent of any modification to a sugar moiety, an internucleoside linkage, or a nucleobase. As such, short antisense compounds defined by a SEQ ID NO may comprise, independently, one or more modifications to a sugar moiety, an internucleoside linkage, or a nucleobase. Short antisense compounds described by Isis Number

(Isis NO.) indicate a combination of nucleobase sequence and one or more modifications to a sugar moiety, an internucleoside linkage, or a nucleobase.

In certain embodiments, short antisense compounds targeted to a GCCR nucleic acid comprise a gapmer motif. In certain embodiments, a short antisense compound targeted to a GCCR nucleic acid comprises a 2-10-2 gapmer motif.

Tables 10 and 11 illustrate examples of short antisense compounds targeted to SEQ ID NO: 8. Table 10 illustrates short antisense compounds that are 100% complementary to SEQ ID NO: 8. Table 11 illustrates short antisense compounds that have one or two mismatches with respect to SEQ ID NO: 8. The column labeled 'gapmer motif' indicates the wing-gap-wing motif of each short antisense compounds. The gap segment comprises 2'-deoxynucleotides and each nucleotide of each wing segment comprises a 2'-modified sugar. The particular 2'-modified sugar is also indicated in the 'gapmer motif' column. For example, '2-10-2 MOE' means a 2-10-2 gapmer motif, where a gap segment of ten 2'-deoxynucleotides is flanked by wing segments of two nucleotides, where the nucleotides of the wing segments are 2'-MOE nucleotides. Internucleoside linkages are phosphorothioate. The short antisense compounds comprise 5-methylcytidine in place of unmodified cytosine, unless "unmodified cytosine" is listed in the gapmer motif column, in which case the indicated cytosines are unmodified cytosines. For example, "5-mC in gap only" indicates that the gap segment has 5-methylcytosines, while the wing segments have unmodified cytosines.

Table 10: Short Antisense Compounds targeted to SEQ ID NO: 8

ISIS NO.	5' Target Site	3' Target Site	Sequence (5'-3')	Gapmer Motif	SEQ ID NO
371644	88142	88155	TTTGGGAGGTGGTC	2-10-2 MOE	413
371645	88156	88169	CACACCAGGCAGAG	2-10-2 MOE	414
371649	88212	88225	CTTTACAGCTTCCA	2-10-2 MOE	415
371651	88242	88255	CACTACCTTCCACT	2-10-2 MOE	416
371652	88248	88261	AACACACACTACCT	2-10-2 MOE	417
371653	88256	88269	CTCTTCAAAACACA	2-10-2 MOE	418
371665	92037	92050	GTAATTGTGCTGTC	2-10-2 MOE	419
371669	92086	92099	TTTTTCTTCGAATT	2-10-2 MOE	420
371671	92114	92127	CATTTTCGATAGCG	2-10-2 MOE	421
371673	92142	92155	ACCTTCCAGGTTCA	2-10-2 MOE	422

Table 11: Short antisense compounds targeted to SEQ ID NO: 8 and having 1 or 2 mismatches

ISIS NO	5' Target Site	3' Target Site	Sequence (5'-3')	Gapmer Motif	SEQ ID NO
371638	2039	2052	ATAGGAAGCATAAA	2-10-2 MOE	423
371650	4949	4962	TCTTTTAAAGAAGA	2-10-2 MOE	424
371673	10187	10200	ACCTTCCAGGTTCA	2-10-2 MOE	422
371660	13465	13478	AAGGATATTTTAAA	2-10-2 MOE	425

371660	14428	14441	AAGGATATTTTAAA	2-10-2 MOE	425
371654	15486	15499	GAACAAAAATTAAA	2-10-2 MOE	427
371661	16638	16651	TTCCACAGATCTGT	2-10-2 MOE	428
371653	17892	17905	CTCTTCAAAACACA	2-10-2 MOE	418
371679	18444	18457	TTTATAAAGTAAAG	2-10-2 MOE	429
371645	19816	19829	CACACCAGGCAGAG	2-10-2 MOE	414
371638	21555	21568	ATAGGAAGCATAAA	2-10-2 MOE	423
371650	21775	21788	TCTTTTAAAGAAGA	2-10-2 MOE	424
371679	21902	21915	TTTATAAAGTAAAG	2-10-2 MOE	429
371655	22507	22520	TACTGTGAGAAATA	2-10-2 MOE	433
371655	22722	22735	TACTGTGAGAAATA	2-10-2 MOE	433
371672	25662	25675	TTCCAGCTTGAAGA	2-10-2 MOE	435
371678	25926	25939	GATCAGTTCTCATG	2-10-2 MOE	436
371655	26041	26054	TACTGTGAGAAATA	2-10-2 MOE	433
371638	29770	29783	ATAGGAAGCATAAA	2-10-2 MOE	423
371668	30551	30564	TTATCAATGATGCA	2-10-2 MOE	439
371670	40584	40597	GCATGCTGGACAGT	2-10-2 MOE	440
371654	43331	43344	GAACAAAAATTAAA	2-10-2 MOE	427
371650	46024	46037	TCTTTTAAAGAAGA	2-10-2 MOE	424
371659	50372	50385	TTGCACCTGAACTA	2-10-2 MOE	443
371634	50565	50578	CAGAATATATTTCT	2-10-2 MOE	444
371673	56942	56955	ACCTTCCAGGTTCA	2-10-2 MOE	422
371654	62372	62385	GAACAAAAATTAAA	2-10-2 MOE	427
371679	63537	63550	TTTATAAAGTAAAG	2-10-2 MOE	429
371654	64908	64921	GAACAAAAATTAAA	2-10-2 MOE	427
371661	65795	65808	TTCCACAGATCTGT	2-10-2 MOE	428
371645	70997	71010	CACACCAGGCAGAG	2-10-2 MOE	414
371661	77400	77413	TTCCACAGATCTGT	2-10-2 MOE	428
371663	82329	82342	ATAAGAGATTAAAA	2-10-2 MOE	450
371633	83426	83439	TCCCCCTTCTCATT	2-10-2 MOE	451
371662	85873	85886	GGGCATTGTTAAAA	2-10-2 MOE	452
371654	86476	86489	GAACAAAAATTAAA	2-10-2 MOE	427
371679	86516	86529	TTTATAAAGTAAAG	2-10-2 MOE	429
371641	88097	88110	AGAACTCACATCTG	2-10-2 MOE	455
371642	88111	88124	GAGCTGGACGGAGG	2-10-2 MOE	456
371646	88170	88183	AAGCTTCATCGGAG	2-10-2 MOE	457
371647	88184	88197	ATAATGGCATCCCG	2-10-2 MOE	458
371650	88226	88239	TCTTTTAAAGAAGA	2-10-2 MOE	424
371673	91493	91506	ACCTTCCAGGTTCA	2-10-2 MOE	422
371664	92030	92043	TGCTGTCCTATAAG	2-10-2 MOE	460
371666	92044	92057	CACAAAGGTAATTG	2-10-2 MOE	461
371667	92058	92071	ATCATTTCTTCCAG	2-10-2 MOE	462
371668	92072	92085	TTATCAATGATGCA	2-10-2 MOE	463
371670	92100	92113	GCATGCTGGACAGT	2-10-2 MOE	440
371672	92128	92141	TTCCAGCTTGAAGA	2-10-2 MOE	435
371674	92147	92160	CCATTACCTTCCAG	2-10-2 MOE	466
371637	92983	92996	GCATAAACAGGGTT	2-10-2 MOE	467
371654	93928	93941	GAACAAAAATTAAA	2-10-2 MOE	427
371641	99772	99785	AGAACTCACATCTG	2-10-2 MOE	455
371679	99883	99896	TTTATAAAGTAAAG	2-10-2 MOE	429

371660	99933	99946	AAGGATATTTTAAA	2-10-2 MOE	425
371635	105004	105017	TATGAAAGGAATGT	2-10-2 MOE	472
371654	105028	105041	GAACAAAAATTAAA	2-10-2 MOE	427
371676	106482	106495	TTCCTTAAGCTTCC	2-10-2 MOE	474
371650	107838	107851	TCTTTTAAAGAAGA	2-10-2 MOE	424
371673	110922	110935	ACCTTCCAGGTTCA	2-10-2 MOE	422
371673	111580	111593	ACCTTCCAGGTTCA	2-10-2 MOE	422
371634	114608	114621	CAGAATATATTTCT	2-10-2 MOE	444
371638	115040	115053	ATAGGAAGCATAAA	2-10-2 MOE	423
371660	116244	116257	AAGGATATTTTAAA	2-10-2 MOE	425
371663	116657	116670	ATAAGAGATTAAAA	2-10-2 MOE	450
371673	118068	118081	ACCTTCCAGGTTCA	2-10-2 MOE	422
371666	118834	118847	CACAAAGGTAATTG	2-10-2 MOE	461
371660	119858	119871	AAGGATATTTTAAA	2-10-2 MOE	425
371660	120210	120223	AAGGATATTTTAAA	2-10-2 MOE	425
371662	120876	120889	GGGCATTGTTAAAA	2-10-2 MOE	452
371655	124004	124017	TACTGTGAGAAATA	2-10-2 MOE	433
371656	124170	124183	GAACAGTTAAACAT	2-10-2 MOE	485

In certain embodiments, a target region is nucleotides 88142-88269 of SEQ ID NO: 8. In certain embodiments, a short antisense compound is targeted to nucleotides 88142-88269 of SEQ ID NO: 8. In certain such embodiments, a short antisense compound targeted to nucleotides 88142-88269 comprises a nucleotide sequence selected from SEQ ID NO 413, 414, 415, 416, 417, or 418. In certain such embodiments, an antisense compound targeted to nucleotides 88142-88269 of SEQ ID NO: 8 is selected from Isis NO. 371644, 371645, 371649, 371651, 371652, or 371653.

In certain embodiments, a target region is nucleotides 88142-88169 of SEQ ID NO: 8. In certain embodiments, a short antisense compound is targeted to nucleotides 88142-88169 of SEQ ID NO: 8. In certain such embodiments, a short antisense compound targeted to nucleotides 88142-88169 comprises a nucleotide sequence selected from SEQ ID NO 413 or 414. In certain such embodiments, an antisense compound targeted to nucleotides 88142-88169 of SEQ ID NO: 8 is selected from Isis NO. 371644 or 371645.

In certain embodiments, a target region is nucleotides 88242-88269 of SEQ ID NO: 8. In certain embodiments, a short antisense compound is targeted to nucleotides 88242-88269 of SEQ ID NO: 8. In certain such embodiments, a short antisense compound targeted to nucleotides 88242-88269 comprises a nucleotide sequence selected from SEQ ID NO 416, 417, or 418. In certain such embodiments, an antisense compound targeted to nucleotides 88242-88269 of SEQ ID NO: 8 is selected from Isis NO. 371651, 371652, or 371653.

In certain embodiments, a target region is nucleotides 92037-92155 of SEQ ID NO: 8. In certain embodiments, a short antisense compound is targeted to nucleotides 92037-92155 of SEQ ID NO: 8. In certain such embodiments, a short antisense compound targeted to nucleotides 92037-92155 comprises a nucleotide sequence selected from SEQ ID NO 419, 420, 421, or 422. In certain such embodiments, an antisense compound targeted to nucleotides 92037-92155 of SEQ ID NO: 8 is selected from Isis NO. 371665, 371669, 371671, or 171673.

In certain embodiments, a target region is nucleotides 92114-92155 of SEQ ID NO: 8. In certain embodiments, a short antisense compound is targeted to nucleotides 92114-92155 of SEQ ID NO: 8. In certain such embodiments, a short antisense compound targeted to nucleotides 92114-92155 comprises a nucleotide sequence selected from SEQ ID NO 421 or 422. In certain such embodiments, an antisense compound targeted to nucleotides 92114-92155 of SEQ ID NO: 8 is selected from Isis NO. 371671 or 171673.

In certain embodiments, short antisense compounds targeted to a GCCR nucleic acid are 8 to 16, preferably 9 to 15, more preferably 9 to 14, more preferably 10 to 14 nucleotides in length. In certain embodiments, short antisense compounds targeted to a GCCR nucleic acid are 9 to 14 nucleotides in length. In certain embodiments, short antisense compounds targeted to a GCCR nucleic acid are 10 to 14 nucleotides in length. In certain embodiments, such short antisense compounds are short antisense oligonucleotides.

In certain embodiments, short antisense compounds targeted to a GCCR nucleic acid are short gapmers. In certain such embodiments, short gapmers targeted to a GCCR nucleic acid comprise at least one high affinity modification in one or more wings of the compound. In certain embodiments, short antisense compounds targeted to a GCCR nucleic acid comprise 1 to 3 high-affinity modifications in each wing. In certain such embodiments, the nucleosides or nucleotides of the wing comprise a 2' modification. In certain such embodiments, the monomers of the wing are BNA's. In certain such embodiments, the monomers of the wing are selected from α-L-Methyleneoxy (4'-CH_2-O-2') BNA , β-D-Methyleneoxy (4'-CH_2-O-2') BNA , Ethyleneoxy (4'-$(CH_2)_2$-O-2') BNA , Aminooxy (4'-CH_2-O-N(R)-2') BNA and Oxyamino (4'-CH_2-N(R)-O-2') BNA. In certain embodiments, the monomers of a wing comprise a substituent at the 2' position selected from allyl, amino, azido, thio, O-allyl, O-C_1-C_{10} alkyl, -OCF_3, O-$(CH_2)_2$-O-CH_3, 2'-O$(CH_2)_2SCH_3$, O-$(CH_2)_2$-O-N(R_m)(R_n), and O-CH_2-C(=O)-N(R_m)(R_n), where each R_m and R_n is, independently, H or substituted or unsubstituted C_1-C_{10} alkyl. In certain embodiments, the monomers of a wing are 2'MOE nucleotides.

In certain embodiments, short antisense compounds targeted to a GCCR nucleic acid comprise a gap between the 5' wing and the 3' wing. In certain embodiments the gap comprises five, six, seven, eight, nine, ten, eleven, twelve, thirteen, or fourteen monomers. In certain embodiments, the monomers of the gap are unmodified deoxyribonucleotides. In certain embodiments, the monomers of the gap are unmodified ribonucleotides. In certain embodiments, gap modifications (if any) gap result in an antisense compound that, when bound to its target nucleic acid, supports cleavage by an RNase, including, but not limited to, RNase H.

In certain embodiments, short antisense compounds targeted to a GCCR nucleic acid have uniform monomeric linkages. In certain such embodiments, those linkages are all phosphorothioate linkages. In certain embodiments, the linkages are all phosphodiester linkages. In certain embodiments, short antisense compounds targeted to a GCCR nucleic acid have mixed backbones.

In certain embodiments, short antisense compounds targeted to a GCCR nucleic acid are 8 monomers in length. In certain embodiments, short antisense compounds targeted to a GCCR nucleic acid are 9 monomers in length. In certain embodiments, short antisense compounds targeted to a GCCR nucleic acid are 10 monomers in length. In certain embodiments, short antisense compounds targeted to a GCCR nucleic acid are 11 monomers in length. In certain embodiments, short antisense compounds targeted to a GCCR nucleic acid are monomers in length. In certain embodiments, short antisense compounds targeted to a GCCR nucleic acid are 13 monomers in length. In certain embodiments, short antisense compounds targeted to a GCCR nucleic acid are 14 monomers in length. In certain embodiments, short antisense compounds targeted to a GCCR nucleic acid are 15 monomers in length. In certain embodiments, short antisense compounds targeted to a GCCR nucleic acid are 16 monomers in length. In certain embodiments, short antisense compounds targeted to a GCCR nucleic acid comprise 9 to 15 monomers. In certain embodiments, short antisense compounds targeted to a GCCR nucleic acid comprise 10 to 15 monomers. In certain embodiments, short antisense compounds targeted to a GCCR nucleic acid comprise 12 to 14 monomers. In certain embodiments, short antisense compounds targeted to a GCCR nucleic acid comprise 12 to 14 nucleotides or nucleosides.

In certain embodiments, the invention provides methods of modulating expression of GCCR. In certain embodiments, such methods comprise use of one or more short antisense compound targeted to a GCCR nucleic acid, wherein the short antisense compound targeted to a GCCR nucleic acid is from about 8 to about 16, preferably 9 to 15, more preferably 9 to 14, more preferably 10 to 14 monomers (i.e. from about 8 to about 16 linked monomers). One of ordinary skill in the art will appreciate that this comprehends methods of modulating expression of GCCR using one or more short antisense compounds targeted to a GCCR nucleic acid of 8, 9, 10, 11, 12, 13, 14, 15 or 16 monomers.

In certain embodiments, methods of modulating GCCR comprise use of a short antisense compound targeted to a GCCR nucleic acid that is 8 monomers in length. In certain embodiments, methods of modulating GCCR comprise use of a short antisense compound targeted to a GCCR nucleic acid that is 9 monomers in length. In certain embodiments, methods of modulating GCCR comprise use of a short antisense compound targeted to a GCCR nucleic acid that is 10 monomers in length. In certain embodiments, methods of modulating GCCR comprise use of a short antisense compound targeted to a GCCR nucleic acid that is 11 monomers in length. In certain embodiments, methods of modulating GCCR comprise use of a short antisense compound targeted to a GCCR nucleic acid that is 12 monomers in length. In certain embodiments, methods of modulating GCCR comprise use of a short antisense compound targeted to a GCCR nucleic acid that is 13 monomers in length. In certain embodiments, methods of modulating GCCR comprise use of a short antisense compound targeted to a GCCR nucleic acid that is 14 monomers in length. In certain embodiments, methods of modulating GCCR comprise use of a short antisense compound targeted to a GCCR nucleic acid that is 15 monomers in length. In certain embodiments, methods of modulating GCCR comprise use of a short antisense compound targeted to a GCCR nucleic acid that is 16 monomers in length.

In certain embodiments, methods of modulating expression of GCCR comprise use of a short antisense compound targeted to a GCCR nucleic acid comprising 9 to 15 monomers. In certain embodiments, methods of modulating expression of GCCR comprise use of a short antisense compound targeted to a GCCR nucleic acid comprising 10 to 15 monomers. In certain embodiments, methods of modulating expression of GCCR comprise use of a short antisense compound targeted to a GCCR nucleic acid comprising 12 to 14 monomers. In certain embodiments, methods of modulating expression of GCCR comprise use of a short antisense compound targeted to a GCCR nucleic acid comprising 12 or 14 nucleotides or nucleosides.

7. Glucagon Receptor (GCGR)

The maintenance of normal glycemia is a carefully regulated metabolic event. Glucagon, the 29-amino acid peptide responsible for maintaining blood glucose levels in the postabsorbative state, increases glucose release from the liver by activating hepatic glycogenolysis, gluconeogenesis, stimulating lipolysis in adipose tissue, and stimulating insulin secretion. During high blood glucose levels, insulin reverses the glucagon-mediated enhancement of glycogenolysis and gluconeogenesis. In patients with diabetes, insulin is either not available or not fully effective. While treatment for diabetes has traditionally focused on increasing insulin levels, antagonism of glucagon function has been considered as an alternative therapy. As glucagon exerts its physiological effects by signaling through the glucagon receptor, the glucagon receptor has been proposed as a potential therapeutic target for diabetes (Madsen et al., Curr. Pharm. Des., 1999, 5, 683-691).

Glucagon receptor is belongs to the superfamily of G-protein-coupled receptors having seven transmembrane domains. It is also a member of the smaller sub-family of homologous receptors which bind peptides that are structurally similar to glucagon. The gene encoding human glucagon receptor was cloned in 1994 and analysis of the genomic sequence revealed multiple introns and an 82% identity to the rat glucagon receptor gene (Lok et al., Gene, 1994, 140, 203-209.; MacNeil et al., Biochem. Biophys. Res. Commun., 1994, 198, 328-334). Cloning of the rat glucagon receptor gene also led to the description of multiple alternative splice variants (Maget et al., FEBS Lett., 1994, 351, 271-275). The human glucagon receptor gene is localized to chromosome 17q25 (Menzel et al., Genomics, 1994, 20, 327-328). A missense mutation of Gly to Ser at codon 40 in the glucagon receptor gene leads to a 3-fold lower affinity for glucagon (Fujisawa et al., Diabetologia, 1995, 38, 983-985) and this mutation has been linked to several disease states, including non-insulin-dependent diabetes mellitus (Fujisawa et al., Diabetologia, 1995, 38, 983-985), hypertension (Chambers and Morris, Nat. Genet., 1996, 12, 122), and central adiposity (Siani et al., Obes.

Res., 2001, 9, 722-726).

Definitions

"Glucagon receptor" is the gene product or protein of which expression is to be modulated by administration of a short antisense compound. Glucagon receptor is generally referred to as GCGR but may also be referred to as GR, GGR, MGC138246, MGC93090.

"GCGR nucleic acid" means any nucleic acid encoding GCGR. For example, in certain embodiments, a GCGR nucleic acid includes, without limitation, a GCGR sequence encoding GCGR, an RNA sequence transcribed from DNA encoding GCGR, and an mRNA sequence encoding GCGR. "GCGR mRNA" means an mRNA encoding a GCGR protein.

Therapeutic Indications

Antisense technology is an effective means for reducing glucagon receptor (GCGR) expression and has proven to be uniquely useful in a number of therapeutic, diagnostic, and research applications. As such, in certain embodiments, the present invention provides short antisense compounds targeted to a nucleic acid encoding glucagon receptor, and which modulate the expression of glucagon receptor. Further provided herein are short antisense compounds capable of inhibiting GCGR expression. Also provided herein are methods of treating an individual comprising administering one or more pharmaceutical compositions comprising a short antisense compound targeted to a GCGR nucleic acid. In certain embodiments, because short antisense compounds targeted to a GCGR nucleic acid inhibit GCGR expression, provided herein are methods of treating a subject having a disease or condition associated with GCGR activity by administering one or more pharmaceutical compositions comprising a short antisense compound targeted to a GCGR nucleic acid. For example, provided herein are methods of treating a subject having high blood glucose, hyperglycemia, prediabetes, diabetes, Type 2 diabetes, metabolic syndrome, obesity and/or insulin resistance.

Also contemplated herein are pharmaceutical composition comprising one or more short antisense compounds targeted to GCGR and optionally a pharmaceutically acceptable carrier, diluent, enhancer or excipient. Certain compounds of the invention can also be used in the manufacture of a medicament for the treatment of diseases and disorders related to glucagon effects mediated by GCGR.

Certain embodiments of the present invention include methods of reducing the expression of GCGR in tissues or cells comprising contacting said cells or tissues with a short antisense compound targeted to a nucleic acid encoding GCGR or pharmaceutical composition comprising such a short antisense compound. In certain such embodiments, the invention provides methods of decreasing blood glucose levels, blood triglyceride levels, or blood cholesterol levels in a subject comprising administering to the subject a short antisense compound or a pharmaceutical composition. Blood levels may be plasma levels or serum levels. Also contemplated are methods of improving insulin sensitivity, methods of increasing GLP-1 levels and methods of inhibiting hepatic glucose output in an animal comprising administering to said animal an antisense oligonucleotide or a pharmaceutical composition of the invention. An improvement in insulin sensitivity may be indicated by a reduction in circulating insulin levels.

In certain embodiments, the invention provides methods of treating a subject having a disease or condition associated with glucagon activity via GCGR comprising administering to the subject a therapeutically or prophylactically effective amount of a short antisense compound or a pharmaceutical composition. In certain embodiments, such disease or condition may be a metabolic disease or condition. In certain embodiments, the metabolic disease or condition is diabetes, hyperglycemia, hyperlipidemia, metabolic syndrome X, obesity, primary hyperglucagonemia, insulin deficiency, or insulin resistance. In some embodiments, the diabetes is Type 2 diabetes. In some embodiments the obesity is diet-induced. In some embodiments, hyperlipidemia is associated with elevated blood lipid levels. Lipids include cholesterol and triglycerides. In one embodiment, the condition is liver steatosis. In some embodiments, the steatosis is steatohepatitis or non-alcoholic steatohepatitis.

In certain embodiments, the invention provides methods of preventing or delaying the onset of elevated blood glucose levels in an animal as well as methods of preserving beta-cell function in an animal using the oligomeric compounds delineated herein.

Certain short antisense compounds targeted to GCGR can be used to modulate the expression of GCGR in a subject in need thereof, such as an animal, including, but not limited to, a human In certain embodiments, such methods comprise the step of administering to said animal an effective amount of a short antisense compound that reduces expression of GCGR RNA. In certain embodiments, short antisense compounds effectively reduce the levels or function of GCGR RNA. Because reduction in GCGR mRNA levels can lead to alteration in GCGR protein products of expression as well, such resultant alterations can also be measured. Certain antisense compounds that effectively reduce the levels or function of GCGR RNA or protein products of expression is considered an active antisense compound. In certain embodiments, short antisense compounds reduce the expression of GCGR causing a reduction of RNA by at least 10%, by at least 20%, by at least 25%, by at least 30%, by at least 40%, by at least 50%, by at least 60%, by at least 70%, by at least 75%, by at least 80%, by at least 85%, by at least 90%, by at least 95%, by at least 98%, by at least 99%, or by 100%.

Further provided are methods of screening for modulators of glucagon receptor and methods of modulating the expression of glucagon receptor in cells, tissues or animals comprising contacting said cells, tissues or animals with one or more short antisense compounds targeted to GCGR or with compositions comprising such compounds. Methods of treating an animal, particularly a human, suspected of having or being prone to a disease or condition associated with expression of glucagon receptor are also set forth herein. Certain such methods comprise administering a therapeutically or prophylactically effective amount of one or more of the compounds or compositions of the invention to the person in need of treatment.

The reduction of the expression of glucagon receptor may be measured, for example, in blood, plasma, serum, adipose tissue, liver or any other body fluid, tissue or organ of the animal. Preferably, the cells contained within said fluids, tissues or organs being analyzed contain a nucleic acid molecule encoding glucagon receptor protein and/or the glucagon receptor protein itself.

Pharmaceutical and other compositions comprising short antisense compounds are also provided. In certain embodiments short antisense compounds targeted to a nucleic acid encoding GCGR are utilized in pharmaceutical compositions by adding an effective amount of a compound to a suitable pharmaceutically acceptable diluent or carrier.

The short antisense compounds targeting a GCGR nucleic acid may have any one or more properties or characteristics of the short antisense compounds generally described herein. In certain embodiments, short antisense compounds targeting a GCGR nucleic acid have a motif (wing – deoxy gap –wing) selected from 1-12-1, 1-1-10-2, 2-10-1-1, 3-10-3, 2-10-3, 2-10-2, 1-10-1,1-10-2, 3-8-3, 2-8-2, 1-8-1, 3-6-3 or 1-6-1. In certain embodiments, short antisense compounds targeting a GCGR nucleic acid have a motif (wing – deoxy gap –wing) selected from 1-12-1, 2-10-2, 3-10-3, 3-8-3, 1-1-10-2.

Certain Short Antisense Compounds Targeted to a GCGR nucleic acid

In certain embodiments, short antisense compounds are targeted to a GCGR nucleic acid having the sequence GENBANK® Accession No. NM_000160.1, incorporated herein as SEQ ID NO: 9. In certain such embodiments, a short antisense compound targeted to SEQ ID NO: 9 is at least 90% complementary to SEQ ID NO: 9. In certain such embodiments, a short antisense compound targeted to SEQ ID NO: 9 is at least 95% complementary to SEQ ID NO: 9. In certain such embodiments, a short antisense compound targeted to SEQ ID NO: 9 is 100% complementary to SEQ ID NO: 9. In certain embodiments, a short antisense compound targeted to SEQ ID NO: 9 includes a nucleotide sequence selected from the nucleotide sequences set forth in Tables 12 and 13.

The nucleotide sequences set forth in each SEQ ID NO in Tables 12 and 13 are independent of any modification to a sugar moiety, an internucleoside linkage, or a nucleobase. As such, short antisense compounds defined by a SEQ ID NO may comprise, independently, one or more modifications to a sugar moiety, an internucleoside linkage, or a nucleobase. Short antisense compounds described by Isis Number (Isis NO.) indicate a combination of nucleobase sequence and one or more modifications to a sugar moiety, an internucleoside linkage, or a nucleobase.

In certain embodiments, short antisense compounds targeted to a GCCR nucleic acid comprise a gapmer motif. In certain embodiments, a short antisense compound targeted to a GCCR nucleic acid comprises a 3-10-3 gapmer motif. In certain embodiments, short antisense compounds targeted to a GCCR nucleic acid comprise a gapmer motif. In certain embodiments, a short antisense compound targeted to a GCCR nucleic acid comprises a 3-8-3 gapmer motif. In certain embodiments, short antisense compounds targeted to a GCCR nucleic acid comprise a gapmer motif. In certain embodiments, a short antisense compound targeted to a GCCR nucleic acid comprises a 2-10-2 gapmer motif.

Tables 12 and 13 illustrate examples of short antisense compounds targeted to SEQ ID NO: 9. Table 12 illustrates short antisense compounds that are 100% complementary to SEQ ID NO: 9. Table 13 illustrates short antisense compounds that have one or two mismatches with respect to SEQ ID NO: 9. The column labeled 'gapmer motif' indicates the wing-gap-wing motif of each short antisense compounds. The gap segment comprises 2'-deoxynucleotides and each nucleotide of each wing segment comprises a 2'-modified sugar. The particular 2'-modified sugar is also indicated in the 'gapmer motif' column. For example, '2-10-2 MOE' means a 2-10-2 gapmer motif, where a gap segment of ten 2'-deoxynucleotides is flanked by wing segments of two nucleotides, where the nucleotides of the wing segments are 2'-MOE nucleotides. Internucleoside linkages are phosphorothioate. The short antisense compounds comprise 5-methylcytidine in place of unmodified cytosine, unless "unmodified cytosine" is listed in the gapmer motif column, in which case the indicated cytosines are unmodified cytosines. For example, "5-mC in gap only" indicates that the gap segment has 5-methylcytosines, while the wing segments have unmodified cytosines.

Table 12: Short Antisense Compounds targeted to SEQ ID NO: 9

ISIS NO.	5' Target Site	3' Target Site	Sequence (5'-3')	Gapmer Motif	SEQ ID NO
338463	378	393	TAGAGCTTCCACTTCT	3-10-3 MOE	486
338534	378	391	GAGCTTCCACTTCT	3-8-3 MOE	487
327130	499	512	TGTTGGCCGTGGTA	3-8-3 MOE	488
327131	500	513	ATGTTGGCCGTGGT	3-8-3 MOE	489
327132	501	514	GATGTTGGCCGTGG	3-8-3 MOE	490
327133	502	515	AGATGTTGGCCGTG	3-8-3 MOE	491
327134	503	516	GAGATGTTGGCCGT	3-8-3 MOE	492
327135	504	517	GGAGATGTTGGCCG	3-8-3 MOE	493
327136	505	518	AGGAGATGTTGGCC	3-8-3 MOE	494
327137	506	519	CAGGAGATGTTGGC	3-8-3 MOE	495
327138	507	520	GCAGGAGATGTTGG	3-8-3 MOE	496
327139	508	521	GGCAGGAGATGTTG	3-8-3 MOE	497
327140	531	544	GTGGTGCCAAGGCA	3-8-3 MOE	498
327141	532	545	TGTGGTGCCAAGGC	3-8-3 MOE	499
327142	533	546	TTGTGGTGCCAAGG	3-8-3 MOE	500
327143	534	547	TTTGTGGTGCCAAG	3-8-3 MOE	501
327144	535	548	CTTTGTGGTGCCAA	3-8-3 MOE	502
327145	536	549	ACTTTGTGGTGCCA	3-8-3 MOE	503
327146	537	550	CACTTTGTGGTGCC	3-8-3 MOE	504
327147	538	551	GCACTTTGTGGTGC	3-8-3 MOE	505
327148	539	552	TGCACTTTGTGGTG	3-8-3 MOE	506
327149	540	553	TTGCACTTTGTGGT	3-8-3 MOE	507
327150	545	558	CGGTGTTGCACTTT	3-8-3 MOE	508
327151	546	559	GCGGTGTTGCACTT	3-8-3 MOE	509

327152	547	560	AGCGGTGTTGCACT	3-8-3 MOE	510
327153	548	561	AAGCGGTGTTGCAC	3-8-3 MOE	511
327154	549	562	GAAGCGGTGTTGCA	3-8-3 MOE	512
327155	550	563	CGAAGCGGTGTTGC	3-8-3 MOE	513
327156	551	564	ACGAAGCGGTGTTG	3-8-3 MOE	514
327157	552	565	CACGAAGCGGTGTT	3-8-3 MOE	515
327158	553	566	ACACGAAGCGGTGT	3-8-3 MOE	516
327159	554	567	AACACGAAGCGGTG	3-8-3 MOE	517
345897	684	697	GCTGCTGTACATCT	2-10-2 MOE	518
327160	684	697	GCTGCTGTACATCT	3-8-3 MOE	518
327161	685	698	AGCTGCTGTACATC	3-8-3 MOE	520
327162	686	699	AAGCTGCTGTACAT	3-8-3 MOE	521
327163	687	700	GAAGCTGCTGTACA	3-8-3 MOE	522
327164	688	701	GGAAGCTGCTGTAC	3-8-3 MOE	523
327165	689	702	TGGAAGCTGCTGTA	3-8-3 MOE	524
327166	690	703	CTGGAAGCTGCTGT	3-8-3 MOE	525
327167	691	704	CCTGGAAGCTGCTG	3-8-3 MOE	526
327168	692	705	ACCTGGAAGCTGCT	3-8-3 MOE	527
327169	693	706	CACCTGGAAGCTGC	3-8-3 MOE	528
327170	694	707	TCACCTGGAAGCTG	3-8-3 MOE	529
327171	695	708	ATCACCTGGAAGCT	3-8-3 MOE	530
327172	696	709	CATCACCTGGAAGC	3-8-3 MOE	531
327173	697	710	ACATCACCTGGAAG	3-8-3 MOE	532
327174	698	711	TACATCACCTGGAA	3-8-3 MOE	533
327175	699	712	GTACATCACCTGGA	3-8-3 MOE	534
327176	700	713	TGTACATCACCTGG	3-8-3 MOE	535
327177	701	714	GTGTACATCACCTG	3-8-3 MOE	536
327178	869	882	TAGCGGGTCCTGAG	3-8-3 MOE	537
327179	870	883	GTAGCGGGTCCTGA	3-8-3 MOE	538
327180	871	884	TGTAGCGGGTCCTG	3-8-3 MOE	539
327181	872	885	CTGTAGCGGGTCCT	3-8-3 MOE	540
327182	873	886	GCTGTAGCGGGTCC	3-8-3 MOE	541
327183	874	887	GGCTGTAGCGGGTC	3-8-3 MOE	542
327184	875	888	TGGCTGTAGCGGGT	3-8-3 MOE	543
327185	876	889	CTGGCTGTAGCGGG	3-8-3 MOE	544
327186	877	890	TCTGGCTGTAGCGG	3-8-3 MOE	545
327187	878	891	TTCTGGCTGTAGCG	3-8-3 MOE	546
327188	955	968	TGAACACCGCGGCC	3-8-3 MOE	547
327189	956	969	ATGAACACCGCGGC	3-8-3 MOE	548
327190	957	970	CATGAACACCGCGG	3-8-3 MOE	549
327191	958	971	GCATGAACACCGCG	3-8-3 MOE	550
327192	959	972	TGCATGAACACCGC	3-8-3 MOE	551
327193	960	973	TTGCATGAACACCG	3-8-3 MOE	552
327194	961	974	ATTGCATGAACACC	3-8-3 MOE	553
327195	962	975	TATTGCATGAACAC	3-8-3 MOE	554
327196	963	976	ATATTGCATGAACA	3-8-3 MOE	555
327197	964	977	CATATTGCATGAAC	3-8-3 MOE	556
327198	1019	1032	AGGTTGTGCAGGTA	3-8-3 MOE	557
327199	1020	1033	CAGGTTGTGCAGGT	3-8-3 MOE	558
327200	1021	1034	GCAGGTTGTGCAGG	3-8-3 MOE	559

327201	1022	1035	AGCAGGTTGTGCAG	3-8-3 MOE	560
327202	1023	1036	CAGCAGGTTGTGCA	3-8-3 MOE	561
327203	1024	1037	CCAGCAGGTTGTGC	3-8-3 MOE	562
327204	1025	1038	CCCAGCAGGTTGTG	3-8-3 MOE	563
327205	1026	1039	GCCCAGCAGGTTGT	3-8-3 MOE	564
327206	1027	1040	GGCCCAGCAGGTTG	3-8-3 MOE	565
327207	1028	1041	AGGCCCAGCAGGTT	3-8-3 MOE	566
338491	1160	1175	TGTCATTGCTGGTCCA	3-10-3 MOE	567
338562	1160	1173	TCATTGCTGGTCCA	3-8-3 MOE	568
338498	1307	1322	TGGCCAGCCGGAACTT	3-10-3 MOE	569
338569	1307	1320	GCCAGCCGGAACTT	3-8-3 MOE	570
338499	1329	1344	GGGATGAGGGTCAGCG	3-10-3 MOE	571
338570	1329	1342	GATGAGGGTCAGCG	3-8-3 MOE	572
385067	1364	1377	AAGGCAAAGACCAC	3-8-3 MOE	573
338573	1401	1414	GGAGCGCAGGGTGC	3-8-3 MOE	574
338580	1487	1500	TGCACCTCCTTGTT	3-8-3 MOE	575

Table 13: Short antisense compounds targeted to SEQ ID NO: 1 and having 1 or 2 mismatches

ISIS NO.	5' Target Site	3' Target Site	Sequence (5'-3')	Gapmer Motif	SEQ ID NO
338577	158	171	CAGCAGACCCTGGA	3-8-3 MOE	576
338458	237	252	ACATCTGGCAGAGGTT	3-10-3 MOE	577
338529	237	250	ATCTGGCAGAGGTT	3-8-3 MOE	578
338466	318	333	CAGGCCAGCAGGAGTA	3-10-3 MOE	579
338537	318	331	GGCCAGCAGGAGTA	3-8-3 MOE	580
338533	364	377	CAAACAAAAAGTCC	3-8-3 MOE	582
338462	364	379	CTCAAACAAAAAGTCC	3-10-3 MOE	581
338535	397	410	GGTGACATTGGTCA	3-8-3 MOE	584
338464	397	412	GTGGTGACATTGGTCA	3-10-3 MOE	583
338466	470	485	CAGGCCAGCAGGAGTA	3-10-3 MOE	579
338537	470	483	GGCCAGCAGGAGTA	3-8-3 MOE	580
385048	497	510	TTGGCAGTGGTGTT	3-8-3 MOE	587
385049	500	513	ATGTTGGCAGTGGT	3-8-3 MOE	588
338467	503	518	AGGAAATGTTGGCAGT	3-10-3 MOE	589
338538	503	516	GAAATGTTGGCAGT	3-8-3 MOE	590
385050	506	519	CAGGAAATGTTGGC	3-8-3 MOE	591
385051	509	522	GGGCAGGAAATGTT	3-8-3 MOE	592
385052	523	536	AAGGTAGGTACCAG	3-8-3 MOE	593
385053	526	539	ACCAAGGTAGGTAC	3-8-3 MOE	594
385056	535	548	CTTTGTGGCACCAA	3-8-3 MOE	595
385057	538	551	GCACTTTGTGGCAC	3-8-3 MOE	596
338539	539	552	TGCACTTTGTGGCA	3-8-3 MOE	597
385058	541	554	GCTGCACTTTGTGG	3-8-3 MOE	598
385059	544	557	GGTGCTGCACTTTG	3-8-3 MOE	599
385060	547	560	GGCGGTGCTGCACT	3-8-3 MOE	600
385063	556	569	TGAACACTAGGCGG	3-8-3 MOE	601
385064	559	572	TCTTGAACACTAGG	3-8-3 MOE	602
338469	561	576	CACCTCTTGAACACTA	3-10-3 MOE	603

338540	561	574	CCTCTTGAACACTA	3-8-3 MOE	604
385065	562	575	ACCTCTTGAACACT	3-8-3 MOE	605
385066	565	578	CACACCTCTTGAAC	3-8-3 MOE	606
338541	590	603	CCTCGAACCCACTG	3-8-3 MOE	607
338473	658	673	CTTCTGGACCTCGATC	3-10-3 MOE	608
338544	658	671	TCTGGACCTCGATC	3-8-3 MOE	609
338474	681	696	CTGCTATACATCTTGG	3-10-3 MOE	610
338545	681	694	GCTATACATCTTGG	3-8-3 MOE	611
338475	703	718	CACGGTGTACATCACC	3-10-3 MOE	612
338546	703	716	CGGTGTACATCACC	3-8-3 MOE	613
338547	718	731	ACAGACTGTAGCCC	3-8-3 MOE	615
338476	718	733	GGACAGACTGTAGCCC	3-10-3 MOE	614
338550	889	902	CATCGCCAATCTTC	3-8-3 MOE	617
338479	889	904	GTCATCGCCAATCTTC	3-10-3 MOE	616
338551	899	912	ACACTGAGGTCATC	3-8-3 MOE	619
338480	899	914	TCACACTGAGGTCATC	3-10-3 MOE	618
338552	924	937	CGCCCCGTCACTGA	3-8-3 MOE	620
338555	992	1005	AGCAACCAGCAATA	3-8-3 MOE	622
338484	992	1007	CCAGCAACCAGCAATA	3-10-3 MOE	621
338485	1018	1033	CAGGCTGTACAGGTAC	3-10-3 MOE	623
338556	1018	1031	GGCTGTACAGGTAC	3-8-3 MOE	624
338558	1051	1064	AGCTCCTCTCAGAG	3-8-3 MOE	626
338487	1051	1066	GAAGCTCCTCTCAGAG	3-10-3 MOE	625
338559	1079	1092	CAGCCAATGCCCAG	3-8-3 MOE	628
338488	1079	1094	CCCAGCCAATGCCCAG	3-10-3 MOE	627
338560	1131	1144	AAACAGACACTTGA	3-8-3 MOE	630
338489	1131	1146	TCAAACAGACACTTGA	3-10-3 MOE	629
338490	1145	1160	AGCACTGAACATTCTC	3-10-3 MOE	631
338561	1145	1158	CACTGAACATTCTC	3-8-3 MOE	632
338563	1181	1194	ATCCACCAGAATCC	3-8-3 MOE	634
338492	1181	1196	GGATCCACCAGAATCC	3-10-3 MOE	633
338564	1216	1229	TGATCAGTAAGGCC	3-8-3 MOE	635
338565	1232	1245	ACAAAGATGAAAAA	3-8-3 MOE	637
338494	1232	1247	GGACAAAGATGAAAAA	3-10-3 MOE	636
338566	1267	1280	CACGCAGCTTGGCC	3-8-3 MOE	639
338495	1267	1282	GGCACGCAGCTTGGCC	3-10-3 MOE	638
338571	1344	1357	GACCCCCAGCAGAG	3-8-3 MOE	641
338500	1344	1359	TGGACCCCCAGCAGAG	3-10-3 MOE	640
385068	1366	1379	CAAAGGCAAAGACC	3-8-3 MOE	642
385069	1369	1382	TCACAAAGGCAAAG	3-8-3 MOE	643
385070	1372	1385	CAGTCACAAAGGCA	3-8-3 MOE	644
385071	1375	1388	CGTCAGTCACAAAG	3-8-3 MOE	645
385072	1378	1391	GCTCGTCAGTCACA	3-8-3 MOE	646
385073	1381	1394	CATGCTCGTCAGTC	3-8-3 MOE	647
386608	1384	1397	GGGCATGCTCGTCA	1-12-1 MOE	648
386593	1384	1397	GGGCATGCTCGTCA	2-10-2 MOE	648
396146	1384	1397	GGGCATGCTCGTCA	2-10-2 MOE	648
338572	1384	1397	GGGCATGCTCGTCA	3-8-3 MOE	648
396149	1384	1397	GGGCATGCTCGTCA	1-1-10-2 2'-(butylacetamido)-	648

				palmitamide/OMe/ OMe	
386627	1384	1397	GGGCATGCTCGTCA	2-10-2 Methyleneoxy BNA	648
386610	1387	1400	CTTGGGCATGCTCG	1-12-1 MOE	654
386595	1387	1400	CTTGGGCATGCTCG	2-10-2 MOE	654
385074	1387	1400	CTTGGGCATGCTCG	3-8-3 MOE	654
385075	1390	1403	TGCCTTGGGCATGC	3-8-3 MOE	657
385076	1393	1406	GGGTGCCTTGGGCA	3-8-3 MOE	648
385077	1396	1409	GCAGGGTGCCTTGG	3-8-3 MOE	659
385078	1399	1412	AGCGCAGGGTGCCT	3-8-3 MOE	660
338502	1401	1416	GTGGAGCGCAGGGTGC	3-10-3 MOE	661
385079	1402	1415	TGGAGCGCAGGGTG	3-8-3 MOE	662
385080	1405	1418	TGGTGGAGCGCAGG	3-8-3 MOE	663
385081	1408	1421	GCTTGGTGGAGCGC	3-8-3 MOE	664
385082	1411	1424	AGAGCTTGGTGGAG	3-8-3 MOE	665
338503	1412	1427	AAAAGAGCTTGGTGGA	3-10-3 MOE	666
338574	1412	1425	AAGAGCTTGGTGGA	3-8-3 MOE	667
385083	1414	1427	AAAAGAGCTTGGTG	3-8-3 MOE	668
385084	1417	1430	CAAAAAAGAGCTTG	3-8-3 MOE	669
338504	1434	1449	AAGGAGCTGAGGAACA	3-10-3 MOE	670
338575	1434	1447	GGAGCTGAGGAACA	3-8-3 MOE	671
327167	1441	1454	CCTGGAAGCTGCTG	3-8-3 MOE	526
338576	1445	1458	AGACCCTGGAAGGA	3-8-3 MOE	673
338505	1445	1460	GCAGACCCTGGAAGGA	3-10-3 MOE	672
338506	1449	1464	ACCAGCAGACCCTGGA	3-10-3 MOE	674
338577	1449	1462	CAGCAGACCCTGGA	3-8-3 MOE	576
338507	1464	1479	CAGTAGAGAACAGCCA	3-10-3 MOE	676
338578	1464	1477	GTAGAGAACAGCCA	3-8-3 MOE	677
338508	1475	1490	TGTTGAGGAAACAGTA	3-10-3 MOE	678
338579	1475	1488	TTGAGGAAACAGTA	3-8-3 MOE	679
338509	1487	1502	CCTGCACCTCCTTGTT	3-10-3 MOE	680
338580	1610	1623	TGCACCTCCTTGTT	3-8-3 MOE	575

In certain embodiments, a target region is nucleotides 378-391 of SEQ ID NO: 9. In certain embodiments, a short antisense compound is targeted to nucleotides 378-391 of SEQ ID NO: 9. In certain such embodiments, a short antisense compound targeted to nucleotides 378-391 comprises a nucleotide sequence selected from SEQ ID NO 486 or 487. In certain such embodiments, a short antisense compound targeted to nucleotides 378-391 of SEQ ID NO: 9 is selected from Isis No 338463 or 338534.

In certain embodiments, a target region is nucleotides 499-521 of SEQ ID NO: 9. In certain embodiments, a short antisense compound is targeted to nucleotides 499-521 of SEQ ID NO: 9. In certain such embodiments, a short antisense compound targeted to nucleotides 499-521 comprises a nucleotide sequence selected from SEQ ID NO 488, 489, 490, 491, 492, 493, 494, 495, 496, or 497. In certain such embodiments, a short antisense compound targeted to nucleotides 499-521 of SEQ ID NO: 9 is selected from

Isis No 327130, 327131, 327132, 327133, 327134, 327135, 327136, 327137, 327138, or 327139.

In certain embodiments, a target region is nucleotides 531-553 of SEQ ID NO: 9. In certain embodiments, a short antisense compound is targeted to nucleotides 531-553 of SEQ ID NO: 9. In certain such embodiments, a short antisense compound targeted to nucleotides 531-553 comprises a nucleotide sequence selected from SEQ ID NO 498, 499, 500, 501, 502, 503, 504, 505, 506, or 507. In certain such embodiments, a short antisense compound targeted to nucleotides 531-553 of SEQ ID NO: 9 is selected from Isis No 327140, 327141, 327142, 327143, 327144, 327145, 327146, 327147, 327148, or 327149.

In certain embodiments, a target region is nucleotides 545-567 of SEQ ID NO: 9. In certain embodiments, a short antisense compound is targeted to nucleotides 545-567 of SEQ ID NO: 9. In certain such embodiments, a short antisense compound targeted to nucleotides 545-567 comprises a nucleotide sequence selected from SEQ ID NO 508, 509, 510, 511, 512, 513, 514, 515, 516, or 517. In certain such embodiments, a short antisense compound targeted to nucleotides 545-567 of SEQ ID NO: 9 is selected from Isis No 327150, 327151, 327152, 327153, 327154, 327155, 327156, 327157, 327158, or 327159.

In certain embodiments, a target region is nucleotides 531-567 of SEQ ID NO: 9. In certain embodiments, a short antisense compound is targeted to nucleotides 531-567 of SEQ ID NO: 9. In certain such embodiments, a short antisense compound targeted to nucleotides 531-567 comprises a nucleotide sequence selected from SEQ ID NO 498, 499, 500, 501, 502, 503, 504, 505, 506, 507, 508, 509, 510, 511, 512, 513, 514, 515, 516, or 517. In certain such embodiments, a short antisense compound targeted to nucleotides 531-567 of SEQ ID NO: 9 is selected from Isis No 327140, 327141, 327142, 327143, 327144, 327145, 327146, 327147, 327148, 327149, 327150, 327151, 327152, 327153, 327154, 327155, 327156, 327157, 327158, or 327159.

In certain embodiments, a target region is nucleotides 684-714 of SEQ ID NO: 9. In certain embodiments, a short antisense compound is targeted to nucleotides 684-714 of SEQ ID NO: 9. In certain such embodiments, a short antisense compound targeted to nucleotides 684-714 comprises a nucleotide sequence selected from SEQ ID NO 518, 520, 521, 522, 523, 524, 525, 526, 527, 528, 529, 530, 531, 532, 533, 534, 535, or 536. In certain such embodiments, a short antisense compound targeted to nucleotides 684-714 of SEQ ID NO: 9 is selected from Isis No 345897, 327160, 327161, 327162, 327163, 327164, 327165, 327166, 327167, 327168, 327169, 327170, 327171, 327172, 327173, 327174, 327175, 327176, or 327177.

In certain embodiments, a target region is nucleotides 869-891 of SEQ ID NO: 9. In certain embodiments, a short antisense compound is targeted to nucleotides 869-891 of SEQ ID NO: 9. In certain such embodiments, a short antisense compound targeted to nucleotides 869-891 comprises a nucleotide sequence selected from SEQ ID NO 537, 538, 539, 540, 541, 542, 543, 544, 545, or 546. In certain such embodiments, a short antisense compound targeted to nucleotides 869-891 of SEQ ID NO: 9 is selected from Isis No 327178, 327179, 327180, 327181, 327182, 327183, 327184, 327185, 327186, or 327187.

In certain embodiments, a target region is nucleotides 955-977 of SEQ ID NO: 9. In certain

embodiments, a short antisense compound is targeted to nucleotides 955-977 of SEQ ID NO: 9. In certain such embodiments, a short antisense compound targeted to nucleotides 955-977 comprises a nucleotide sequence selected from SEQ ID NO 547, 548, 549, 550, 551, 552, 553, 554, 555, or 556. In certain such embodiments, a short antisense compound targeted to nucleotides 955-977 of SEQ ID NO: 9 is selected from Isis No 327188, 327189, 327190, 327191, 327192, 327193, 327194, 327195, 327196, or 327197.

In certain embodiments, a target region is nucleotides 1019-1041 of SEQ ID NO: 9. In certain embodiments, a short antisense compound is targeted to nucleotides 1019-1041 of SEQ ID NO: 9. In certain such embodiments, a short antisense compound targeted to nucleotides 1019-1041 comprises a nucleotide sequence selected from SEQ ID NO 557, 558, 559, 560, 561, 562, 563, 564, 565, or 566. In certain such embodiments, a short antisense compound targeted to nucleotides 1019-1041 of SEQ ID NO: 9 is selected from Isis No 327198, 327199, 327200, 327201, 327202, 327203, 327204, 327205, 327206, or 327207.

In certain embodiments, a target region is nucleotides 1160-1175 of SEQ ID NO: 9. In certain embodiments, a short antisense compound is targeted to nucleotides 1160-1175 of SEQ ID NO: 9. In certain such embodiments, a short antisense compound targeted to nucleotides 1160-1175 comprises a nucleotide sequence selected from SEQ ID NO 567 or 568. In certain such embodiments, a short antisense compound targeted to nucleotides 1160-1175 of SEQ ID NO: 9 is selected from Isis No 338491 or 338562.

In certain embodiments, a target region is nucleotides 1307-1377 of SEQ ID NO: 9. In certain embodiments, a short antisense compound is targeted to nucleotides 1307-1377 of SEQ ID NO: 9. In certain such embodiments, a short antisense compound targeted to nucleotides 1307-1377 comprises a nucleotide sequence selected from SEQ ID NO 569, 570, 571, 572, or 573. In certain such embodiments, a short antisense compound targeted to nucleotides 1307-1377 of SEQ ID NO: 9 is selected from Isis No 338498, 338569, 338499, 338570, or 385067.

In certain embodiments, a target region is nucleotides 1307-1414 of SEQ ID NO: 9. In certain embodiments, a short antisense compound is targeted to nucleotides 1307-1414 of SEQ ID NO: 9. In certain such embodiments, a short antisense compound targeted to nucleotides 1307-1414 comprises a nucleotide sequence selected from SEQ ID NO 569, 570, 571, 572, 573, or 574. In certain such embodiments, a short antisense compound targeted to nucleotides 1307-1414 of SEQ ID NO: 9 is selected from Isis No 338498, 338569, 338499, 338570, 385067, or 338573.

In certain embodiments, short antisense compounds targeted to a GCGR nucleic acid are 8 to 16, preferably 9 to 15, more preferably 9 to 14, more preferably 10 to 14 nucleotides in length. In certain embodiments, short antisense compounds targeted to a GCGR nucleic acid are 9 to 14 nucleotides in length. In certain embodiments, short antisense compounds targeted to a GCGR nucleic acid are 10 to 14 nucleotides in length. In certain embodiments, such short antisense compounds are short antisense oligonucleotides.

In certain embodiments, short antisense compounds targeted to a GCGR nucleic acid are short gapmers. In certain such embodiments, short gapmers targeted to a GCGR nucleic acid comprise at least one high affinity modification in one or more wings of the compound. In certain embodiments, short antisense compounds targeted to a GCGR nucleic acid comprise 1 to 3 high-affinity modifications in each wing. In certain such embodiments, the nucleosides or nucleotides of the wing comprise a 2' modification. In certain such embodiments, the monomers of the wing are BNA's. In certain such embodiments, the monomers of the wing are selected from α-L-Methyleneoxy (4'-CH_2-O-2') BNA , β-D-Methyleneoxy (4'-CH_2-O-2') BNA , Ethyleneoxy (4'-$(CH_2)_2$-O-2') BNA , Aminooxy (4'-CH_2-O-N(R)-2') BNA and Oxyamino (4'-CH_2-N(R)-O-2') BNA. In certain embodiments, the monomers of a wing comprise a substituent at the 2' position selected from allyl, amino, azido, thio, O-allyl, O-C_1-C_{10} alkyl, -OCF_3, O-$(CH_2)_2$-O-CH_3, 2'-O$(CH_2)_2SCH_3$, O-$(CH_2)_2$-O-N(R_m)(R_n), and O-CH_2-C(=O)-N(R_m)(R_n), where each R_m and R_n is, independently, H or substituted or unsubstituted C_1-C_{10} alkyl. In certain embodiments, the monomers of a wing are 2'MOE nucleotides.

In certain embodiments, short antisense compounds targeted to a GCGR nucleic acid comprise a gap between the 5' wing and the 3' wing. In certain embodiments the gap comprises five, six, seven, eight, nine, ten, eleven, twelve, thirteen, or fourteen monomers. In certain embodiments, the monomers of the gap are unmodified deoxyribonucleotides. In certain embodiments, the monomers of the gap are unmodified ribonucleotides. In certain embodiments, gap modifications (if any) gap result in an antisense compound that, when bound to its target nucleic acid, supports cleavage by an RNase, including, but not limited to, RNase H.

In certain embodiments, short antisense compounds targeted to a GCGR nucleic acid have uniform monomeric linkages. In certain such embodiments, those linkages are all phosphorothioate linkages. In certain embodiments, the linkages are all phosphodiester linkages. In certain embodiments, short antisense compounds targeted to a GCGR nucleic acid have mixed backbones.

In certain embodiments, short antisense compounds targeted to a GCGR nucleic acid are 8 monomers in length. In certain embodiments, short antisense compounds targeted to a GCGR nucleic acid are 9 monomers in length. In certain embodiments, short antisense compounds targeted to a GCGR nucleic acid are 10 monomers in length. In certain embodiments, short antisense compounds targeted to a GCGR nucleic acid are 11 monomers in length. In certain embodiments, short antisense compounds targeted to a GCGR nucleic acid are monomers in length. In certain embodiments, short antisense compounds targeted to a GCGR nucleic acid are 13 monomers in length. In certain embodiments, short antisense compounds targeted to a GCGR nucleic acid are 14 monomers in length. In certain embodiments, short antisense compounds targeted to a GCGR nucleic acid are 15 monomers in length. In certain embodiments, short antisense compounds targeted to a GCGR nucleic acid are 16 monomers in length. In certain embodiments, short antisense compounds targeted to a GCGR nucleic acid comprise 9 to 15 monomers. In certain embodiments, short antisense compounds targeted to a GCGR nucleic acid comprise 10 to 15 monomers. In certain embodiments, short antisense compounds targeted to a GCGR nucleic acid comprise 12 to 14 monomers. In certain embodiments, short antisense compounds targeted to a GCGR nucleic acid comprise 12 to 14 nucleotides or nucleosides.

In certain embodiments, the invention provides methods of modulating expression of GCGR. In certain embodiments, such methods comprise use of one or more short antisense compound targeted to a GCGR nucleic acid, wherein the short antisense compound targeted to a GCGR nucleic acid is from about 8 to about 16, preferably 9 to 15, more preferably 9 to 14, more preferably 10 to 14 monomers (i.e. from about 8 to about 16 linked monomers). One of ordinary skill in the art will appreciate that this comprehends methods of modulating expression of GCGR using one or more short antisense compounds targeted to a GCGR nucleic acid of 8, 9, 10, 11, 12, 13, 14, 15 or 16 monomers.

In certain embodiments, methods of modulating GCGR comprise use of a short antisense compound targeted to a GCGR nucleic acid that is 8 monomers in length. In certain embodiments, methods of modulating GCGR comprise use of a short antisense compound targeted to a GCGR nucleic acid that is 9 monomers in length. In certain embodiments, methods of modulating GCGR comprise use of a short antisense compound targeted to a GCGR nucleic acid that is 10 monomers in length. In certain embodiments, methods of modulating GCGR comprise use of a short antisense compound targeted to a GCGR nucleic acid that is 11 monomers in length. In certain embodiments, methods of modulating GCGR comprise use of a short antisense compound targeted to a GCGR nucleic acid that is 12 monomers in length. In certain embodiments, methods of modulating GCGR comprise use of a short antisense compound targeted to a GCGR nucleic acid that is 13 monomers in length. In certain embodiments, methods of modulating GCGR comprise use of a short antisense compound targeted to a GCGR nucleic acid that is 14 monomers in length. In certain embodiments, methods of modulating GCGR comprise use of a short antisense compound targeted to a GCGR nucleic acid that is 15 monomers in length. In certain embodiments, methods of modulating GCGR comprise use of a short antisense compound targeted to a GCGR nucleic acid that is 16 monomers in length.

In certain embodiments, methods of modulating expression of GCGR comprise use of a short antisense compound targeted to a GCGR nucleic acid comprising 9 to 15 monomers. In certain embodiments, methods of modulating expression of GCGR comprise use of a short antisense compound targeted to a GCGR nucleic acid comprising 10 to 15 monomers. In certain embodiments, methods of modulating expression of GCGR comprise use of a short antisense compound targeted to a GCGR nucleic acid comprising 12 to 14 monomers. In certain embodiments, methods of modulating expression of GCGR comprise use of a short antisense compound targeted to a GCGR nucleic acid comprising 12 or 14 nucleotides or nucleosides.

8. DGAT2

Diacylglycerol transferase 2 (also known as DGAT2, diacylglycerol O-transferase 2, acyl-

CoA:diacylglycerol acyltransferase 2), Diacylglycerol transferase 2 has been shown to be implicated in the absorption process of triglycerides (also called triacylglycerols) from food.

The absorption of triglycerides from food is a very efficient process which occurs by a series of steps wherein the dietary triacylglycerols are hydrolyzed in the intestinal lumen and then resynthesized within enterocytes. The resynthesis of triacylglycerols can occur via the monoacylglycerol pathwaywhich commences with monoacylglycerol acyltransferase (MGAT) catalyzing the synthesis of diacylglycerol from monoacylglycerol and fatty acyl-CoA. An alternative synthesis of diacylglycerols is provided by the glycerol-phosphate pathway which describes the coupling of two molecules of fatty acyl-CoA to glycerol-3-phosphate. In either case, diacylglycerol is then acylated with another molecule of fatty acyl-CoA in a reaction catalyzed by one of two diacylglycerol acyltransferase enzymes to form the triglyceride (Farese et al., *Curr. Opin. Lipidol.*, 2000, *11*, 229-234).

The reaction catalyzed by diacylglycerol acyltransferase is the final and only committed step in triglyceride synthesis. As such, diacylglycerol acyltransferase is involved in intestinal fat absorption, lipoprotein assembly, regulating plasma triglyceride concentrations, and fat storage in adipocytes. The first diacylglycerol acyltransferase, diacylglycerol transferase 1, was identified in 1960 and the human and mouse genes encoding this protein were isolated in 1998 (Cases et al., *Proc. Natl. Acad. Sci. U. S. A.*, 1998, *95*, 13018-13023; Oelkers et al., *J. Biol. Chem.*, 1998, *273*, 26765-26771). Mice lacking diacylglycerol acyltransferase 1 are viable and can still synthesize triglycerides through other biological routes, suggesting the existence of multiple mechanisms for triglyceride synthesis (Smith et al., *Nat. Genet.*, 2000, *25*, 87-90).

A second diacylglycerol transferase, diacylglycerol transferase 2 (also known as DGAT2, diacylglycerol O-transferase 2, acyl-CoA:diacylglycerol acyltransferase 2), was subsequently identified in the fungus Mortierella, humans and mice (Cases et al., *J. Biol. Chem.*, 2001, *276*, 38870-38876; Lardizabal et al., *J. Biol. Chem.*, 2001, *276*, 38862-38869). Enzymatic assays indicate that this recently identified protein does possess diacylglycerol transferase activity that utilizes a broad range of long chain fatty acyl-CoA substrates (Cases et al., *J. Biol. Chem.*, 2001, *276*, 38870-38876).

Diacylglycerol transferase 2 is a member of a family of genes whose sequences are unrelated to diacylglycerol transferase 1. In addition to differing in sequence compared to diacylglycerol transferase 1, *in vitro* assays illustrate that diacylglycerol transferase 2 has higher activity at lower concentrations of magnesium chloride and oleoyl-CoA (Cases et al., *J. Biol. Chem.*, 2001, *276*, 38870-38876). The predicted protein sequence of diacylglycerol transferase 2 contains at least one putative transmembrane domain, three potential N-linked glycosylation sites, six potential protein kinase C phosphorylation consensus sites, as well as sequences in common with a putative glycerol phosphorylation site found in acyltransferase enzymes (Cases et al., *J. Biol. Chem.*, 2001, *276*, 38870-38876). The International Radiation Hybrid Mapping Consortium has mapped human diacylglycerol transferase 2 to chromosome 11q13.3.

In human tissues, the highest levels of diacylglycerol transferase 2 are detected in liver and white adipose tissues, with lower levels found in mammary gland, testis and peripheral blood leukocytes (Cases et al., *J. Biol. Chem.*, 2001, *276*, 38870-38876). Two mRNA species of 2.4 and 1.8 kilobases are detected in human tissues, whereas the major diacylglycerol transferase 2 mRNA species in mouse tissues is 2.4 kilobases. In addition to liver and white adipose tissues, diacylglycerol transferase 2 is expressed in all segments of the small intestine in mice, with higher expression in the proximal intestine and lower expression in the distal intestine (Cases et al., *J. Biol. Chem.*, 2001, *276*, 38870-38876).

Diacylglycerol transferase activity exhibits distinct patterns during postnatal development of the rat liver. As there is no correlation between the mRNA expression and activity patterns, post-translational modifications may participate in the regulation of diacylglycerol transferase 2 activity during rat development (Waterman et al., *J. Lipid. Res.*, 2002, *43*, 1555-1562).

Diacylglycerol transferase 2 mRNA is preferentially upregulated by insulin treatment, as shown by in vitro assays measuring the diacylglycerol activity from the membrane fraction of cultured mouse adipocytes (Meegalla et al., *Biochem. Biophys. Res. Commun.*, 2002, *298*, 317-323). In fasting mice, diacylglycerol transferase 2 expression is greatly reduced, and dramatically increases upon refeeding. The expression patterns of two enzymes that participate in fatty acid synthesis, acetyl-CoA carboxylase and fatty acid synthase, respond to fasting and refeeding in a similar fashion. These results, combined with the observation that diacylglycerol transferase 2 is abundantly expressed in liver, suggest that diacylglycerol transferase 2 is tightly linked to the endogenous fatty acid synthesis pathway (Meegalla et al., *Biochem. Biophys. Res. Commun.*, 2002, *298*, 317-323).

Studies of mice harboring a disruption in the diacylglycerol acyltransferase 1 gene provide evidence that diacylglycerol acyltransferase 2 contributes to triglyceride synthesis. Levels of diacylglycerol transferase 2 mRNA expression are similar in intestinal segments from both wild type and diacylglycerol transferase 1-deficient mice (Buhman et al., *J. Biol. Chem.*, 2002, *277*, 25474-25479). Using magnesium chloride to distinguish between diacylglycerol transferase 1 and 2 activity, Buhman, et al. observed that, in diacylglycerol transferase 1-deficient mice, diacylglycerol transferase activity is reduced to 50% in the proximal intestine and to 10-15% in the distal intestine (Buhman et al., *J. Biol. Chem.*, 2002, *277*, 25474-25479).

Additionally, diacylglycerol transferase 2 mRNA levels are not up-regulated the liver or adipose tissues of diacylglycerol transferase 1-deficient mice, even after weeks of high-fat diet (Cases et al., *J. Biol. Chem.*, 2001, *276*, 38870-38876; Chen et al., *J. Clin. Invest.*, 2002, *109*, 1049-1055). However, in ob/ob mice, which have a mutation in the leptin gene that results in obesity, diacylglycerol transferase 2 is more highly expressed than in wild type mice, suggesting that diacylglycerol transferase 2 may be partly responsible for the highly accumulated fat mass seen in these mice. Furthermore, the combined mutations of leptin and diacylglycerol transferase 1 leads to a three-fold elevation in diacylglycerol transferase 2 expression in white adipose tissue, compared to the levels in the same tissue from diacylglycerol transferase

1-deficient mice (Chen et al., *J. Clin. Invest.*, 2002, *109*, 1049-1055). Diacylglycerol transferase 2 mRNA is also upregulated in the skin of these mice (Chen et al., *J. Clin. Invest.*, 2002, *109*, 175-181). These data suggest leptin normally downregulates diacylglycerol transferase 2 expression, and that the upregulation of diacylglycerol transferase 2 in white adipose tissue in these mice may provide an alternate pathway for the triglyceride synthesis that still occurs in leptin deficient/ diacylglycerol transferase 1-deficient mice (Chen et al., *J. Clin. Invest.*, 2002, *109*, 1049-1055).

Diacylglycerol acyltransferase 1 knockout mice exhibit interesting phenotypes in that they are lean, resistant to diet-induce obesity, have decreased levels of tissue triglycerides and increased sensitivity to insulin and leptin (Chen et al., *J. Clin. Invest.*, 2002, *109*, 1049-1055; Smith et al., *Nat. Genet.*, 2000, *25*, 87-90). As diacylglycerol transferase 2 also participates in triglyceride synthesis, interfering with diacylglycerol transferase 2 may similarly lead to reduced body fat content.

Definitions

"DGAT2" means the gene product or protein of which expression is to be modulated by administration of a short antisense compound.

"DGAT2 nucleic acid" means any nucleic acid encoding DGAT2. For example, in certain embodiments, a DGAT2 nucleic acid includes, without limitation, a DNA sequence encoding DGAT2, an RNA sequence transcribed from DNA encoding DGAT2, and an mRNA sequence encoding DGAT2.

"DGAT2 mRNA" means an mRNA encoding DGAT2.

Therapeutic indications

Antisense technology is an effective means for reducing DGAT2 expression and has proven to be uniquely useful in a number of therapeutic, diagnostic, and research applications. As such, in certain embodiments, the present invention provides compounds targeted to nucleic acid encoding DGAT2, which modulate the expression of DGAT2. Further provided herein are short antisense compounds capable of effectively inhibiting DGAT2 expression.

In certain embodiments, a subject, suspected of having a disease or associated with DGAT2 is treated by administering one or more short antisense compounds targeted to a nucleic acid encoding DGAT2. For example, in a non-limiting embodiment, such methods comprise the step of administering to an animal a therapeutically effective amount of a short antisense compound. In certain such embodiments, short antisense compounds effectively inhibit the activity of DGAT2 or inhibit the expression of DGAT2. In one embodiment, the activity or expression of DGAT2 in a subject is inhibited by at least 10%, by at least 20%, by at least 25%, by at least 30%, by at least 40%, by at least 50%, by at least 60%, by at least 70%, by at least 75%, by at least 80%, by at least 85%, by at least 90%, by at least 95%, by at least 98%, by at least 99%, or by 100%. In certain embodiments, the activity or expression of DGAT2 in a subject is inhibited by about

30%. More preferably, the activity or expression of DGAT2 in a subject is inhibited by 50% or more.

The reduction of the expression of DGAT2 may be measured, for example, in blood, plasma, serum, adipose tissue, liver or any other body fluid, tissue or organ of the animal. Preferably, the cells contained within said fluids, tissues or organs being analyzed contain a nucleic acid molecule encoding DGAT2 and/or the DGAT2 protein itself.

In certain embodiments, pharmaceutical and other compositions comprising the compounds of the invention are also provided. For example, short antisense compounds targeted to a DGAT2 nucleic acid can be utilized in pharmaceutical compositions by adding an effective amount of a compound to a suitable pharmaceutically acceptable diluent or carrier.

Certain short antisense compounds targeting DGAT2 may have any one or more properties or characteristics of the short antisense compounds generally described herein. In certain embodiments, short antisense compounds targeting a DGAT2 nucleic acid have a motif (wing – deoxy gap –wing) selected from 1-12-1, 1-1-10-2, 2-10-1-1, 3-10-3, 2-10-3, 2-10-2, 1-10-1,1-10-2, 3-8-3, 2-8-2, 1-8-1, 3-6-3 or 1-6-1. In certain embodiments, short antisense compounds targeting a DGAT2 nucleic acid have a motif (wing – deoxy gap –wing) selected from 1-10-1, 2-10-2 and 3-10-3.

Provided herein are methods of treating an individual by administering one or more short antisense compound targeted to a DGAT2 nucleic acid or a pharmaceutical composition comprising such compound. Further provided are methods of treating a subject having a disease or conditions associated with DGAT2 activity by administering a short antisense compound targeted to a DGAT2 nucleic acid. Diseases and conditions associated with DGAT2 include, but are not limited to, cardiovascular disorders, obesity, diabetes, cholesterolemia, and liver steatosis.

Certain Short Antisense Compounds Targeted to a DGAT2 Nucleic Acid

In certain embodiments, short antisense compounds are targeted to a DGAT2 nucleic acid having the sequence of GENBANK® Accession No. NM_032564.2, incorporated herein as SEQ ID NO: 10. In certain such embodiments, a short antisense compound targeted to SEQ ID NO: 10 is at least 90% complementary to SEQ ID NO: 10. In certain such embodiments, a short antisense compound targeted to SEQ ID NO: 10 is at least 95% complementary to SEQ ID NO: 10. In certain such embodiments, a short antisense compound targeted to SEQ ID NO: 10 is 100% complementary to SEQ ID NO: 10. In certain embodiments, a short antisense compound targeted to SEQ ID NO: 10 includes a nucleotide sequence selected from the nucleotide sequences set forth in Tables 14 and 15.

Each nucleotide sequence set forth in each Tables 14 and 15 is independent of any modification to a sugar moiety, an internucleoside linkage, or a nucleobase. As such, short antisense compounds comprising a nucleotide sequence as set forth in Tables 14 and 15 may comprise, independently, one or more modifications to a sugar moiety, an internucleoside linkage, or a nucleobase. Antisense compounds described by Isis

Number (Isis NO.) indicate a combination of nucleobase sequence and one or more modifications to a sugar moiety, an internucleoside linkage, or a nucleobase.

Tables 14 and 15 illustrate examples of short antisense compounds targeted to SEQ ID NO: 10. Table 14 illustrates short antisense compounds that are 100% complementary to SEQ ID NO: 10. Table 15 illustrates short antisense compounds that have one or two mismatches with respect to SEQ ID NO: 10. The column labeled 'gapmer motif' indicates the wing-gap-wing motif of each short antisense compounds. The gap segment comprises 2'-deoxynucleotides and each nucleotide of each wing segment comprises a 2'-modified sugar. The particular 2'-modified sugar is also indicated in the 'gapmer motif' column. For example, '2-10-2 MOE' means a 2-10-2 gapmer motif, where a gap segment of ten 2'-deoxynucleotides is flanked by wing segments of two nucleotides, where the nucleotides of the wing segments are 2'-MOE nucleotides. Internucleoside linkages are phosphorothioate. The short antisense compounds comprise 5-methylcytidine in place of unmodified cytosine, unless "unmodified cytosine" is listed in the gapmer motif column, in which case the indicated cytosines are unmodified cytosines. For example, "5-mC in gap only" indicates that the gap segment has 5-methylcytosines, while the wing segments have unmodified cytosines.

Table 14: Short Antisense Compounds targeted to SEQ ID NO: 10

ISIS NO.	5' Target Site	3' Target Site	Sequence (5'-3')	Gapmer Motif	SEQ ID NO
372556	231	244	ATGAGGGTCTTCAT	2-10-2 MOE	681
372557	249	262	ACCCCGGAGTAGGC	2-10-2 MOE	682
382601	249	260	CCCGGAGTAGGC	1-10-1 MOE	683
372480	251	266	CAGGACCCCGGAGTAG	3-10-3 MOE	684
372481	252	267	GCAGGACCCCGGAGTA	3-10-3 MOE	685
372558	252	265	AGGACCCCGGAGTA	2-10-2 MOE	686
372559	253	266	CAGGACCCCGGAGT	2-10-2 MOE	687
382603	331	342	CAGACCCCTCGC	1-10-1 MOE	688
382604	361	372	AGAGGATGCTGG	1-10-1 MOE	689
372485	392	407	GAGCCAGGTGACAGAG	3-10-3 MOE	690
372563	393	406	AGCCAGGTGACAGA	2-10-2 MOE	691
382605	397	408	TGAGCCAGGTGA	1-10-1 MOE	692
372565	414	427	TTTTCCACCTTGGA	2-10-2 MOE	693
382606	482	493	CTGCAGGCCACT	1-10-1 MOE	694
372497	651	666	TCACCAGCTGGATGGG	3-10-3 MOE	695
372498	652	667	TTCACCAGCTGGATGG	3-10-3 MOE	696
372575	652	665	CACCAGCTGGATGG	2-10-2 MOE	697
372576	653	666	TCACCAGCTGGATG	2-10-2 MOE	698
382607	655	666	TCACCAGCTGGA	1-10-1 MOE	699
372499	656	671	TGTCTTCACCAGCTGG	3-10-3 MOE	700
372577	657	670	GTCTTCACCAGCTG	2-10-2 MOE	701
372500	659	674	GTGTGTCTTCACCAGC	3-10-3 MOE	702
372578	660	673	TGTGTCTTCACCAG	2-10-2 MOE	703
372501	661	676	TTGTGTGTCTTCACCA	3-10-3 MOE	704

372579	662	675	TGTGTGTCTTCACC	2-10-2 MOE	705
372502	664	679	AGGTTGTGTGTCTTCA	3-10-3 MOE	706
372580	665	678	GGTTGTGTGTCTTC	2-10-2 MOE	707
372503	666	681	GCAGGTTGTGTGTCTT	3-10-3 MOE	708
372581	667	680	CAGGTTGTGTGTCT	2-10-2 MOE	709
372504	669	684	TCAGCAGGTTGTGTGT	3-10-3 MOE	710
372582	670	683	CAGCAGGTTGTGTG	2-10-2 MOE	711
372505	671	686	GGTCAGCAGGTTGTGT	3-10-3 MOE	712
372506	672	687	TGGTCAGCAGGTTGTG	3-10-3 MOE	713
372583	672	685	GTCAGCAGGTTGTG	2-10-2 MOE	714
372584	673	686	GGTCAGCAGGTTGT	2-10-2 MOE	715
372507	676	691	CTGGTGGTCAGCAGGT	3-10-3 MOE	716
372585	677	690	TGGTGGTCAGCAGG	2-10-2 MOE	717
382608	680	691	CTGGTGGTCAGC	1-10-1 MOE	718
372508	681	696	AGTTCCTGGTGGTCAG	3-10-3 MOE	719
372586	682	695	GTTCCTGGTGGTCA	2-10-2 MOE	720
372509	684	699	TATAGTTCCTGGTGGT	3-10-3 MOE	721
372587	685	698	ATAGTTCCTGGTGG	2-10-2 MOE	722
372510	686	701	GATATAGTTCCTGGTG	3-10-3 MOE	723
372588	687	700	ATATAGTTCCTGGT	2-10-2 MOE	724
372511	691	706	CCAAAGATATAGTTCC	3-10-3 MOE	725
372512	692	707	TCCAAAGATATAGTTC	3-10-3 MOE	726
372589	692	705	CAAAGATATAGTTC	2-10-2 MOE	727
372590	693	706	CCAAAGATATAGTT	2-10-2 MOE	728
382609	724	735	CCAGGCCCATGA	1-10-1 MOE	729
372514	725	740	GGCACCCAGGCCCATG	3-10-3 MOE	730
372592	726	739	GCACCCAGGCCCAT	2-10-2 MOE	731
372515	730	745	CAGAAGGCACCCAGGC	3-10-3 MOE	732
372593	731	744	AGAAGGCACCCAGG	2-10-2 MOE	733
382610	851	862	CCAGACATCAGG	1-10-1 MOE	734
382611	867	878	GACAGGGCAGAT	1-10-1 MOE	735
382602	868	879	TGACAGGGCAGA	1-10-1 MOE	736
382612	911	922	CCACTCCCATTC	1-10-1 MOE	737
372524	965	980	GCCAGGCATGGAGCTC	3-10-3 MOE	738
372602	966	979	CCAGGCATGGAGCT	2-10-2 MOE	739
382613	968	979	CCAGGCATGGAG	1-10-1 MOE	740
382614	987	998	CAGGGTGACTGC	1-10-1 MOE	741
372525	989	1004	GTTCCGCAGGGTGACT	3-10-3 MOE	742
372603	990	1003	TTCCGCAGGGTGAC	2-10-2 MOE	743
372526	992	1007	GCGGTTCCGCAGGGTG	3-10-3 MOE	744
372604	993	1006	CGGTTCCGCAGGGT	2-10-2 MOE	745
372530	1106	1121	TCGGCCCCAGGAGCCC	3-10-3 MOE	746
372608	1107	1120	CGGCCCCAGGAGCC	2-10-2 MOE	747
372531	1109	1124	CCATCGGCCCCAGGAG	3-10-3 MOE	748
372609	1110	1123	CATCGGCCCCAGGA	2-10-2 MOE	749
372532	1112	1127	GACCCATCGGCCCCAG	3-10-3 MOE	750
372610	1113	1126	ACCCATCGGCCCCA	2-10-2 MOE	751
372533	1117	1132	TTCTGGACCCATCGGC	3-10-3 MOE	752
382615	1117	1128	GGACCCATCGGC	1-10-1 MOE	753
372611	1118	1131	TCTGGACCCATCGG	2-10-2 MOE	754

372536	1199	1214	CACCAGCCCCCAGGTG	3-10-3 MOE	755
372614	1200	1213	ACCAGCCCCCAGGT	2-10-2 MOE	756
372537	1204	1219	TAGGGCACCAGCCCCC	3-10-3 MOE	757
372615	1205	1218	AGGGCACCAGCCCC	2-10-2 MOE	758
372538	1209	1224	TGGAGTAGGGCACCAG	3-10-3 MOE	759
372616	1210	1223	GGAGTAGGGCACCA	2-10-2 MOE	760
382616	1215	1226	CTTGGAGTAGGG	1-10-1 MOE	761
372539	1218	1233	TGATGGGCTTGGAGTA	3-10-3 MOE	762
372617	1219	1232	GATGGGCTTGGAGT	2-10-2 MOE	763
372540	1293	1308	TGTGGTACAGGTCGAT	3-10-3 MOE	764
372618	1294	1307	GTGGTACAGGTCGA	2-10-2 MOE	765
382617	1294	1305	GGTACAGGTCGA	1-10-1 MOE	766
372541	1295	1310	GGTGTGGTACAGGTCG	3-10-3 MOE	767
372619	1296	1309	GTGTGGTACAGGTC	2-10-2 MOE	768
372542	1298	1313	CATGGTGTGGTACAGG	3-10-3 MOE	769
372620	1299	1312	ATGGTGTGGTACAG	2-10-2 MOE	770
372543	1300	1315	TACATGGTGTGGTACA	3-10-3 MOE	771
372621	1301	1314	ACATGGTGTGGTAC	2-10-2 MOE	772
372544	1303	1318	ATGTACATGGTGTGGT	3-10-3 MOE	773
372622	1304	1317	TGTACATGGTGTGG	2-10-2 MOE	774
382618	1313	1324	GCCTCCATGTAC	1-10-1 MOE	775
382619	1325	1336	AGCTTCACCAGG	1-10-1 MOE	776
382620	1383	1394	GTTCACCTCCAG	1-10-1 MOE	777

Table 15: Short antisense compounds targeted to SEQ ID NO: 10 and having 1 or 2 mismatches

ISIS NO	5' Target Site	3' Target Site	Sequence (5'-3')	Gapmer Motif	SEQ ID NO
372608	151	164	CGGCCCCAGGAGCC	2-10-2 MOE	747
372474	156	171	CATGCCCCAGCCGCCG	3-10-3 MOE	778
372552	157	170	ATGCCCCAGCCGCC	2-10-2 MOE	779
382609	167	178	CCAGGCCCATGA	1-10-1 MOE	729
372478	230	245	GATGAGGGTCTTCATG	3-10-3 MOE	780
372479	248	263	GACCCCGGAGTAGGCA	3-10-3 MOE	781
382611	317	328	GACAGGGCAGAT	1-10-1 MOE	735
372483	352	367	ATGCTGGAGCCAGTGC	3-10-3 MOE	782
372561	353	366	TGCTGGAGCCAGTG	2-10-2 MOE	783
372562	373	386	GTCTTGGAGGGCCG	2-10-2 MOE	784
382602	388	399	TGACAGGGCAGA	1-10-1 MOE	736
372613	392	405	CCCAGGTGTCAGAG	2-10-2 MOE	785
372486	412	427	TTTTCCACCTTGGATC	3-10-3 MOE	786
372564	413	426	TTTCCACCTTGGAT	2-10-2 MOE	787
372487	413	428	TTTTTCCACCTTGGAT	3-10-3 MOE	788
372488	418	433	AGGTGTTTTTCCACCT	3-10-3 MOE	789
372566	419	432	GGTGTTTTTCCACC	2-10-2 MOE	790
372489	459	474	CCAGGAAGGATAGGAC	3-10-3 MOE	791
372567	460	473	CAGGAAGGATAGGA	2-10-2 MOE	792
382612	475	486	CCACTCCCATTC	1-10-1 MOE	737
372490	483	498	TGACACTGCAGGCCAC	3-10-3 MOE	793

372568	484	497	GACACTGCAGGCCA	2-10-2 MOE	794
372491	492	507	ACATGAGGATGACACT	3-10-3 MOE	795
372569	493	506	CATGAGGATGACAC	2-10-2 MOE	796
372492	503	518	GCAGAAGGTGTACATG	3-10-3 MOE	797
372570	504	517	CAGAAGGTGTACAT	2-10-2 MOE	798
372493	512	527	GCAGTCAGTGCAGAAG	3-10-3 MOE	799
372571	513	526	CAGTCAGTGCAGAA	2-10-2 MOE	800
372496	612	627	ACACGGCCCAGTTTCG	3-10-3 MOE	801
372574	613	626	CACGGCCCAGTTTC	2-10-2 MOE	802
372513	717	732	GGCCCATGATGCCATG	3-10-3 MOE	803
372591	718	731	GCCCATGATGCCAT	2-10-2 MOE	804
372516	732	747	TACAGAAGGCACCCAG	3-10-3 MOE	805
372594	733	746	ACAGAAGGCACCCA	2-10-2 MOE	806
372518	812	827	GAAGTTGCCAGCCAAT	3-10-3 MOE	807
372596	813	826	AAGTTGCCAGCCAA	2-10-2 MOE	808
372560	863	876	CAGGGCAGATCCTT	2-10-2 MOE	809
372519	887	902	CAAGTAGTCTATGGTG	3-10-3 MOE	810
372597	888	901	AAGTAGTCTATGGT	2-10-2 MOE	811
372520	894	909	TGGAAAGCAAGTAGTC	3-10-3 MOE	812
372598	895	908	GGAAAGCAAGTAGT	2-10-2 MOE	813
372527	1013	1028	GGCCAGCTTTACAAAG	3-10-3 MOE	814
372605	1014	1027	GCCAGCTTTACAAA	2-10-2 MOE	815
372606	1020	1033	CGCAGGGCCAGCTT	2-10-2 MOE	816
372529	1052	1067	AAAGGAATAGGTGGGA	3-10-3 MOE	817
372607	1053	1066	AAGGAATAGGTGGG	2-10-2 MOE	818
372534	1144	1159	GCGAAACCAATATACT	3-10-3 MOE	819
372612	1145	1158	CGAAACCAATATAC	2-10-2 MOE	820
372535	1192	1207	CCCCAGGTGTCAGAGG	3-10-3 MOE	821
372613	1193	1206	CCCAGGTGTCAGAG	2-10-2 MOE	822
372545	1332	1347	GATTGTCAAAGAGCTT	3-10-3 MOE	823
372623	1333	1346	ATTGTCAAAGAGCT	2-10-2 MOE	824
372546	1342	1357	TTGGTCTTGTGATTGT	3-10-3 MOE	825
372624	1343	1356	TGGTCTTGTGATTG	2-10-2 MOE	826
372547	1352	1367	AAGGCCGAATTTGGTC	3-10-3 MOE	827
372625	1353	1366	AGGCCGAATTTGGT	2-10-2 MOE	828
382601	1617	1628	CCCGGAGTAGGC	1-10-1 MOE	683
382606	1971	1982	CTGCAGGCCACT	1-10-1 MOE	694
382612	1988	1999	CCACTCCCATTC	1-10-1 MOE	737

In certain embodiments, a target region is nucleotides 231-267 of SEQ ID NO: 10. In certain embodiments, a short antisense compound is targeted to nucleotides 231-267 of SEQ ID NO: 10. In certain such embodiments, a short antisense compound targeted to nucleotides 231-267 comprises a nucleotide sequence selected from SEQ ID NO 681, 682, 683, 684, 685, 686, or 687. In certain such embodiments, a short antisense compound targeted to nucleotides 231-267 of SEQ ID NO: 10 is selected from Isis No 372556, 372557, 382601, 372480, 372481, 372558, or 372559.

In certain embodiments, a target region is nucleotides 249-267 of SEQ ID NO: 10. In certain

embodiments, a short antisense compound is targeted to nucleotides 249-267 of SEQ ID NO: 10. In certain such embodiments, a short antisense compound targeted to nucleotides 249-267 comprises a nucleotide sequence selected from SEQ ID NO 683, 684, 685, 686, or 687. In certain such embodiments, a short antisense compound targeted to nucleotides 249-267 of SEQ ID NO: 10 is selected from Isis No 382601, 372480, 372481, 372558, or 372559.

In certain embodiments, a target region is nucleotides 331-493 of SEQ ID NO: 10. In certain embodiments, a short antisense compound is targeted to nucleotides 331-493 of SEQ ID NO: 10. In certain such embodiments, a short antisense compound targeted to nucleotides 331-493 comprises a nucleotide sequence selected from SEQ ID NO 688, 689, 690, 691, 692, 693, or 694. In certain such embodiments, a short antisense compound targeted to nucleotides 331-493 of SEQ ID NO: 10 is selected from Isis No 382603, 382604, 372485, 372563, 382605, 372565, or 382606.

In certain embodiments, a target region is nucleotides 331-427 of SEQ ID NO: 10. In certain embodiments, a short antisense compound is targeted to nucleotides 331-427 of SEQ ID NO: 10. In certain such embodiments, a short antisense compound targeted to nucleotides 331-427 comprises a nucleotide sequence selected from SEQ ID NO 688, 689, 690, 691, 692, or 693. In certain such embodiments, a short antisense compound targeted to nucleotides 331-427 of SEQ ID NO: 10 is selected from Isis No 382603, 382604, 372485, 372563, 382605, or 372565.

In certain embodiments, a target region is nucleotides 392-408 of SEQ ID NO: 10. In certain embodiments, a short antisense compound is targeted to nucleotides 392-408 of SEQ ID NO: 10. In certain such embodiments, a short antisense compound targeted to nucleotides 392-408 comprises a nucleotide sequence selected from SEQ ID NO 690, 691, or 692. In certain such embodiments, a short antisense compound targeted to nucleotides 392-408 of SEQ ID NO: 10 is selected from Isis No 372485, 372563, or 382605.

In certain embodiments, a target region is nucleotides 651-707 of SEQ ID NO: 10. In certain embodiments, a short antisense compound is targeted to nucleotides 651-707 of SEQ ID NO: 10. In certain such embodiments, a short antisense compound targeted to nucleotides 651-707 comprises a nucleotide sequence selected from SEQ ID NO 695, 696, 697, 698, 699, 700, 701, 702, 703, 704, 705, 706, 707, 708, 709, 710, 711, 712, 713, 714, 715, 716, 717, 718, 719, 720, 721, 722, 723, 724, 725, 726, 727, or 728. In certain such embodiments, a short antisense compound targeted to nucleotides 651-707 of SEQ ID NO: 10 is selected from Isis No 372497, 372498, 372575, 372576, 382607, 372499, 372577, 372500, 372578, 372501, 372579, 372502, 372580, 372503, 372581, 372504, 372582, 372505, 372506, 372583, 372584, 372507, 372585, 382608, 372508, 372586, 372509, 372587, 372510, 372588, 372511, 372512, 372589, or 372590.

In certain embodiments, a target region is nucleotides 724-745 of SEQ ID NO: 10. In certain embodiments, a short antisense compound is targeted to nucleotides 724-745 of SEQ ID NO: 10. In certain such embodiments, a short antisense compound targeted to nucleotides 724-745 comprises a nucleotide

sequence selected from SEQ ID NO 729, 730, 731, 732, or 733. In certain such embodiments, a short antisense compound targeted to nucleotides 724-745 of SEQ ID NO: 10 is selected from Isis No 382609, 372514, 372592, 372515, or 372593.

In certain embodiments, a target region is nucleotides 651-745 of SEQ ID NO: 10. In certain embodiments, a short antisense compound is targeted to nucleotides 651-745 of SEQ ID NO: 10. In certain such embodiments, a short antisense compound targeted to nucleotides 651-745 comprises a nucleotide sequence selected from SEQ ID NO 695, 696, 697, 698, 699, 700, 701, 702, 703, 704, 705, 706, 707, 708, 709, 710, 711, 712, 713, 714, 715, 716, 717, 718, 719, 720, 721, 722, 723, 724, 725, 726, 727, 728, 729, 730, 731, 732, or 733. In certain such embodiments, a short antisense compound targeted to nucleotides 651-745 of SEQ ID NO: 10 is selected from Isis No 372497, 372498, 372575, 372576, 382607, 372499, 372577, 372500, 372578, 372501, 372579, 372502, 372580, 372503, 372581, 372504, 372582, 372505, 372506, 372583, 372584, 372507, 372585, 382608, 372508, 372586, 372509, 372587, 372510, 372588, 372511, 372512, 372589, 372590, 382609, 372514, 372592, 372515, or 372593.

In certain embodiments, a target region is nucleotides 851-922 of SEQ ID NO: 10. In certain embodiments, a short antisense compound is targeted to nucleotides 851-922 of SEQ ID NO: 10. In certain such embodiments, a short antisense compound targeted to nucleotides 851-922 comprises a nucleotide sequence selected from SEQ ID NO 734, 735, 736, or 737. In certain such embodiments, a short antisense compound targeted to nucleotides 851-922 of SEQ ID NO: 10 is selected from Isis No 382610, 382611, 382602, or 382612.

In certain embodiments, a target region is nucleotides 851-879 of SEQ ID NO: 10. In certain embodiments, a short antisense compound is targeted to nucleotides 851-879 of SEQ ID NO: 10. In certain such embodiments, a short antisense compound targeted to nucleotides 851-879 comprises a nucleotide sequence selected from SEQ ID NO 734, 735, or 736. In certain such embodiments, a short antisense compound targeted to nucleotides 851-879 of SEQ ID NO: 10 is selected from Isis No 382610, 382611, or 382602.

In certain embodiments, a target region is nucleotides 965-1007 of SEQ ID NO: 10. In certain embodiments, a short antisense compound is targeted to nucleotides 965-1007 of SEQ ID NO: 10. In certain such embodiments, a short antisense compound targeted to nucleotides 965-1007 comprises a nucleotide sequence selected from SEQ ID NO 738, 739, 740, 741, 742, 743, 744, or 745. In certain such embodiments, a short antisense compound targeted to nucleotides 965-1007 of SEQ ID NO: 10 is selected from Isis No 372524, 372602, 382613, 382614, 372525, 372603, 372526, or 372604.

In certain embodiments, a target region is nucleotides 965-979 of SEQ ID NO: 10. In certain embodiments, a short antisense compound is targeted to nucleotides 965-979 of SEQ ID NO: 10. In certain such embodiments, a short antisense compound targeted to nucleotides 965-979 comprises a nucleotide sequence selected from SEQ ID NO 738, 739, or 740. In certain such embodiments, a short antisense compound targeted to nucleotides 965-979 of SEQ ID NO: 10 is selected from Isis No 372524, 372602, or 382613.

In certain embodiments, a target region is nucleotides 987-1007 of SEQ ID NO: 10. In certain embodiments, a short antisense compound is targeted to nucleotides 987-1007 of SEQ ID NO: 10. In certain such embodiments, a short antisense compound targeted to nucleotides 987-1007 comprises a nucleotide sequence selected from SEQ ID NO 741, 742, 743, 744, or 745. In certain such embodiments, a short antisense compound targeted to nucleotides 987-1007 of SEQ ID NO: 10 is selected from Isis No 382614, 372525, 372603, 372526, or 372604.

In certain embodiments, a target region is nucleotides 1106-1132 of SEQ ID NO: 10. In certain embodiments, a short antisense compound is targeted to nucleotides 1106-1132 of SEQ ID NO: 10. In certain such embodiments, a short antisense compound targeted to nucleotides 1106-1132 comprises a nucleotide sequence selected from SEQ ID NO 746, 747, 748, 749, 750, 751, 752, 753, or 754. In certain such embodiments, a short antisense compound targeted to nucleotides 1106-1132 of SEQ ID NO: 10 is selected from Isis No 372530, 372608, 372531, 372609, 372532, 372610, 372533, 382615, or 372611.

In certain embodiments, a target region is nucleotides 1199-1233 of SEQ ID NO: 10. In certain embodiments, a short antisense compound is targeted to nucleotides 1199-1233 of SEQ ID NO: 10. In certain such embodiments, a short antisense compound targeted to nucleotides 1199-1233 comprises a nucleotide sequence selected from SEQ ID NO 755, 756, 757, 758, 759, 760, 761, 762, or 763. In certain such embodiments, a short antisense compound targeted to nucleotides 1199-1233 of SEQ ID NO: 10 is selected from Isis No 372536, 372614, 372537, 372615, 372538, 372616, 382616, 372539, or 372617.

In certain embodiments, a target region is nucleotides 1293-1394 of SEQ ID NO: 10. In certain embodiments, a short antisense compound is targeted to nucleotides 1293-1394 of SEQ ID NO: 10. In certain such embodiments, a short antisense compound targeted to nucleotides 1293-1394 comprises a nucleotide sequence selected from SEQ ID NO 764, 765, 766, 767, 768, 769, 770, 771, 772, 773, 774, 775, 776, or 777. In certain such embodiments, a short antisense compound targeted to nucleotides 1293-1394 of SEQ ID NO: 10 is selected from Isis No 372540, 372618, 382617, 372541, 372619, 372542, 372620, 372543, 372621, 372544, 372622, 382618, 382619, or 382620.

In certain embodiments, a target region is nucleotides 1293-1336 of SEQ ID NO: 10. In certain embodiments, a short antisense compound is targeted to nucleotides 1293-1336 of SEQ ID NO: 10. In certain such embodiments, a short antisense compound targeted to nucleotides 1293-1336 comprises a nucleotide sequence selected from SEQ ID NO 764, 765, 766, 767, 768, 769, 770, 771, 772, 773, 774, 775, or 776. In certain such embodiments, a short antisense compound targeted to nucleotides 1293-1336 of SEQ ID NO: 10 is selected from Isis No 372540, 372618, 382617, 372541, 372619, 372542, 372620, 372543, 372621, 372544, 372622, 382618, or 382619.

In certain embodiments, a target region is nucleotides 1293-1324 of SEQ ID NO: 10. In certain

embodiments, a short antisense compound is targeted to nucleotides 1293-1324 of SEQ ID NO: 10. In certain such embodiments, a short antisense compound targeted to nucleotides 1293-1324 comprises a nucleotide sequence selected from SEQ ID NO 764, 765, 766, 767, 768, 769, 770, 771, 772, 773, 774, or 775. In certain such embodiments, a short antisense compound targeted to nucleotides 1293-1324 of SEQ ID NO: 10 is selected from Isis No 372540, 372618, 382617, 372541, 372619, 372542, 372620, 372543, 372621, 372544, 372622, or 382618.

In certain embodiments, short antisense compounds targeted to a DGAT2 nucleic acid are 8 to 16, preferably 9 to 15, more preferably 9 to 14, more preferably 10 to 14 nucleotides in length. In certain embodiments, short antisense compounds targeted to a DGAT2 nucleic acid are 9 to 14 nucleotides in length. In certain embodiments, short antisense compounds targeted to a DGAT2 nucleic acid are 10 to 14 nucleotides in length. In certain embodiments, such short antisense compounds are short antisense oligonucleotides.

In certain embodiments, short antisense compounds targeted to a DGAT2 nucleic acid are short gapmers. In certain such embodiments, short gapmers targeted to a DGAT2 nucleic acid comprise at least one high affinity modification in one or more wings of the compound. In certain embodiments, short antisense compounds targeted to a DGAT2 nucleic acid comprise 1 to 3 high-affinity modifications in each wing. In certain such embodiments, the nucleosides or nucleotides of the wing comprise a 2' modification. In certain such embodiments, the monomers of the wing are BNA's. In certain such embodiments, the monomers of the wing are selected from α-L-Methyleneoxy (4'-CH_2-O-2') BNA , β-D-Methyleneoxy (4'-CH_2-O-2') BNA , Ethyleneoxy (4'-$(CH_2)_2$-O-2') BNA , Aminooxy (4'-CH_2-O-N(R)-2') BNA and Oxyamino (4'-CH_2-N(R)-O-2') BNA. In certain embodiments, the monomers of a wing comprise a substituent at the 2' position selected from allyl, amino, azido, thio, O-allyl, O-C_1-C_{10} alkyl, -OCF_3, O-$(CH_2)_2$-O-CH_3, 2'-$O(CH_2)_2SCH_3$, O-$(CH_2)_2$-O-N(R_m)(R_n), and O-CH_2-C(=O)-N(R_m)(R_n), where each R_m and R_n is, independently, H or substituted or unsubstituted C_1-C_{10} alkyl. In certain embodiments, the monomers of a wing are 2'MOE nucleotides.

In certain embodiments, short antisense compounds targeted to a DGAT2 nucleic acid comprise a gap between the 5' wing and the 3' wing. In certain embodiments the gap comprises five, six, seven, eight, nine, ten, eleven, twelve, thirteen, or fourteen monomers. In certain embodiments, the monomers of the gap are unmodified deoxyribonucleotides. In certain embodiments, the monomers of the gap are unmodified ribonucleotides. In certain embodiments, gap modifications (if any) gap result in a short antisense compound that, when bound to its target nucleic acid, supports cleavage by an RNase, including, but not limited to, RNase H.

In certain embodiments, short antisense compounds targeted to a DGAT2 nucleic acid have uniform monomeric linkages. In certain such embodiments, those linkages are all phosphorothioate linkages. In certain embodiments, the linkages are all phosphodiester linkages. In certain embodiments, short antisense compounds targeted to a DGAT2 nucleic acid have mixed backbones.

In certain embodiments, short antisense compounds targeted to a DGAT2 nucleic acid are 8 monomers in length. In certain embodiments, short antisense compounds targeted to a DGAT2 nucleic acid are 9 monomers in length. In certain embodiments, short antisense compounds targeted to a DGAT2 nucleic acid are 10 monomers in length. In certain embodiments, short antisense compounds targeted to a DGAT2 nucleic acid are 11 monomers in length. In certain embodiments, short antisense compounds targeted to a DGAT2 nucleic acid are monomers in length. In certain embodiments, short antisense compounds targeted to a DGAT2 nucleic acid are 13 monomers in length. In certain embodiments, short antisense compounds targeted to a DGAT2 nucleic acid are 14 monomers in length. In certain embodiments, short antisense compounds targeted to a DGAT2 nucleic acid are 15 monomers in length. In certain embodiments, short antisense compounds targeted to a DGAT2 nucleic acid are 16 monomers in length. In certain embodiments, short antisense compounds targeted to a DGAT2 nucleic acid comprise 9 to 15 monomers. In certain embodiments, short antisense compounds targeted to a DGAT2 nucleic acid comprise 10 to 15 monomers. In certain embodiments, short antisense compounds targeted to a DGAT2 nucleic acid comprise 12 to 14 monomers. In certain embodiments, short antisense compounds targeted to a DGAT2 nucleic acid comprise 12 to 14 nucleotides or nucleosides.

In certain embodiments, the invention provides methods of modulating expression of DGAT2. In certain embodiments, such methods comprise use of one or more short antisense compound targeted to a DGAT2 nucleic acid, wherein the short antisense compound targeted to a DGAT2 nucleic acid is from about 8 to about 16, preferably 9 to 15, more preferably 9 to 14, more preferably 10 to 14 monomers (i.e. from about 8 to about 16 linked monomers). One of ordinary skill in the art will appreciate that this comprehends methods of modulating expression of DGAT2 using one or more short antisense compounds targeted to a DGAT2 nucleic acid of 8, 9, 10, 11, 12, 13, 14, 15 or 16 monomers.

In certain embodiments, methods of modulating DGAT2 comprise use of a short antisense compound targeted to a DGAT2 nucleic acid that is 8 monomers in length. In certain embodiments, methods of modulating DGAT2 comprise use of a short antisense compound targeted to a DGAT2 nucleic acid that is 9 monomers in length. In certain embodiments, methods of modulating DGAT2 comprise use of a short antisense compound targeted to a DGAT2 nucleic acid that is 10 monomers in length. In certain embodiments, methods of modulating DGAT2 comprise use of a short antisense compound targeted to a DGAT2 nucleic acid that is 11 monomers in length. In certain embodiments, methods of modulating DGAT2 comprise use of a short antisense compound targeted to a DGAT2 nucleic acid that is 12 monomers in length. In certain embodiments, methods of modulating DGAT2 comprise use of a short antisense compound targeted to a DGAT2 nucleic acid that is 13 monomers in length. In certain embodiments, methods of modulating DGAT2 comprise use of a short antisense compound targeted to a DGAT2 nucleic acid that is 14 monomers in length. In certain embodiments, methods of modulating DGAT2 comprise use of a short antisense compound targeted to a DGAT2 nucleic acid that is 15 monomers in length. In certain embodiments, methods of modulating DGAT2 comprise use of a short antisense compound targeted to a DGAT2 nucleic acid that is 16 monomers in length.

In certain embodiments, methods of modulating expression of DGAT2 comprise use of a short antisense compound targeted to a DGAT2 nucleic acid comprising 9 to 15 monomers. In certain embodiments, methods of modulating expression of DGAT2 comprise use of a short antisense compound targeted to a DGAT2 nucleic acid comprising 10 to 15 monomers. In certain embodiments, methods of modulating expression of DGAT2 comprise use of a short antisense compound targeted to a DGAT2 nucleic acid comprising 12 to 14 monomers. In certain embodiments, methods of modulating expression of DGAT2 comprise use of a short antisense compound targeted to a DGAT2 nucleic acid comprising 12 or 14 nucleotides or nucleosides.

<u>9. PTP1B</u>

PTP1B (also known as protein phosphatase 1B and PTPN1) is an endoplasmic reticulum (ER)-associated enzyme originally isolated as the major protein tyrosine phosphatase of the human placenta (Tonks *et al.*, *J. Biol. Chem.*, 1988, *263*, 6731-6737; Tonks *et al.*, *J. Biol. Chem.*, 1988, *263*, 6722-6730).

An essential regulatory role in signaling mediated by the insulin receptor has been established for PTP1B. In certain instances, PTP1B interacts with and dephosphorylates the activated insulin receptor both *in vitro* and in intact cells resulting in the downregulation of the signaling pathway (Goldstein *et al.*, *Mol. Cell. Biochem.*, 1998, *182*, 91-99; Seely *et al.*, *Diabetes*, 1996, *45*, 1379-1385). In addition, PTP1B modulates the mitogenic actions of insulin (Goldstein *et al.*, *Mol. Cell. Biochem.*, 1998, *182*, 91-99). In rat adipose cells overexpressing PTP1B, the translocation of the GLUT4 glucose transporter was inhibited, implicating PTP1B as a negative regulator of glucose transport as well (Chen *et al.*, *J. Biol. Chem.*, 1997, *272*, 8026-8031).

Mouse knockout models lacking the PTP1B gene also point toward the negative regulation of insulin signaling by PTP1B. Mice harboring a disrupted PTP1B gene showed increased insulin sensitivity and increased phosphorylation of the insulin receptor. When placed on a high-fat diet, PTP1B -/- mice were resistant to weight gain and remained insulin sensitive (Elchebly *et al.*, *Science*, 1999, *283*, 1544-1548). These studies clearly establish PTP1B as a therapeutic target in the treatment of diabetes and obesity.

Diabetes and obesity (sometimes now collectively referred to as "diabesity") are interrelated. Most human obesity is associated with insulin resistance and leptin resistance. In fact obesity may have an even greater impact on insulin action than does diabetes itself (Sindelka et al., *Physiol Res.*, 2002, *51*, 85-91). Syndrome X or metabolic syndrome is a new term for a cluster of conditions, that, when occurring together, may indicate a predisposition to diabetes and cardiovascular disease. These symptoms, including high blood pressure, high triglycerides, decreased HDL and obesity, tend to appear together in some individuals. Because of its role in both diabetes and obesity, PTP1B is believed to be a therapeutic target for a range of metabolic conditions, including diabetes, obesity and metabolic syndrome. By improving blood glucose control, inhibitors of PTP1B may also be useful in slowing, preventing, delaying or ameliorating the sequelae of diabetes, which include retinopathy, neuropathy, cardiovascular complications and nephropathy.

PTP1B, which is differentially regulated during the cell cycle (Schievella *et al.*, *Cell. Growth Differ.*, 1993, *4*, 239-246), is expressed in insulin sensitive tissues as two different isoforms that arise from alternate splicing of the pre-mRNA (Shifrin and Neel, *J. Biol. Chem.*, 1993, *268*, 25376-25384). The ratio of the alternatively spliced products is affected by growth factors, such as insulin, and differs in various tissues examined (Sell and Reese, *Mol. Genet. Metab.*, 1999, *66*, 189-192). In these studies the levels of the variants correlated with the plasma insulin concentration and percentage body fat. These variants may therefore be used as a biomarker for patients with chronic hyperinsulinemia or type 2 diabetes.

Definitions

"Protein tyrosine phosphatase 1B" is the gene product or protein of which expression is to be modulated by administration of a short antisense compound. Protein tyrosine phosphatase 1B is generally referred to as PTP1B but may also be referred to as protein tyrosine phosphatase; PTPN1; RKPTP; protein tyrosine phosphatase, non-receptor type 1.

"PTP1B nucleic acid" means any nucleic acid encoding PTP1B. For example, in certain embodiments, a PTP1B nucleic acid includes, without limitation, a DNA sequence encoding PTP1B, an RNA sequence transcribed from DNA encoding PTP1B, and an mRNA sequence encoding PTP1B. "PTP1B mRNA" means an mRNA encoding a PTP1B protein.

Therapeutic indications

Antisense technology is an effective means for reducing PTP1B expression and has proven to be uniquely useful in a number of therapeutic, diagnostic, and research applications. As such, in certain embodiments, the present invention provides compounds targeted to a nucleic acid encoding PTP1B, which modulate the expression of PTP1B. Further provided herein are short antisense compounds capable of effectively inhibiting PTP1B expression.

In certain therapeutics, a subject, suspected of having a disease or disorder which can be treated by modulating the expression of PTP1B is treated by administering one or more short antisense compounds targeted to a nucleic acid encoding PTP1B. For example, in one non-limiting embodiment, the methods comprise the step of administering to an animal a therapeutically effective amount of a short antisense compound. The short antisense compounds of the present invention effectively inhibit the activity of PTP1B or inhibit the expression of PTP1B. In one embodiment, the activity or expression of PTP1B in a subject is inhibited by at least 10%, by at least 20%, by at least 25%, by at least 30%, by at least 40%, by at least 50%, by at least 60%, by at least 70%, by at least 75%, by at least 80%, by at least 85%, by at least 90%, by at least

95%, by at least 98%, by at least 99%, or by 100%. In certain embodiments, activity or expression of PTP1B in a subject is inhibited by about 30%. In certain embodiments, the activity or expression of PTP1B in a subject is inhibited by 50% or more.

The reduction of the expression of PTP1B may be measured, for example, in blood, plasma, serum, adipose tissue, liver or any other body fluid, tissue or organ of the animal. Preferably, the cells contained within said fluids, tissues or organs being analyzed contain a nucleic acid molecule encoding PTP1B and/or the PTP1B protein itself.

Certain pharmaceutical and other compositions comprising the compounds of the invention are also provided. In certain embodiments short antisense compounds targeted to a PTP1B nucleic acid are utilized in pharmaceutical compositions by adding an effective amount of a compound to a suitable pharmaceutically acceptable diluent or carrier.

The short antisense compounds targeting PTP1B may have any one or more properties or characteristics of the short antisense compounds generally described herein. In certain embodiments, short antisense compounds targeting a PTP1B nucleic acid have a motif (wing – deoxy gap –wing) selected from 1-12-1, 1-1-10-2, 2-10-1-1, 3-10-3, 2-10-3, 2-10-2, 1-10-1,1-10-2, 3-8-3, 2-8-2, 1-8-1, 3-6-3 or 1-6-1, more preferably 1-10-1, 2-10-2, 3-10-3, and 1-9-2.

In certain embodiments provided herein are methods of treating an individual by administering one or more short antisense compound targeted to a PTP1B nucleic acid or a pharmaceutical composition comprising such compound. Further provided are methods of treating a subject having a disease or conditions associated with PTP1B activity by administering a short antisense compound targeted to a PTP1B nucleic acid. Diseases and conditions associated with PTP1B include but are not limited to high blood glucose or hyperglycemia, prediabetes, diabetes, Type 2 diabetes, metabolic syndrome, obesity and insulin resistance. Therefore, provided herein are methods of treating to high blood glucose or hyperglycemia, prediabetes, diabetes, Type 2 diabetes, metabolic syndrome, obesity and insulin resistance by administering a short antisense compound targeted to a PTP1B nucleic acid.

In certain embodiments the present invention provides compositions and methods for decreasing blood glucose levels in a subject or for preventing or delaying the onset of a rise in blood glucose levels in a subject, by administering to the subject a short antisense inhibitor of PTP1B expression.

In certain embodiments, the present invention provides compositions and methods for improving insulin sensitivity in a subject or for preventing or delaying the onset of insulin resistance in a subject, by administering to the subject a short antisense inhibitor of PTP1B expression.

In certain embodiments, the present invention provides compositions and methods for treating a metabolic condition in a subject or for preventing or delaying the onset of a metabolic condition in a subject, by administering to the subject a short antisense compound targeted to a PTP1B nucleic acid. Such metabolic condition may be any metabolic condition associated with PTP1B expression, including but not limited to diabetes and obesity. Also provided are methods of reducing adiposity. Also provided is a method of treating obesity wherein metabolic rate is increased.

In certain embodiments, the subject has Type 2 diabetes. In certain embodiments the subject exhibits elevated HbA1c levels In certain embodiments, HbA1c levels are at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10% or at least about 11%. In preferred embodiments, HbA_{1c} levels are reduced to about 7% or below about 7%. In certain embodiments, the subject exhibits an elevated body mass index In certain embodiments, the elevated body mass index is greater than 25 kg/m2. In certain embodiments, the subject exhibits hyperglycemia or elevated blood glucose levels. In a particular embodiment, the blood glucose levels are fasting blood glucose levels. In certain embodiments, the elevated fasting blood glucose levels are at least 130 mg/dL. In certain embodiments, the subject exhibits hyperglycemia prior to the start of treatment or exhibits fasting blood glucose levels above about 130 mg/dL, baseline HbA_{1c} levels of at least about 7%, or body mass index of greater than 25 kg/m^2 or any combination thereof.

In certain embodiments a method of reducing one or more such levels by administering a short antisense compound targeted to a PTP1B nucleic acid is provided. For example, provided is a method of reducing fasting glucose levels, HbA_{1c} levels or, body mass index levels or any combination thereof in a subject by administering to a subject a short antisense compound targeting PTP1B. Fasting glucose may be fasting blood glucose, fasting serum glucose, or fasting plasma glucose. In some embodiments, fasting plasma glucose levels are reduced by at least about 25 mg/dL or by at least about 10 mg/dL. In a certain embodiments, said subject does not achieve normal glucose levels on a therapeutic regimen of a glucose-lowering agent such as insulin, sulfonylurea, or metformin.

In certain embodiments the invention provides methods of altering lipid levels. Certain such methods reduce cholesterol, LDL and/or VLDL levels or any combination thereof in a subject by administering to the subject a short antisense compound targeted to a PTP1B nucleic acid. In certain embodiments HDL levels in a subject are increased by administering to the subject a short antisense compound targeted to a PTP1B nucleic acid. In certain embodiments, LDL:HDL ratio and/or total cholesterol:HDL ratio in a subject is reduced by administering to the subject a short antisense compound targeted to a PTP1B nucleic acid. In certain embodiments HDL:LDL ratio and/or HDL:total cholesterol ratio in a subject's increased by administering to the subject a short antisense compound targeted to a PTP1B nucleic acid. In certain embodiments lipid profile in a subject is improved by increasing HDL, lowering LDL, lowering VLDL, lowering triglycerides, lowering apolipoprotein B levels, or lowering total cholesterol levels, or a combination thereof, by administering to the subject a short antisense compound targeted to a PTP1B nucleic acid . In such embodiments, the subject is an animal, including a human.

Combination Therapy

In certain embodiments, one or more pharmaceutical compositions comprising a short antisense compound targeted to a PTP1B nucleic acid are co-administered with one or more other pharmaceutical agents. In certain embodiments, such one or more other pharmaceutical agents are designed to treat the same disease or condition as the one or more pharmaceutical compositions of the present invention. In certain embodiments, such one or more other pharmaceutical agents are designed to treat a different disease or condition as the one or more pharmaceutical compositions of the present invention. In certain embodiments, such one or more other pharmaceutical agents are designed to treat an undesired effect of one or more pharmaceutical compositions of the present invention. In certain embodiments, one or more pharmaceutical compositions of the present invention are co-administered with another pharmaceutical agent to treat an undesired effect of that other pharmaceutical agent. In certain embodiments, one or more pharmaceutical compositions of the present invention and one or more other pharmaceutical agents are administered at the same time. In certain embodiments, one or more pharmaceutical compositions of the present invention and one or more other pharmaceutical agents are administered at different times. In certain embodiments, one or more pharmaceutical compositions of the present invention and one or more other pharmaceutical agents are prepared together in a single formulation. In certain embodiments, one or more pharmaceutical compositions of the present invention and one or more other pharmaceutical agents are prepared separately.

In certain embodiments, pharmaceutical agents that may be co-administered with a pharmaceutical composition comprising a short antisense compound targeted to a PTP1B nucleic acid include glucose-lowering agents and therapies. In some embodiments, the glucose-lowering agent is a PPAR agonist (gamma, dual, or pan), a dipeptidyl peptidase (IV) inhibitor, a GLP-1 analog, insulin or an insulin analog, an insulin secretagogue, a SGLT2 inhibitor, a human amylin analog, a biguanide, an alpha-glucosidase inhibitor, a meglitinide, a thiazolidinedione, or a sulfonylurea.

In some embodiments, the glucose-lowering therapeutic is a GLP-1 analog. In some embodiments, the GLP-1 analog is exendin-4 or liraglutide.

In other embodiments, the glucose-lowering therapeutic is a sulfonylurea. In some embodiments, the sulfonylurea is acetohexamide, chlorpropamide, tolbutamide, tolazamide, glimepiride, a glipizide, a glyburide, or a gliclazide.

In some embodiments, the glucose lowering drug is a biguanide. In some embodiments, the biguanide is metformin, and in some embodiments, blood glucose levels are decreased without increased lactic acidosis as compared to the lactic acidosis observed after treatment with metformin alone.

In some embodiments, the glucose lowering drug is a meglitinide. In some embodiments, the meglitinide is nateglinide or repaglinide.

In some embodiments, the glucose-lowering drug is a thiazolidinedione. In some embodiments, the thiazolidinedione is pioglitazone, rosiglitazone, or troglitazone. In some embodiments, blood glucose levels are decreased without greater weight gain than observed with rosiglitazone treatment alone.

In some embodiments, the glucose-lowering drug is an alpha-glucosidase inhibitor. In some embodiments, the alpha-glucosidase inhibitor is acarbose or miglitol.

In a certain embodiment, a co-administered glucose-lowering agent is ISIS 113715.

In a certain embodiment, glucose-lowering therapy is therapeutic lifestyle change.

In certain such embodiments, the glucose-lowering agent is administered prior to administration of a pharmaceutical composition of the present invention. In certain such embodiments, the glucose -lowering agent is administered following administration of a pharmaceutical composition of the present invention. In certain such embodiments the glucose -lowering agent is administered at the same time as a pharmaceutical composition of the present invention. In certain such embodiments the dose of a co-administered glucose - lowering agent is the same as the dose that would be administered if the glucose -lowering agent was administered alone. In certain such embodiments the dose of a co-administered glucose -lowering agent is lower than the dose that would be administered if the glucose -lowering agent was administered alone. In certain such embodiments the dose of a co-administered glucose -lowering agent is greater than the dose that would be administered if the glucose -lowering agent was administered alone.

In certain embodiments, pharmaceutical agents that may be co-administered with a pharmaceutical composition comprising a short antisense compound targeted to a PTP1B nucleic acid include lipid-lowering agents. Such lipid lowering agents are discussed elsewhere in the application and are included here with respect to PTP1B. Such lipid lowering agents may be administered as described above for glucose lowering agents.

In certain embodiments, pharmaceutical agents that may be co-administered with a pharmaceutical composition comprising a short antisense compound targeted to a PTP1B nucleic acid include anti-obesity agents therapeutics. Such anti-obesity agents therapeutics may be administered as described above for glucose lowering agents.

Further provided is a method of administering a short antisense compound targeted to a PTP1B nucleic acid via injection and further including administering a topical steroid at the injection site.

Medicaments

Also provided herein are uses of a short antisense compound which is targeted to a PTP1B nucleic acid for the preparation of a medicament for reducing blood glucose levels including fasting glucose levels, and HbA_{1c} levels, body mass index levels or any combination thereof. The medicament can be administered during a loading period and a maintenance period. In some embodiments, the medicament is administered subcutaneously or intravenously. In other embodiments, the administration of said medicament occurs at least once daily, at least once weekly, or at least once monthly. In a particular embodiment the short antisense compound present in the medicament is administered in a dose lower than a short antisense compound with a longer sequence and particularly a sequence 20 or more nucleobases. The medicament may be administered to a subject that exhibits high blood glucose or hyperglycemia, prediabetes, diabetes, Type 2 diabetes, metabolic syndrome, obesity and insulin resistance.

Other aspects and advantages of short antisense compounds are provided herein. All aspect and advantages disclosed herein and specifically with regard to other targets is applicable with regard to compositions including short antisense compounds targeted to a PTP1B nucleic acid and methods of their use.

Certain Short Antisense Compounds Targeted to a PTP1B Nucleic Acid

In certain embodiments, short antisense compounds are targeted to a PTP1B nucleic acid having the sequence of GENBANK® Accession No. NM_002827.2, incorporated herein as SEQ ID NO: 11 or the nucleotides 14178000 to 1425600 of the sequence of GENBANK® Accession No. NT_011362.9, incorporated herein as SEQ ID NO: 12. In certain such embodiments, a short antisense compound targeted to SEQ ID NO: 11 is at least 90% complementary to SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted to SEQ ID NO: 11 is at least 95% complementary to SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted to SEQ ID NO: 12 is 100% complementary to SEQ ID NO: 12. In certain such embodiments, a short antisense compound targeted to SEQ ID NO: 12 is at least 90% complementary to SEQ ID NO: 12. In certain such embodiments, a short antisense compound targeted to SEQ ID NO: 12 is at least 95% complementary to SEQ ID NO: 12. In certain such embodiments, a short antisense compound targeted to SEQ ID NO: 12 is 100% complementary to SEQ ID NO: 12.

In certain embodiments, a short antisense compound targeted to SEQ ID NO: 11 comprises a nucleotide sequence selected from the nucleotide sequences set forth in Tables 16 and 17. In certain embodiments, a short antisense compound targeted to SEQ ID NO: 12 comprises a nucleotide sequence selected from the nucleotide sequences set forth in Tables 18 and 19.

Each nucleotide sequence set forth in each Tables 16, 17, 18, and 19 is independent of any modification to a sugar moiety, an internucleoside linkage, or a nucleobase. As such, short antisense compounds comprising a nucleotide sequence as set forth in Tables 16, 17, 18, and 19 may comprise, independently, one or more modifications to a sugar moiety, an internucleoside linkage, or a nucleobase. Antisense compounds described by Isis Number (Isis NO.) indicate a combination of nucleobase sequence and one or more modifications to a sugar moiety, an internucleoside linkage, or a nucleobase.

Tables 16 and 17 illustrate examples of short antisense compounds targeted to SEQ ID NO: 11. Table 16 illustrates short antisense compounds that are 100% complementary to SEQ ID NO: 11. Table 17 illustrates short antisense compounds that have one or two mismatches with respect to SEQ ID NO: 11. Table 18 illustrates short antisense compounds that are 100% complementary to SEQ ID NO: 12. Table 19 illustrates short antisense compounds that have 1 or 2 mismatches with respect to SEQ ID NO: 12. The column labeled 'gapmer motif' indicates the wing-gap-wing motif of each short antisense compounds. The gap segment comprises 2'-deoxynucleotides and each nucleotide of each wing segment comprises a 2'-modified sugar. The particular 2'-modified sugar is also indicated in the 'gapmer motif' column. For example, '2-10-2 MOE' means a 2-10-2 gapmer motif, where a gap segment of ten 2'-deoxynucleotides is flanked by wing segments of two nucleotides, where the nucleotides of the wing segments are 2'-MOE nucleotides. Internucleoside linkages are phosphorothioate. The short antisense compounds comprise 5-methylcytidine in place of unmodified cytosine, unless "unmodified cytosine" is listed in the gapmer motif column, in which case the indicated cytosines are unmodified cytosines. For example, "5-mC in gap only" indicates that the gap segment has 5-methylcytosines, while the wing segments have unmodified cytosines.

Table 16: Short Antisense Compounds targeted to SEQ ID NO: 11

ISIS NO.	5' Target Site	3' Target Site	Sequence (5'-3')	Gapmer Motif	SEQ ID NO
147022	177	188	TTGTCGATCTCC	1-10-1 MOE	886
147023	178	189	CTTGTCGATCTC	1-10-1 MOE	859
147024	179	190	CCTTGTCGATCT	1-10-1 MOE	853
147019	195	206	TCGATCTCCTCG	1-10-1 MOE	877
147020	196	207	GTCGATCTCCTC	1-10-1 MOE	868
147021	197	208	TGTCGATCTCCT	1-10-1 MOE	882
147022	198	209	TTGTCGATCTCC	1-10-1 MOE	886
147023	199	210	CTTGTCGATCTC	1-10-1 MOE	859
147024	200	211	CCTTGTCGATCT	1-10-1 MOE	853
147025	201	212	GCCTTGTCGATC	1-10-1 MOE	865
147026	202	213	AGCCTTGTCGAT	1-10-1 MOE	835
147027	203	214	CAGCCTTGTCGA	1-10-1 MOE	843
147028	204	215	CCAGCCTTGTCG	1-10-1 MOE	846
147073	204	215	CACTGATCCTGC	1-10-1 MOE	842
147029	205	216	CCCAGCCTTGTC	1-10-1 MOE	848
147030	206	217	TCCCAGCCTTGT	1-10-1 MOE	874
147036	212	223	CCCAGTTCCCAG	1-10-1 MOE	849
147037	213	224	GCCCAGTTCCCA	1-10-1 MOE	863
147038	214	225	CGCCCAGTTCCC	1-10-1 MOE	855
147039	215	226	CCGCCCAGTTCC	1-10-1 MOE	850
147040	216	227	GCCGCCCAGTTC	1-10-1 MOE	864
147041	217	228	AGCCGCCCAGTT	1-10-1 MOE	834
147073	311	322	CACTGATCCTGC	1-10-1 MOE	842
147042	323	334	GGTCAAAAGGGC	1-10-1 MOE	866
147043	324	335	TGGTCAAAAGGG	1-10-1 MOE	881
147044	325	336	GTGGTCAAAAGG	1-10-1 MOE	869
147045	326	337	TGTGGTCAAAAG	1-10-1 MOE	883
147046	327	338	CTGTGGTCAAAA	1-10-1 MOE	858
147047	328	339	ACTGTGGTCAAA	1-10-1 MOE	833
147051	332	343	TCCGACTGTGGT	1-10-1 MOE	875
147052	333	344	ATCCGACTGTGG	1-10-1 MOE	837
147053	334	345	AATCCGACTGTG	1-10-1 MOE	829

147054	335	346	TAATCCGACTGT	1-10-1 MOE	871
147055	336	347	TTAATCCGACTG	1-10-1 MOE	884
147056	337	348	TTTAATCCGACT	1-10-1 MOE	887
147057	338	349	ATTTAATCCGAC	1-10-1 MOE	839
147058	339	350	AATTTAATCCGA	1-10-1 MOE	830
147059	340	351	CAATTTAATCCG	1-10-1 MOE	840
147060	341	352	GCAATTTAATCC	1-10-1 MOE	861
147061	342	353	TGCAATTTAATC	1-10-1 MOE	879
147045	679	690	TGTGGTCAAAAG	1-10-1 MOE	883
147046	680	691	CTGTGGTCAAAA	1-10-1 MOE	858
147045	787	798	TGTGGTCAAAAG	1-10-1 MOE	883
147046	788	799	CTGTGGTCAAAA	1-10-1 MOE	858
147066	816	827	CCTGCACTGACG	1-10-1 MOE	851
404131	992	1005	ACCTTCGATCACAG	2-10-2 MOE	831
147062	1024	1035	CACTGACGAGTC	1-10-1 MOE	841
147063	1025	1036	GCACTGACGAGT	1-10-1 MOE	862
147064	1026	1037	TGCACTGACGAG	1-10-1 MOE	880
147065	1027	1038	CTGCACTGACGA	1-10-1 MOE	857
147066	1028	1039	CCTGCACTGACG	1-10-1 MOE	851
147067	1029	1040	TCCTGCACTGAC	1-10-1 MOE	876
147068	1030	1041	ATCCTGCACTGA	1-10-1 MOE	838
147069	1031	1042	GATCCTGCACTG	1-10-1 MOE	860
147070	1032	1043	TGATCCTGCACT	1-10-1 MOE	878
147071	1033	1044	CTGATCCTGCAC	1-10-1 MOE	856
147072	1034	1045	ACTGATCCTGCA	1-10-1 MOE	832
147073	1035	1046	CACTGATCCTGC	1-10-1 MOE	842
147067	1199	1210	TCCTGCACTGAC	1-10-1 MOE	876
147040	1288	1299	GCCGCCCAGTTC	1-10-1 MOE	864
147040	1396	1407	GCCGCCCAGTTC	1-10-1 MOE	864
147022	1868	1879	TTGTCGATCTCC	1-10-1 MOE	886
147023	1869	1880	CTTGTCGATCTC	1-10-1 MOE	859
147024	1870	1881	CCTTGTCGATCT	1-10-1 MOE	853
147019	1886	1897	TCGATCTCCTCG	1-10-1 MOE	877
147020	1887	1898	GTCGATCTCCTC	1-10-1 MOE	868
147021	1888	1899	TGTCGATCTCCT	1-10-1 MOE	882
147022	1889	1900	TTGTCGATCTCC	1-10-1 MOE	886
147023	1890	1901	CTTGTCGATCTC	1-10-1 MOE	859
147025	1892	1903	GCCTTGTCGATC	1-10-1 MOE	865
147027	1894	1905	CAGCCTTGTCGA	1-10-1 MOE	843
147028	1895	1906	CCAGCCTTGTCG	1-10-1 MOE	846
147030	1897	1908	TCCCAGCCTTGT	1-10-1 MOE	874
147037	1904	1915	GCCCAGTTCCCA	1-10-1 MOE	863
147038	1905	1916	CGCCCAGTTCCC	1-10-1 MOE	855
147040	1907	1918	GCCGCCCAGTTC	1-10-1 MOE	864
147041	1908	1919	AGCCGCCCAGTT	1-10-1 MOE	834
147022	1976	1987	TTGTCGATCTCC	1-10-1 MOE	886
147023	1977	1988	CTTGTCGATCTC	1-10-1 MOE	859
147024	1978	1989	CCTTGTCGATCT	1-10-1 MOE	853
147020	1995	2006	GTCGATCTCCTC	1-10-1 MOE	868
147021	1996	2007	TGTCGATCTCCT	1-10-1 MOE	882

147022	1997	2008	TTGTCGATCTCC	1-10-1 MOE	886
147023	1998	2009	CTTGTCGATCTC	1-10-1 MOE	859
147024	1999	2010	CCTTGTCGATCT	1-10-1 MOE	853
147025	2000	2011	GCCTTGTCGATC	1-10-1 MOE	865
147026	2001	2012	AGCCTTGTCGAT	1-10-1 MOE	835
147027	2002	2013	CAGCCTTGTCGA	1-10-1 MOE	843
147028	2003	2014	CCAGCCTTGTCG	1-10-1 MOE	846
147029	2004	2015	CCCAGCCTTGTC	1-10-1 MOE	848
147030	2005	2016	TCCCAGCCTTGT	1-10-1 MOE	874
147036	2011	2022	CCCAGTTCCCAG	1-10-1 MOE	849
147037	2012	2023	GCCCAGTTCCCA	1-10-1 MOE	863
147038	2013	2024	CGCCCAGTTCCC	1-10-1 MOE	855
147039	2014	2025	CCGCCCAGTTCC	1-10-1 MOE	850
147040	2015	2026	GCCGCCCAGTTC	1-10-1 MOE	864
147041	2016	2027	AGCCGCCCAGTT	1-10-1 MOE	834
404199	2366	2379	GGTCATGCACAGGC	2-10-2 MOE	867
404134	2369	2382	TCAGGTCATGCACA	2-10-2 MOE	873
404132	2548	2561	CCTTGGAATGTCTG	2-10-2 MOE	852
147020	2613	2624	GTCGATCTCCTC	1-10-1 MOE	868
147020	2721	2732	GTCGATCTCCTC	1-10-1 MOE	868
404133	3289	3302	TATTCCATGGCCAT	2-10-2 MOE	872
147032	6220	6231	GTTCCCAGCCTT	1-10-1 MOE	870
147033	6221	6232	AGTTCCCAGCCT	1-10-1 MOE	836
147034	6222	6233	CAGTTCCCAGCC	1-10-1 MOE	844
147044	6288	6299	GTGGTCAAAAGG	1-10-1 MOE	869
147045	6289	6300	TGTGGTCAAAAG	1-10-1 MOE	883
147032	6329	6340	GTTCCCAGCCTT	1-10-1 MOE	870
147033	6330	6341	AGTTCCCAGCCT	1-10-1 MOE	836
147034	6331	6342	CAGTTCCCAGCC	1-10-1 MOE	844
147044	6397	6408	GTGGTCAAAAGG	1-10-1 MOE	869
147045	6398	6409	TGTGGTCAAAAG	1-10-1 MOE	883
147058	7057	7068	AATTTAATCCGA	1-10-1 MOE	830
147059	7058	7069	CAATTTAATCCG	1-10-1 MOE	840
147060	7059	7070	GCAATTTAATCC	1-10-1 MOE	861
147058	7166	7177	AATTTAATCCGA	1-10-1 MOE	830
147059	7167	7178	CAATTTAATCCG	1-10-1 MOE	840
147041	8084	8095	AGCCGCCCAGTT	1-10-1 MOE	834
147041	8192	8203	AGCCGCCCAGTT	1-10-1 MOE	834
147027	8630	8641	CAGCCTTGTCGA	1-10-1 MOE	843
147028	8631	8642	CCAGCCTTGTCG	1-10-1 MOE	846
147027	8738	8749	CAGCCTTGTCGA	1-10-1 MOE	843
147028	8739	8750	CCAGCCTTGTCG	1-10-1 MOE	846
147043	10957	10968	TGGTCAAAAGGG	1-10-1 MOE	881
147044	10958	10969	GTGGTCAAAAGG	1-10-1 MOE	869
147043	11065	11076	TGGTCAAAAGGG	1-10-1 MOE	881
147044	11066	11077	GTGGTCAAAAGG	1-10-1 MOE	869
147071	11605	11616	CTGATCCTGCAC	1-10-1 MOE	856
147070	11611	11622	TGATCCTGCACT	1-10-1 MOE	878
147071	11612	11623	CTGATCCTGCAC	1-10-1 MOE	856
147072	12294	12305	ACTGATCCTGCA	1-10-1 MOE	832

147072	12299	12310	ACTGATCCTGCA	1-10-1 MOE	832
147030	12805	12816	TCCCAGCCTTGT	1-10-1 MOE	874
147031	12806	12817	TTCCCAGCCTTG	1-10-1 MOE	885
147053	12939	12950	AATCCGACTGTG	1-10-1 MOE	829
147030	12986	12997	TCCCAGCCTTGT	1-10-1 MOE	874
147031	12987	12998	TTCCCAGCCTTG	1-10-1 MOE	885
147053	13120	13131	AATCCGACTGTG	1-10-1 MOE	829
147051	13162	13173	TCCGACTGTGGT	1-10-1 MOE	875
147061	13316	13327	TGCAATTTAATC	1-10-1 MOE	879
147047	13339	13350	ACTGTGGTCAAA	1-10-1 MOE	833
147029	14058	14069	CCCAGCCTTGTC	1-10-1 MOE	848
147029	14239	14250	CCCAGCCTTGTC	1-10-1 MOE	848
147067	15560	15571	TCCTGCACTGAC	1-10-1 MOE	876
147068	15561	15572	ATCCTGCACTGA	1-10-1 MOE	838
147067	15742	15753	TCCTGCACTGAC	1-10-1 MOE	876
147069	15744	15755	GATCCTGCACTG	1-10-1 MOE	860
147042	16561	16572	GGTCAAAAGGGC	1-10-1 MOE	866
147042	16727	16738	GGTCAAAAGGGC	1-10-1 MOE	866
147030	17619	17630	TCCCAGCCTTGT	1-10-1 MOE	874
147064	17762	17773	TGCACTGACGAG	1-10-1 MOE	880
147030	17787	17798	TCCCAGCCTTGT	1-10-1 MOE	874
147064	17930	17941	TGCACTGACGAG	1-10-1 MOE	880
147042	19201	19212	GGTCAAAAGGGC	1-10-1 MOE	866
147042	19369	19380	GGTCAAAAGGGC	1-10-1 MOE	866
147027	21190	21201	CAGCCTTGTCGA	1-10-1 MOE	843
147028	21191	21202	CCAGCCTTGTCG	1-10-1 MOE	846
147027	21358	21369	CAGCCTTGTCGA	1-10-1 MOE	843
147028	21359	21370	CCAGCCTTGTCG	1-10-1 MOE	846
147070	22021	22032	TGATCCTGCACT	1-10-1 MOE	878
147070	22189	22200	TGATCCTGCACT	1-10-1 MOE	878
147047	22606	22617	ACTGTGGTCAAA	1-10-1 MOE	833
147043	24318	24329	TGGTCAAAAGGG	1-10-1 MOE	881
147044	24319	24330	GTGGTCAAAAGG	1-10-1 MOE	869
147045	24320	24331	TGTGGTCAAAAG	1-10-1 MOE	883
147046	24321	24332	CTGTGGTCAAAA	1-10-1 MOE	858
147043	24486	24497	TGGTCAAAAGGG	1-10-1 MOE	881
147044	24487	24498	GTGGTCAAAAGG	1-10-1 MOE	869
147046	24489	24500	CTGTGGTCAAAA	1-10-1 MOE	858
147047	24490	24501	ACTGTGGTCAAA	1-10-1 MOE	833
147040	25065	25076	GCCGCCCAGTTC	1-10-1 MOE	864
147041	25066	25077	AGCCGCCCAGTT	1-10-1 MOE	834
147046	25160	25171	CTGTGGTCAAAA	1-10-1 MOE	858
147039	25232	25243	CCGCCCAGTTCC	1-10-1 MOE	850
147040	25233	25244	GCCGCCCAGTTC	1-10-1 MOE	864
147041	25234	25245	AGCCGCCCAGTT	1-10-1 MOE	834
147046	25328	25339	CTGTGGTCAAAA	1-10-1 MOE	858
147057	25508	25519	ATTTAATCCGAC	1-10-1 MOE	839
147061	25512	25523	TGCAATTTAATC	1-10-1 MOE	879
147057	25676	25687	ATTTAATCCGAC	1-10-1 MOE	839
147069	28878	28889	GATCCTGCACTG	1-10-1 MOE	860

147070	28879	28890	TGATCCTGCACT	1-10-1 MOE	878
147053	30133	30144	AATCCGACTGTG	1-10-1 MOE	829
147053	30278	30289	AATCCGACTGTG	1-10-1 MOE	829
147054	30864	30875	TAATCCGACTGT	1-10-1 MOE	871
147043	30985	30996	TGGTCAAAAGGG	1-10-1 MOE	881
147054	31011	31022	TAATCCGACTGT	1-10-1 MOE	871
147043	31133	31144	TGGTCAAAAGGG	1-10-1 MOE	881
147036	32233	32244	CCCAGTTCCCAG	1-10-1 MOE	849
147072	32372	32383	ACTGATCCTGCA	1-10-1 MOE	832
147072	32520	32531	ACTGATCCTGCA	1-10-1 MOE	832
147069	33056	33067	GATCCTGCACTG	1-10-1 MOE	860
147070	33057	33068	TGATCCTGCACT	1-10-1 MOE	878
147071	33058	33069	CTGATCCTGCAC	1-10-1 MOE	856
147051	33126	33137	TCCGACTGTGGT	1-10-1 MOE	875
147070	33205	33216	TGATCCTGCACT	1-10-1 MOE	878
147071	33206	33217	CTGATCCTGCAC	1-10-1 MOE	856
147051	33274	33285	TCCGACTGTGGT	1-10-1 MOE	875
147046	33318	33329	CTGTGGTCAAAA	1-10-1 MOE	858
147049	33321	33332	CGACTGTGGTCA	1-10-1 MOE	854
147051	33323	33334	TCCGACTGTGGT	1-10-1 MOE	875
147046	33466	33477	CTGTGGTCAAAA	1-10-1 MOE	858
147047	33467	33478	ACTGTGGTCAAA	1-10-1 MOE	833
147051	33471	33482	TCCGACTGTGGT	1-10-1 MOE	875
147046	33640	33651	CTGTGGTCAAAA	1-10-1 MOE	858
147051	33645	33656	TCCGACTGTGGT	1-10-1 MOE	875
147046	33788	33799	CTGTGGTCAAAA	1-10-1 MOE	858
147051	33793	33804	TCCGACTGTGGT	1-10-1 MOE	875
147059	35437	35448	CAATTTAATCCG	1-10-1 MOE	840
147060	35438	35449	GCAATTTAATCC	1-10-1 MOE	861
147060	35586	35597	GCAATTTAATCC	1-10-1 MOE	861
147021	36093	36104	TGTCGATCTCCT	1-10-1 MOE	882
147061	36250	36261	TGCAATTTAATC	1-10-1 MOE	879
147061	36398	36409	TGCAATTTAATC	1-10-1 MOE	879
147073	37485	37496	CACTGATCCTGC	1-10-1 MOE	842
147073	37633	37644	CACTGATCCTGC	1-10-1 MOE	842
147043	40214	40225	TGGTCAAAAGGG	1-10-1 MOE	881
147061	40353	40364	TGCAATTTAATC	1-10-1 MOE	879
147043	40362	40373	TGGTCAAAAGGG	1-10-1 MOE	881
147061	40501	40512	TGCAATTTAATC	1-10-1 MOE	879
147031	42527	42538	TTCCCAGCCTTG	1-10-1 MOE	885
147032	42528	42539	GTTCCCAGCCTT	1-10-1 MOE	870
147034	42530	42541	CAGTTCCCAGCC	1-10-1 MOE	844
147031	42675	42686	TTCCCAGCCTTG	1-10-1 MOE	885
147032	42676	42687	GTTCCCAGCCTT	1-10-1 MOE	870
147033	42677	42688	AGTTCCCAGCCT	1-10-1 MOE	836
147034	42678	42689	CAGTTCCCAGCC	1-10-1 MOE	844
147074	43848	43859	CCACTGATCCTG	1-10-1 MOE	845
147074	43996	44007	CCACTGATCCTG	1-10-1 MOE	845
147051	45402	45413	TCCGACTGTGGT	1-10-1 MOE	875
147051	45550	45561	TCCGACTGTGGT	1-10-1 MOE	875

147074	46125	46136	CCACTGATCCTG	1-10-1 MOE	845
147057	46313	46324	ATTTAATCCGAC	1-10-1 MOE	839
147058	46314	46325	AATTTAATCCGA	1-10-1 MOE	830
147059	46315	46326	CAATTTAATCCG	1-10-1 MOE	840
147061	46317	46328	TGCAATTTAATC	1-10-1 MOE	879
147057	46461	46472	ATTTAATCCGAC	1-10-1 MOE	839
147059	46463	46474	CAATTTAATCCG	1-10-1 MOE	840
147061	46465	46476	TGCAATTTAATC	1-10-1 MOE	879
147058	47413	47424	AATTTAATCCGA	1-10-1 MOE	830
147073	48221	48232	CACTGATCCTGC	1-10-1 MOE	842
147073	48369	48380	CACTGATCCTGC	1-10-1 MOE	842
147074	48370	48381	CCACTGATCCTG	1-10-1 MOE	845
147027	48566	48577	CAGCCTTGTCGA	1-10-1 MOE	843
147027	48714	48725	CAGCCTTGTCGA	1-10-1 MOE	843
147028	48715	48726	CCAGCCTTGTCG	1-10-1 MOE	846
147067	49050	49061	TCCTGCACTGAC	1-10-1 MOE	876
147068	49051	49062	ATCCTGCACTGA	1-10-1 MOE	838
147067	49198	49209	TCCTGCACTGAC	1-10-1 MOE	876
147073	49524	49535	CACTGATCCTGC	1-10-1 MOE	842
147073	49672	49683	CACTGATCCTGC	1-10-1 MOE	842
147074	49673	49684	CCACTGATCCTG	1-10-1 MOE	845
147036	50421	50432	CCCAGTTCCCAG	1-10-1 MOE	849
147036	52292	52303	CCCAGTTCCCAG	1-10-1 MOE	849
147037	52293	52304	GCCCAGTTCCCA	1-10-1 MOE	863
147036	52438	52449	CCCAGTTCCCAG	1-10-1 MOE	849
147037	52439	52450	GCCCAGTTCCCA	1-10-1 MOE	863
147034	53148	53159	CAGTTCCCAGCC	1-10-1 MOE	844
147034	53294	53305	CAGTTCCCAGCC	1-10-1 MOE	844
147042	53445	53456	GGTCAAAAGGGC	1-10-1 MOE	866
147043	53446	53457	TGGTCAAAAGGG	1-10-1 MOE	881
147044	53447	53458	GTGGTCAAAAGG	1-10-1 MOE	869
147042	53591	53602	GGTCAAAAGGGC	1-10-1 MOE	866
147030	53592	53603	TCCCAGCCTTGT	1-10-1 MOE	874
147043	53592	53603	TGGTCAAAAGGG	1-10-1 MOE	881
147031	53593	53604	TTCCCAGCCTTG	1-10-1 MOE	885
147044	53593	53604	GTGGTCAAAAGG	1-10-1 MOE	869
147030	53738	53749	TCCCAGCCTTGT	1-10-1 MOE	874
147031	53739	53750	TTCCCAGCCTTG	1-10-1 MOE	885
147040	53783	53794	GCCGCCCAGTTC	1-10-1 MOE	864
147041	53784	53795	AGCCGCCCAGTT	1-10-1 MOE	834
147041	53930	53941	AGCCGCCCAGTT	1-10-1 MOE	834
147042	55008	55019	GGTCAAAAGGGC	1-10-1 MOE	866
147043	55009	55020	TGGTCAAAAGGG	1-10-1 MOE	881
147042	55154	55165	GGTCAAAAGGGC	1-10-1 MOE	866
147043	55155	55166	TGGTCAAAAGGG	1-10-1 MOE	881
147058	55281	55292	AATTTAATCCGA	1-10-1 MOE	830
147058	55427	55438	AATTTAATCCGA	1-10-1 MOE	830
147019	55682	55693	TCGATCTCCTCG	1-10-1 MOE	877
147021	55684	55695	TGTCGATCTCCT	1-10-1 MOE	882
147021	55830	55841	TGTCGATCTCCT	1-10-1 MOE	882

147054	56275	56286	TAATCCGACTGT	1-10-1 MOE	871
147055	56276	56287	TTAATCCGACTG	1-10-1 MOE	884
147056	56277	56288	TTTAATCCGACT	1-10-1 MOE	887
147058	56279	56290	AATTTAATCCGA	1-10-1 MOE	830
147059	56280	56291	CAATTTAATCCG	1-10-1 MOE	840
147060	56281	56292	GCAATTTAATCC	1-10-1 MOE	861
147061	56282	56293	TGCAATTTAATC	1-10-1 MOE	879
147051	56418	56429	TCCGACTGTGGT	1-10-1 MOE	875
147053	56420	56431	AATCCGACTGTG	1-10-1 MOE	829
147054	56421	56432	TAATCCGACTGT	1-10-1 MOE	871
147055	56422	56433	TTAATCCGACTG	1-10-1 MOE	884
147056	56423	56434	TTTAATCCGACT	1-10-1 MOE	887
147057	56424	56435	ATTTAATCCGAC	1-10-1 MOE	839
147058	56425	56436	AATTTAATCCGA	1-10-1 MOE	830
147061	56428	56439	TGCAATTTAATC	1-10-1 MOE	879
147045	57118	57129	TGTGGTCAAAAG	1-10-1 MOE	883
147045	57264	57275	TGTGGTCAAAAG	1-10-1 MOE	883
147046	57265	57276	CTGTGGTCAAAA	1-10-1 MOE	858
147071	58028	58039	CTGATCCTGCAC	1-10-1 MOE	856
147071	58174	58185	CTGATCCTGCAC	1-10-1 MOE	856
147043	61111	61122	TGGTCAAAAGGG	1-10-1 MOE	881
147071	61130	61141	CTGATCCTGCAC	1-10-1 MOE	856
147020	61226	61237	GTCGATCTCCTC	1-10-1 MOE	868
147043	61257	61268	TGGTCAAAAGGG	1-10-1 MOE	881
147071	61276	61287	CTGATCCTGCAC	1-10-1 MOE	856
147035	61277	61288	CCAGTTCCCAGC	1-10-1 MOE	847
147036	61278	61289	CCCAGTTCCCAG	1-10-1 MOE	849
147037	61279	61290	GCCCAGTTCCCA	1-10-1 MOE	863
147038	61280	61291	CGCCCAGTTCCC	1-10-1 MOE	855
147039	61281	61292	CCGCCCAGTTCC	1-10-1 MOE	850
147040	61282	61293	GCCGCCCAGTTC	1-10-1 MOE	864
147071	61309	61320	CTGATCCTGCAC	1-10-1 MOE	856
147020	61372	61383	GTCGATCTCCTC	1-10-1 MOE	868
147034	61422	61433	CAGTTCCCAGCC	1-10-1 MOE	844
147035	61423	61434	CCAGTTCCCAGC	1-10-1 MOE	847
147036	61424	61435	CCCAGTTCCCAG	1-10-1 MOE	849
147037	61425	61436	GCCCAGTTCCCA	1-10-1 MOE	863
147038	61426	61437	CGCCCAGTTCCC	1-10-1 MOE	855
147040	61428	61439	GCCGCCCAGTTC	1-10-1 MOE	864
147071	61455	61466	CTGATCCTGCAC	1-10-1 MOE	856
147073	62003	62014	CACTGATCCTGC	1-10-1 MOE	842
147073	62149	62160	CACTGATCCTGC	1-10-1 MOE	842
147066	63065	63076	CCTGCACTGACG	1-10-1 MOE	851
147068	63067	63078	ATCCTGCACTGA	1-10-1 MOE	838
147069	63146	63157	GATCCTGCACTG	1-10-1 MOE	860
147062	63207	63218	CACTGACGAGTC	1-10-1 MOE	841
147066	63211	63222	CCTGCACTGACG	1-10-1 MOE	851
147057	64054	64065	ATTTAATCCGAC	1-10-1 MOE	839
147036	64538	64549	CCCAGTTCCCAG	1-10-1 MOE	849
147037	64539	64550	GCCCAGTTCCCA	1-10-1 MOE	863

147037	64685	64696	GCCCAGTTCCCA	1-10-1 MOE	863
147066	64864	64875	CCTGCACTGACG	1-10-1 MOE	851
147067	64865	64876	TCCTGCACTGAC	1-10-1 MOE	876
147066	65010	65021	CCTGCACTGACG	1-10-1 MOE	851
147067	65011	65022	TCCTGCACTGAC	1-10-1 MOE	876
147045	65017	65028	TGTGGTCAAAAG	1-10-1 MOE	883
147045	65163	65174	TGTGGTCAAAAG	1-10-1 MOE	883
147046	65164	65175	CTGTGGTCAAAA	1-10-1 MOE	858
147068	65408	65419	ATCCTGCACTGA	1-10-1 MOE	838
147071	65411	65422	CTGATCCTGCAC	1-10-1 MOE	856
147069	65549	65560	GATCCTGCACTG	1-10-1 MOE	860
147068	65554	65565	ATCCTGCACTGA	1-10-1 MOE	838
147071	65557	65568	CTGATCCTGCAC	1-10-1 MOE	856
147029	67741	67752	CCCAGCCTTGTC	1-10-1 MOE	848
147030	67742	67753	TCCCAGCCTTGT	1-10-1 MOE	874
147031	67743	67754	TTCCCAGCCTTG	1-10-1 MOE	885
147028	67886	67897	CCAGCCTTGTCG	1-10-1 MOE	846
147029	67887	67898	CCCAGCCTTGTC	1-10-1 MOE	848
147030	67888	67899	TCCCAGCCTTGT	1-10-1 MOE	874
147031	67889	67900	TTCCCAGCCTTG	1-10-1 MOE	885
147043	68867	68878	TGGTCAAAAGGG	1-10-1 MOE	881
147044	68868	68879	GTGGTCAAAAGG	1-10-1 MOE	869
147045	68869	68880	TGTGGTCAAAAG	1-10-1 MOE	883
147043	69013	69024	TGGTCAAAAGGG	1-10-1 MOE	881
147044	69014	69025	GTGGTCAAAAGG	1-10-1 MOE	869
147045	69015	69026	TGTGGTCAAAAG	1-10-1 MOE	883
147046	69016	69027	CTGTGGTCAAAA	1-10-1 MOE	858
147071	69519	69530	CTGATCCTGCAC	1-10-1 MOE	856
147072	69520	69531	ACTGATCCTGCA	1-10-1 MOE	832
147073	69521	69532	CACTGATCCTGC	1-10-1 MOE	842
147071	69665	69676	CTGATCCTGCAC	1-10-1 MOE	856
147072	69666	69677	ACTGATCCTGCA	1-10-1 MOE	832
147073	69667	69678	CACTGATCCTGC	1-10-1 MOE	842
147074	69668	69679	CCACTGATCCTG	1-10-1 MOE	845
147066	69869	69880	CCTGCACTGACG	1-10-1 MOE	851
147066	70015	70026	CCTGCACTGACG	1-10-1 MOE	851
147023	70465	70476	CTTGTCGATCTC	1-10-1 MOE	859
147023	70611	70622	CTTGTCGATCTC	1-10-1 MOE	859
147062	70615	70626	CACTGACGAGTC	1-10-1 MOE	841
147063	70616	70627	GCACTGACGAGT	1-10-1 MOE	862
147064	70617	70628	TGCACTGACGAG	1-10-1 MOE	880
147065	70618	70629	CTGCACTGACGA	1-10-1 MOE	857
147066	70619	70630	CCTGCACTGACG	1-10-1 MOE	851
147063	70762	70773	GCACTGACGAGT	1-10-1 MOE	862
147064	70763	70774	TGCACTGACGAG	1-10-1 MOE	880
147065	70764	70775	CTGCACTGACGA	1-10-1 MOE	857
147066	70765	70776	CCTGCACTGACG	1-10-1 MOE	851
147072	70998	71009	ACTGATCCTGCA	1-10-1 MOE	832
147073	70999	71010	CACTGATCCTGC	1-10-1 MOE	842
147072	71144	71155	ACTGATCCTGCA	1-10-1 MOE	832

147073	71145	71156	CACTGATCCTGC	1-10-1 MOE	842
147074	71146	71157	CCACTGATCCTG	1-10-1 MOE	845
147037	71351	71362	GCCCAGTTCCCA	1-10-1 MOE	863
147038	71352	71363	CGCCCAGTTCCC	1-10-1 MOE	855
147039	71353	71364	CCGCCCAGTTCC	1-10-1 MOE	850
147037	71497	71508	GCCCAGTTCCCA	1-10-1 MOE	863
147038	71498	71509	CGCCCAGTTCCC	1-10-1 MOE	855
147039	71499	71510	CCGCCCAGTTCC	1-10-1 MOE	850
147061	71641	71652	TGCAATTTAATC	1-10-1 MOE	879
147061	71787	71798	TGCAATTTAATC	1-10-1 MOE	879

Table 17: Short antisense compounds targeted to SEQ ID NO: 11 and having 1 or 2 mismatches

ISIS NO.	5' Target Site	3' Target Site	Sequence (5'-3')	Gapmer Motif	SEQ ID NO
147022	177	188	TTGTCGATCTCC	1-10-1 MOE	886
147023	178	189	CTTGTCGATCTC	1-10-1 MOE	859
147020	196	207	GTCGATCTCCTC	1-10-1 MOE	868
147022	198	209	TTGTCGATCTCC	1-10-1 MOE	886
147024	200	211	CCTTGTCGATCT	1-10-1 MOE	853
147026	202	213	AGCCTTGTCGAT	1-10-1 MOE	835
147028	204	215	CCAGCCTTGTCG	1-10-1 MOE	846
147029	205	216	CCCAGCCTTGTC	1-10-1 MOE	848
147030	206	217	TCCCAGCCTTGT	1-10-1 MOE	874
147036	212	223	CCCAGTTCCCAG	1-10-1 MOE	849
147073	311	322	CACTGATCCTGC	1-10-1 MOE	842
147046	327	338	CTGTGGTCAAAA	1-10-1 MOE	858
147047	328	339	ACTGTGGTCAAA	1-10-1 MOE	833
147048	329	340	GACTGTGGTCAA	1-10-1 MOE	888
147049	330	341	CGACTGTGGTCA	1-10-1 MOE	854
147050	331	342	CCGACTGTGGTC	1-10-1 MOE	889
147051	332	343	TCCGACTGTGGT	1-10-1 MOE	875
147052	333	344	ATCCGACTGTGG	1-10-1 MOE	837
147053	334	345	AATCCGACTGTG	1-10-1 MOE	829
147054	335	346	TAATCCGACTGT	1-10-1 MOE	871
147055	336	347	TTAATCCGACTG	1-10-1 MOE	884
147056	337	348	TTTAATCCGACT	1-10-1 MOE	887
147057	338	349	ATTTAATCCGAC	1-10-1 MOE	839
147058	339	350	AATTTAATCCGA	1-10-1 MOE	830
147060	341	352	GCAATTTAATCC	1-10-1 MOE	861
147061	342	353	TGCAATTTAATC	1-10-1 MOE	879
147062	1024	1035	CACTGACGAGTC	1-10-1 MOE	841
147063	1025	1036	GCACTGACGAGT	1-10-1 MOE	862
147068	1030	1041	ATCCTGCACTGA	1-10-1 MOE	838
147071	1033	1044	CTGATCCTGCAC	1-10-1 MOE	856
147073	1035	1046	CACTGATCCTGC	1-10-1 MOE	842
147074	1036	1047	CCACTGATCCTG	1-10-1 MOE	845
147067	1091	1102	TCCTGCACTGAC	1-10-1 MOE	876
147024	1891	1902	CCTTGTCGATCT	1-10-1 MOE	853

147026	1893	1904	AGCCTTGTCGAT	1-10-1 MOE	835
147029	1896	1907	CCCAGCCTTGTC	1-10-1 MOE	848
147036	1903	1914	CCCAGTTCCCAG	1-10-1 MOE	849
147039	1906	1917	CCGCCCAGTTCC	1-10-1 MOE	850
147019	1994	2005	TCGATCTCCTCG	1-10-1 MOE	877
401385	2815	2828	CCCAGTGGGTTTGA	2-10-2 MOE	890
147033	5265	5276	AGTTCCCAGCCT	1-10-1 MOE	836
147033	5373	5384	AGTTCCCAGCCT	1-10-1 MOE	836
147060	7168	7179	GCAATTTAATCC	1-10-1 MOE	861
147053	10527	10538	AATCCGACTGTG	1-10-1 MOE	829
147053	10635	10646	AATCCGACTGTG	1-10-1 MOE	829
147070	11604	11615	TGATCCTGCACT	1-10-1 MOE	878
147071	11612	11623	CTGATCCTGCAC	1-10-1 MOE	856
147072	12294	12305	ACTGATCCTGCA	1-10-1 MOE	832
147072	12299	12310	ACTGATCCTGCA	1-10-1 MOE	832
147052	12938	12949	ATCCGACTGTGG	1-10-1 MOE	837
147052	13119	13130	ATCCGACTGTGG	1-10-1 MOE	837
147047	13158	13169	ACTGTGGTCAAA	1-10-1 MOE	833
147048	13159	13170	GACTGTGGTCAA	1-10-1 MOE	888
147049	13160	13171	CGACTGTGGTCA	1-10-1 MOE	854
147048	13340	13351	GACTGTGGTCAA	1-10-1 MOE	888
147049	13341	13352	CGACTGTGGTCA	1-10-1 MOE	854
147051	13343	13354	TCCGACTGTGGT	1-10-1 MOE	875
147061	13497	13508	TGCAATTTAATC	1-10-1 MOE	879
147069	15562	15573	GATCCTGCACTG	1-10-1 MOE	860
147068	15743	15754	ATCCTGCACTGA	1-10-1 MOE	838
147049	17181	17192	CGACTGTGGTCA	1-10-1 MOE	854
147049	17349	17360	CGACTGTGGTCA	1-10-1 MOE	854
147047	22438	22449	ACTGTGGTCAAA	1-10-1 MOE	833
147047	24322	24333	ACTGTGGTCAAA	1-10-1 MOE	833
147045	24488	24499	TGTGGTCAAAAG	1-10-1 MOE	883
147039	25064	25075	CCGCCCAGTTCC	1-10-1 MOE	850
147057	25508	25519	ATTTAATCCGAC	1-10-1 MOE	839
147057	25676	25687	ATTTAATCCGAC	1-10-1 MOE	839
147061	25680	25691	TGCAATTTAATC	1-10-1 MOE	879
147069	28731	28742	GATCCTGCACTG	1-10-1 MOE	860
147052	30132	30143	ATCCGACTGTGG	1-10-1 MOE	837
147052	30277	30288	ATCCGACTGTGG	1-10-1 MOE	837
147036	32085	32096	CCCAGTTCCCAG	1-10-1 MOE	849
147072	32520	32531	ACTGATCCTGCA	1-10-1 MOE	832
147071	33058	33069	CTGATCCTGCAC	1-10-1 MOE	856
147050	33125	33136	CCGACTGTGGTC	1-10-1 MOE	889
147069	33204	33215	GATCCTGCACTG	1-10-1 MOE	860
147050	33273	33284	CCGACTGTGGTC	1-10-1 MOE	889
147047	33319	33330	ACTGTGGTCAAA	1-10-1 MOE	833
147050	33322	33333	CCGACTGTGGTC	1-10-1 MOE	889
147052	33324	33335	ATCCGACTGTGG	1-10-1 MOE	837
147049	33469	33480	CGACTGTGGTCA	1-10-1 MOE	854
147050	33470	33481	CCGACTGTGGTC	1-10-1 MOE	889
147052	33472	33483	ATCCGACTGTGG	1-10-1 MOE	837

147047	33641	33652	ACTGTGGTCAAA	1-10-1 MOE	833
147047	33789	33800	ACTGTGGTCAAA	1-10-1 MOE	833
147059	35585	35596	CAATTTAATCCG	1-10-1 MOE	840
147021	36241	36252	TGTCGATCTCCT	1-10-1 MOE	882
147073	37633	37644	CACTGATCCTGC	1-10-1 MOE	842
147033	42529	42540	AGTTCCCAGCCT	1-10-1 MOE	836
147050	45401	45412	CCGACTGTGGTC	1-10-1 MOE	889
147050	45549	45560	CCGACTGTGGTC	1-10-1 MOE	889
147074	46125	46136	CCACTGATCCTG	1-10-1 MOE	845
147057	46313	46324	ATTTAATCCGAC	1-10-1 MOE	839
147058	46462	46473	AATTTAATCCGA	1-10-1 MOE	830
147058	47413	47424	AATTTAATCCGA	1-10-1 MOE	830
147058	47561	47572	AATTTAATCCGA	1-10-1 MOE	830
147073	48221	48232	CACTGATCCTGC	1-10-1 MOE	842
147073	48369	48380	CACTGATCCTGC	1-10-1 MOE	842
147028	48567	48578	CCAGCCTTGTCG	1-10-1 MOE	846
147068	49199	49210	ATCCTGCACTGA	1-10-1 MOE	838
147036	50273	50284	CCCAGTTCCCAG	1-10-1 MOE	849
147040	53929	53940	GCCGCCCAGTTC	1-10-1 MOE	864
147047	54769	54780	ACTGTGGTCAAA	1-10-1 MOE	833
147048	54770	54781	GACTGTGGTCAA	1-10-1 MOE	888
147047	54915	54926	ACTGTGGTCAAA	1-10-1 MOE	833
147048	54916	54927	GACTGTGGTCAA	1-10-1 MOE	888
147019	55828	55839	TCGATCTCCTCG	1-10-1 MOE	877
147047	56268	56279	ACTGTGGTCAAA	1-10-1 MOE	833
147048	56269	56280	GACTGTGGTCAA	1-10-1 MOE	888
147049	56270	56281	CGACTGTGGTCA	1-10-1 MOE	854
147050	56271	56282	CCGACTGTGGTC	1-10-1 MOE	889
147051	56272	56283	TCCGACTGTGGT	1-10-1 MOE	875
147052	56273	56284	ATCCGACTGTGG	1-10-1 MOE	837
147053	56274	56285	AATCCGACTGTG	1-10-1 MOE	829
147056	56277	56288	TTTAATCCGACT	1-10-1 MOE	887
147057	56278	56289	ATTTAATCCGAC	1-10-1 MOE	839
147047	56414	56425	ACTGTGGTCAAA	1-10-1 MOE	833
147048	56415	56426	GACTGTGGTCAA	1-10-1 MOE	888
147049	56416	56427	CGACTGTGGTCA	1-10-1 MOE	854
147050	56417	56428	CCGACTGTGGTC	1-10-1 MOE	889
147052	56419	56430	ATCCGACTGTGG	1-10-1 MOE	837
147057	56424	56435	ATTTAATCCGAC	1-10-1 MOE	839
147058	56425	56436	AATTTAATCCGA	1-10-1 MOE	830
147059	56426	56437	CAATTTAATCCG	1-10-1 MOE	840
147060	56427	56438	GCAATTTAATCC	1-10-1 MOE	861
147046	57119	57130	CTGTGGTCAAAA	1-10-1 MOE	858
147071	58174	58185	CTGATCCTGCAC	1-10-1 MOE	856
147071	61130	61141	CTGATCCTGCAC	1-10-1 MOE	856
147034	61276	61287	CAGTTCCCAGCC	1-10-1 MOE	844
147071	61309	61320	CTGATCCTGCAC	1-10-1 MOE	856
147039	61427	61438	CCGCCCAGTTCC	1-10-1 MOE	850
147071	61455	61466	CTGATCCTGCAC	1-10-1 MOE	856
147073	62003	62014	CACTGATCCTGC	1-10-1 MOE	842

147062	63061	63072	CACTGACGAGTC	1-10-1 MOE	841
147068	63213	63224	ATCCTGCACTGA	1-10-1 MOE	838
147069	63292	63303	GATCCTGCACTG	1-10-1 MOE	860
147057	64054	64065	ATTTAATCCGAC	1-10-1 MOE	839
147057	64200	64211	ATTTAATCCGAC	1-10-1 MOE	839
147070	64427	64438	TGATCCTGCACT	1-10-1 MOE	878
147070	64573	64584	TGATCCTGCACT	1-10-1 MOE	878
147036	64684	64695	CCCAGTTCCCAG	1-10-1 MOE	849
147046	65018	65029	CTGTGGTCAAAA	1-10-1 MOE	858
147071	65557	65568	CTGATCCTGCAC	1-10-1 MOE	856
147069	65695	65706	GATCCTGCACTG	1-10-1 MOE	860
147047	66163	66174	ACTGTGGTCAAA	1-10-1 MOE	833
147047	66309	66320	ACTGTGGTCAAA	1-10-1 MOE	833
147028	67740	67751	CCAGCCTTGTCG	1-10-1 MOE	846
147046	68870	68881	CTGTGGTCAAAA	1-10-1 MOE	858
147047	68871	68882	ACTGTGGTCAAA	1-10-1 MOE	833
147048	68872	68883	GACTGTGGTCAA	1-10-1 MOE	888
147049	68873	68884	CGACTGTGGTCA	1-10-1 MOE	854
147047	69017	69028	ACTGTGGTCAAA	1-10-1 MOE	833
147048	69018	69029	GACTGTGGTCAA	1-10-1 MOE	888
147049	69019	69030	CGACTGTGGTCA	1-10-1 MOE	854
147071	69519	69530	CTGATCCTGCAC	1-10-1 MOE	856
147073	69521	69532	CACTGATCCTGC	1-10-1 MOE	842
147071	69665	69676	CTGATCCTGCAC	1-10-1 MOE	856
147072	69666	69677	ACTGATCCTGCA	1-10-1 MOE	832
147024	70466	70477	CCTTGTCGATCT	1-10-1 MOE	853
147024	70612	70623	CCTTGTCGATCT	1-10-1 MOE	853
147062	70761	70772	CACTGACGAGTC	1-10-1 MOE	841
147072	70998	71009	ACTGATCCTGCA	1-10-1 MOE	832
147073	70999	71010	CACTGATCCTGC	1-10-1 MOE	842
147072	71144	71155	ACTGATCCTGCA	1-10-1 MOE	832
147073	71145	71156	CACTGATCCTGC	1-10-1 MOE	842
147048	71366	71377	GACTGTGGTCAA	1-10-1 MOE	888
147048	71512	71523	GACTGTGGTCAA	1-10-1 MOE	888

Table 18: Short Antisense Compounds targeted to SEQ ID NO: 12

ISIS NO.	5' Target Site	3' Target Site	Sequence (5'-3')	Gapmer Motif	Seq ID NO
398163	20	31	ATGTCAACCGGC	1-10-1 MOE	908
384545	23	34	CAAGTAGGATGT	1-10-1 MOE	951
147705	159	170	CGGTTTTTGTTC	1-10-1 MOE	1002
147703	245	256	TGGCTTCATGTC	1-10-1 MOE	971
398090	283	296	TTGTTCTTAGGAAG	2-10-2 MOE	972
147704	285	296	TTGTTCTTAGGA	1-10-1 MOE	1012
147705	291	302	CGGTTTTTGTTC	1-10-1 MOE	1002
147709	311	322	CCATTTTTATCA	1-10-1 MOE	978
147733	349	360	TTCTTGATGTCC	1-10-1 MOE	891

147707	360	371	TAGTCATTATCT	1-10-1 MOE	977
147708	366	377	TTGATATAGTCA	1-10-1 MOE	997
390030	381	392	TTTATAAAACTG	1-10-1 MOE	1074
147709	386	397	CCATTTTTATCA	1-10-1 MOE	978
147081	393	404	GCTCCTTCCACT	1-10-1 MOE	1006
398091	393	406	GGGCTTCTTCCATT	2-10-2 MOE	979
398166	395	406	GGGCTTCTTCCA	1-10-1 MOE	1070
147709	418	429	CCATTTTTATCA	1-10-1 MOE	978
147711	425	436	AAGGGCCCTGGG	1-10-1 MOE	1040
147712	461	472	ACACCATCTCCC	1-10-1 MOE	1005
147713	466	477	CTCCCACACCAT	1-10-1 MOE	985
147714	471	482	TTCTGCTCCCAC	1-10-1 MOE	986
147715	496	507	GTTGAGCATGAC	1-10-1 MOE	1077
147716	521	532	TTAACGAGCCTT	1-10-1 MOE	949
147717	574	585	ATCTTCAGAGAT	1-10-1 MOE	996
147717	607	618	ATCTTCAGAGAT	1-10-1 MOE	996
147708	612	623	TTGATATAGTCA	1-10-1 MOE	997
147718	621	632	TAATATGACTTG	1-10-1 MOE	998
147746	625	636	TAAAAACAACAA	1-10-1 MOE	1073
398167	704	715	CAGGCCATGTGG	1-10-1 MOE	1059
398092	705	718	AGTCAGGCCATGTG	2-10-2 MOE	1060
147723	715	726	GACTCCAAAGTC	1-10-1 MOE	892
398093	758	771	TCGGACTTTGAAAA	2-10-2 MOE	1009
398168	760	771	TCGGACTTTGAA	1-10-1 MOE	1008
147738	780	791	TGGGTGGCCGGG	1-10-1 MOE	1069
398094	848	861	ATCAGCCAGACAGA	2-10-2 MOE	1010
398169	849	860	TCAGCCAGACAG	1-10-1 MOE	909
398164	873	884	TTGTCGATCTGC	1-10-1 MOE	1014
147735	973	984	GGAGAAGCGCAG	1-10-1 MOE	1016
147737	984	995	ACAGCCAGGTAG	1-10-1 MOE	1067
368369	1025	1040	TCCTGCACTGACGAGT	3-10-3 MOE	893
368372	1031	1046	CACTGATCCTGCACTG	3-10-3 MOE	894
368353	1033	1046	CACTGATCCTGCAC	2-10-2 MOE	1007
368354	1035	1048	TCCACTGATCCTGC	2-10-2 MOE	1024
368388	1035	1050	CTTCCACTGATCCTTA	3-10-3 MOE	895
368355	1036	1049	TTCCACTGATCCTG	2-10-2 MOE	1025
368356	1037	1050	CTTCCACTGATCCT	2-10-2 MOE	1027
368376	1037	1052	TCCTTCCACTGATCCT	3-10-3 MOE	1028
147076	1038	1049	TTCCACTGATCC	1-10-1 MOE	1029
368357	1038	1051	CCTTCCACTGATCC	2-10-2 MOE	1046
147077	1039	1050	CTTCCACTGATC	1-10-1 MOE	1047
368358	1039	1052	TCCTTCCACTGATC	2-10-2 MOE	1031
368378	1039	1054	GCTCCTTCCACTGATC	3-10-3 MOE	1032
368359	1041	1054	GCTCCTTCCACTGA	2-10-2 MOE	1033
147080	1042	1053	CTCCTTCCACTG	1-10-1 MOE	1021
147081	1043	1054	GCTCCTTCCACT	1-10-1 MOE	1006
368360	1043	1056	AAGCTCCTTCCACT	2-10-2 MOE	1035
368380	1043	1058	GAAAGCTCCTTCCACT	3-10-3 MOE	896
147082	1044	1055	AGCTCCTTCCAC	1-10-1 MOE	1036
368381	1045	1060	GGGAAAGCTCCTTCCA	3-10-3 MOE	1037

147739	1107	1118	CGTTTGGGTGGC	1-10-1 MOE	1023
147741	1165	1176	CACCCACTGGTG	1-10-1 MOE	1055
398097	1194	1207	GGCAGTCTTTATCC	2-10-2 MOE	897
147742	1273	1284	AACTTCAGTGTC	1-10-1 MOE	1041
147743	1388	1399	AGGGCTTCCAGT	1-10-1 MOE	1042
147744	1392	1403	AGGAAGGGCTTC	1-10-1 MOE	1043
147745	1398	1409	TTGACCAGGAAG	1-10-1 MOE	1058
398157	1455	1468	GGAAACATACCCTG	2-10-2 MOE	1045
398167	1475	1486	CAGGCCATGTGG	1-10-1 MOE	1059
398092	1476	1489	AGTCAGGCCATGTG	2-10-2 MOE	1060
368357	1596	1609	CCTTCCACTGATCC	2-10-2 MOE	1046
398160	1691	1704	GAATAGGTTAAGGC	2-10-2 MOE	1048
398163	1711	1722	ATGTCAACCGGC	1-10-1 MOE	908
147746	1750	1761	TAAAAACAACAA	1-10-1 MOE	1073
389949	1777	1788	GCGCGAGCCCGA	1-10-1 MOE	1061
398161	1790	1803	AACAATGTGTTGTA	2-10-2 MOE	1049
147746	1799	1810	TAAAAACAACAA	1-10-1 MOE	1073
398163	1819	1830	ATGTCAACCGGC	1-10-1 MOE	908
389950	1848	1859	CCCTGAAGGTTC	1-10-1 MOE	1063
398164	1889	1900	TTGTCGATCTGC	1-10-1 MOE	1014
147702	1917	1928	CTGGTAAATAGC	1-10-1 MOE	898
147088	1971	1982	CCCTCTACACCA	1-10-1 MOE	1050
398102	2003	2016	CTACCTGAGGATTT	2-10-2 MOE	899
398103	2010	2023	CCCAGTACTACCTG	2-10-2 MOE	900
147737	2386	2397	ACAGCCAGGTAG	1-10-1 MOE	1067
398095	2407	2420	CATCAGCAAGAGGC	2-10-2 MOE	1011
398106	2441	2454	TGGAAAACTGCACC	2-10-2 MOE	1068
147745	2497	2508	TTGACCAGGAAG	1-10-1 MOE	1058
147712	2499	2510	ACACCATCTCCC	1-10-1 MOE	1005
147712	2607	2618	ACACCATCTCCC	1-10-1 MOE	1005
147745	2689	2700	TTGACCAGGAAG	1-10-1 MOE	1058
398167	2706	2717	CAGGCCATGTGG	1-10-1 MOE	1059
398092	2707	2720	AGTCAGGCCATGTG	2-10-2 MOE	1060
398166	2966	2977	GGGCTTCTTCCA	1-10-1 MOE	1070
147091	2992	3003	GTTCCCTCTACA	1-10-1 MOE	1004
147092	2993	3004	TGTTCCCTCTAC	1-10-1 MOE	901
389949	3008	3019	GCGCGAGCCCGA	1-10-1 MOE	1061
147087	3149	3160	CCTCTACACCAG	1-10-1 MOE	982
147088	3150	3161	CCCTCTACACCA	1-10-1 MOE	1050
398113	3160	3173	AGGAGGTTAAACCA	2-10-2 MOE	905
147087	3257	3268	CCTCTACACCAG	1-10-1 MOE	982
147088	3258	3269	CCCTCTACACCA	1-10-1 MOE	1050
147737	3591	3602	ACAGCCAGGTAG	1-10-1 MOE	1067
147737	3617	3628	ACAGCCAGGTAG	1-10-1 MOE	1067
147079	3637	3648	TCCTTCCACTGA	1-10-1 MOE	1001
147080	3638	3649	CTCCTTCCACTG	1-10-1 MOE	1021
398095	3638	3651	CATCAGCAAGAGGC	2-10-2 MOE	1011
398106	3672	3685	TGGAAAACTGCACC	2-10-2 MOE	1068
398107	3678	3691	TATTCCTGGAAAAC	2-10-2 MOE	902
147691	3806	3817	GAGGTGGGAAAA	1-10-1 MOE	966

147683	3848	3859	GCTTACGATTGT	1-10-1 MOE	922
147738	3853	3864	TGGGTGGCCGGG	1-10-1 MOE	1069
398167	3926	3937	CAGGCCATGTGG	1-10-1 MOE	1059
398109	3945	3958	CAAGAAGTGTGGTT	2-10-2 MOE	903
398167	4034	4045	CAGGCCATGTGG	1-10-1 MOE	1059
398110	4083	4096	GTTCCCTTTGCAGG	2-10-2 MOE	952
398111	4168	4181	GTGAAAATGCTGGC	2-10-2 MOE	904
147706	4238	4249	GCTGACATCTCG	1-10-1 MOE	1071
398112	4282	4295	CAGCCTGGCACCTA	2-10-2 MOE	1072
147746	4315	4326	TAAAAACAACAA	1-10-1 MOE	1073
398113	4391	4404	AGGAGGTTAAACCA	2-10-2 MOE	905
398115	4484	4497	AGTAAATATTGGCT	2-10-2 MOE	1076
390030	4491	4502	TTTATAAAACTG	1-10-1 MOE	1074
390030	4537	4548	TTTATAAAACTG	1-10-1 MOE	1074
147703	5034	5045	TGGCTTCATGTC	1-10-1 MOE	971
147684	5035	5046	ACCCAGTCAGGG	1-10-1 MOE	964
398125	5075	5088	CAGTAAGGAATTTT	2-10-2 MOE	913
147696	5083	5094	TGGATGATTGGC	1-10-1 MOE	906
147684	5143	5154	ACCCAGTCAGGG	1-10-1 MOE	964
147712	5366	5377	ACACCATCTCCC	1-10-1 MOE	1005
147714	5416	5427	TTCTGCTCCCAC	1-10-1 MOE	986
398128	5443	5456	CTAAATTTAGTTCA	2-10-2 MOE	911
147712	5474	5485	ACACCATCTCCC	1-10-1 MOE	1005
147746	5498	5509	TAAAAACAACAA	1-10-1 MOE	1073
147714	5524	5535	TTCTGCTCCCAC	1-10-1 MOE	986
147736	5600	5611	AGGTAGGAGAAG	1-10-1 MOE	963
147085	5762	5773	TCTACACCAGGT	1-10-1 MOE	961
147679	5825	5836	CAAAAGGATCCC	1-10-1 MOE	907
390030	6803	6814	TTTATAAAACTG	1-10-1 MOE	1074
398142	6885	6898	CCAGCACACTGGAA	2-10-2 MOE	923
398142	6994	7007	CCAGCACACTGGAA	2-10-2 MOE	923
398166	7306	7317	GGGCTTCTTCCA	1-10-1 MOE	1070
147684	7551	7562	ACCCAGTCAGGG	1-10-1 MOE	964
147085	8308	8319	TCTACACCAGGT	1-10-1 MOE	961
147085	8416	8427	TCTACACCAGGT	1-10-1 MOE	961
398163	8473	8484	ATGTCAACCGGC	1-10-1 MOE	908
147718	8523	8534	TAATATGACTTG	1-10-1 MOE	998
147718	8631	8642	TAATATGACTTG	1-10-1 MOE	998
147691	8806	8817	GAGGTGGGAAAA	1-10-1 MOE	966
147728	8835	8846	GCCAGACAGAAG	1-10-1 MOE	1013
147728	8943	8954	GCCAGACAGAAG	1-10-1 MOE	1013
398169	8946	8957	TCAGCCAGACAG	1-10-1 MOE	909
147742	9060	9071	AACTTCAGTGTC	1-10-1 MOE	1041
404136	9162	9175	TAAGTGTCCCTTTG	2-10-2 MOE	910
147746	9963	9974	TAAAAACAACAA	1-10-1 MOE	1073
147746	9966	9977	TAAAAACAACAA	1-10-1 MOE	1073
147746	9969	9980	TAAAAACAACAA	1-10-1 MOE	1073
147746	9991	10002	TAAAAACAACAA	1-10-1 MOE	1073
147746	10071	10082	TAAAAACAACAA	1-10-1 MOE	1073
147746	10074	10085	TAAAAACAACAA	1-10-1 MOE	1073

147746	10077	10088	TAAAAACAACAA	1-10-1 MOE	1073
390030	10170	10181	TTTATAAAACTG	1-10-1 MOE	1074
147084	10220	10231	CTACACCAGGTC	1-10-1 MOE	993
390030	10278	10289	TTTATAAAACTG	1-10-1 MOE	1074
147085	10329	10340	TCTACACCAGGT	1-10-1 MOE	961
147711	10684	10695	AAGGGCCCTGGG	1-10-1 MOE	1040
147711	10792	10803	AAGGGCCCTGGG	1-10-1 MOE	1040
398128	11333	11346	CTAAATTTAGTTCA	2-10-2 MOE	911
147707	11960	11971	TAGTCATTATCT	1-10-1 MOE	977
147707	11965	11976	TAGTCATTATCT	1-10-1 MOE	977
147090	12013	12024	TTCCCTCTACAC	1-10-1 MOE	955
398096	12146	12159	GGAGAAGCGCAGCT	2-10-2 MOE	1015
398166	12214	12225	GGGCTTCTTCCA	1-10-1 MOE	1070
398135	12308	12321	GACTACATTTTACA	2-10-2 MOE	912
147741	12389	12400	CACCCACTGGTG	1-10-1 MOE	1055
398125	12431	12444	CAGTAAGGAATTTT	2-10-2 MOE	913
147714	12585	12596	TTCTGCTCCCAC	1-10-1 MOE	986
147718	12594	12605	TAATATGACTTG	1-10-1 MOE	998
398125	12612	12625	CAGTAAGGAATTTT	2-10-2 MOE	913
147737	12803	12814	ACAGCCAGGTAG	1-10-1 MOE	1067
147746	12876	12887	TAAAAACAACAA	1-10-1 MOE	1073
147691	12900	12911	GAGGTGGGAAAA	1-10-1 MOE	966
398137	13111	13124	TGTGTCCCTCAGTC	2-10-2 MOE	914
398138	13254	13267	AACATCAAGCTTGA	2-10-2 MOE	931
398137	13292	13305	TGTGTCCCTCAGTC	2-10-2 MOE	914
398138	13435	13448	AACATCAAGCTTGA	2-10-2 MOE	931
389764	14020	14031	CTGCAACATGAT	1-9-2 MOE	1018
389948	14067	14078	CCGTTGGACCCC	1-10-1 MOE	915
389948	14248	14259	CCGTTGGACCCC	1-10-1 MOE	915
147738	14279	14290	TGGGTGGCCGGG	1-10-1 MOE	1069
147698	14572	14583	CCCGCCACCACC	1-10-1 MOE	928
147717	14750	14761	ATCTTCAGAGAT	1-10-1 MOE	996
147717	14932	14943	ATCTTCAGAGAT	1-10-1 MOE	996
398167	15374	15385	CAGGCCATGTGG	1-10-1 MOE	1059
147736	16444	16455	AGGTAGGAGAAG	1-10-1 MOE	963
147746	16510	16521	TAAAAACAACAA	1-10-1 MOE	1073
147738	16590	16601	TGGGTGGCCGGG	1-10-1 MOE	1069
147746	16676	16687	TAAAAACAACAA	1-10-1 MOE	1073
398167	16797	16808	CAGGCCATGTGG	1-10-1 MOE	1059
398144	16911	16924	GACAGCTTCTATAA	2-10-2 MOE	916
389764	17096	17107	CTGCAACATGAT	1-9-2 MOE	1018
147709	17238	17249	CCATTTTTATCA	1-10-1 MOE	978
147709	17406	17417	CCATTTTTATCA	1-10-1 MOE	978
147695	17466	17477	TCATTCCCCACT	1-10-1 MOE	984
147746	17497	17508	TAAAAACAACAA	1-10-1 MOE	1073
147088	17539	17550	CCCTCTACACCA	1-10-1 MOE	1050
147711	17808	17819	AAGGGCCCTGGG	1-10-1 MOE	1040
147711	17976	17987	AAGGGCCCTGGG	1-10-1 MOE	1040
398139	18049	18062	AGTGACTGACCACA	2-10-2 MOE	917
398139	18217	18230	AGTGACTGACCACA	2-10-2 MOE	917

398140	18596	18609	GTAGCATAGAGCCT	2-10-2 MOE	918
398140	18764	18777	GTAGCATAGAGCCT	2-10-2 MOE	918
398167	18927	18938	CAGGCCATGTGG	1-10-1 MOE	1059
398141	18947	18960	CAGATCTTGTCAAG	2-10-2 MOE	919
398167	19095	19106	CAGGCCATGTGG	1-10-1 MOE	1059
398141	19115	19128	CAGATCTTGTCAAG	2-10-2 MOE	919
147746	19207	19218	TAAAAACAACAA	1-10-1 MOE	1073
147711	19508	19519	AAGGGCCCTGGG	1-10-1 MOE	1040
147729	19554	19565	GTAAGAGGCAGG	1-10-1 MOE	920
147718	19617	19628	TAATATGACTTG	1-10-1 MOE	998
390030	19618	19629	TTTATAAAACTG	1-10-1 MOE	1074
147701	19671	19682	CCATGGCGGGAC	1-10-1 MOE	921
147711	19676	19687	AAGGGCCCTGGG	1-10-1 MOE	1040
147718	19785	19796	TAATATGACTTG	1-10-1 MOE	998
147079	20515	20526	TCCTTCCACTGA	1-10-1 MOE	1001
389764	20620	20631	CTGCAACATGAT	1-9-2 MOE	1018
398142	20653	20666	CCAGCACACTGGAA	2-10-2 MOE	923
147078	20682	20693	CCTTCCACTGAT	1-10-1 MOE	1044
147079	20683	20694	TCCTTCCACTGA	1-10-1 MOE	1001
147080	20704	20715	CTCCTTCCACTG	1-10-1 MOE	1021
147081	20705	20716	GCTCCTTCCACT	1-10-1 MOE	1006
389965	20788	20799	CTGCAACATGAT	1-10-1 MOE	1018
147746	20870	20881	TAAAAACAACAA	1-10-1 MOE	1073
147746	21038	21049	TAAAAACAACAA	1-10-1 MOE	1073
147717	21080	21091	ATCTTCAGAGAT	1-10-1 MOE	996
147076	21222	21233	TTCCACTGATCC	1-10-1 MOE	1029
398094	21441	21454	ATCAGCCAGACAGA	2-10-2 MOE	1010
147746	21633	21644	TAAAAACAACAA	1-10-1 MOE	1073
147738	21884	21895	TGGGTGGCCGGG	1-10-1 MOE	1069
147683	21939	21950	GCTTACGATTGT	1-10-1 MOE	922
147743	22213	22224	AGGGCTTCCAGT	1-10-1 MOE	1042
147736	22759	22770	AGGTAGGAGAAG	1-10-1 MOE	963
147736	22927	22938	AGGTAGGAGAAG	1-10-1 MOE	963
398142	23008	23021	CCAGCACACTGGAA	2-10-2 MOE	923
398147	23784	23797	CTACAGGACAATAC	2-10-2 MOE	957
398147	23952	23965	CTACAGGACAATAC	2-10-2 MOE	957
147713	24434	24445	CTCCCACACCAT	1-10-1 MOE	985
389965	24543	24554	CTGCAACATGAT	1-10-1 MOE	1018
147713	24602	24613	CTCCCACACCAT	1-10-1 MOE	985
389965	24711	24722	CTGCAACATGAT	1-10-1 MOE	1018
147746	25384	25395	TAAAAACAACAA	1-10-1 MOE	1073
398143	25505	25518	GTCAGTCCCAGCTA	2-10-2 MOE	924
147691	25610	25621	GAGGTGGGAAAA	1-10-1 MOE	966
398130	25672	25685	TTAGTATGACAGCT	2-10-2 MOE	925
147746	25810	25821	TAAAAACAACAA	1-10-1 MOE	1073
147746	25978	25989	TAAAAACAACAA	1-10-1 MOE	1073
147746	26172	26183	TAAAAACAACAA	1-10-1 MOE	1073
398151	26718	26731	TCAGTGTAGGAAGA	2-10-2 MOE	926
147728	26917	26928	GCCAGACAGAAG	1-10-1 MOE	1013
398152	27708	27721	TGAATATACAGATG	2-10-2 MOE	927

147698	28629	28640	CCCGCCACCACC	1-10-1 MOE	928
389965	28714	28725	CTGCAACATGAT	1-10-1 MOE	1018
389764	28714	28725	CTGCAACATGAT	1-9-2 MOE	1018
389764	28861	28872	CTGCAACATGAT	1-9-2 MOE	1018
390030	29945	29956	TTTATAAAACTG	1-10-1 MOE	1074
147744	30654	30665	AGGAAGGGCTTC	1-10-1 MOE	1043
147093	30836	30847	TTGTTCCCTCTA	1-10-1 MOE	929
147746	30957	30968	TAAAAACAACAA	1-10-1 MOE	1073
147746	31105	31116	TAAAAACAACAA	1-10-1 MOE	1073
390030	31477	31488	TTTATAAAACTG	1-10-1 MOE	1074
384545	31829	31840	CAAGTAGGATGT	1-10-1 MOE	951
384545	31977	31988	CAAGTAGGATGT	1-10-1 MOE	951
401382	32094	32107	TCTACCTGAGTCCA	2-10-2 MOE	930
147089	32387	32398	TCCCTCTACACC	1-10-1 MOE	956
389950	32949	32960	CCCTGAAGGTTC	1-10-1 MOE	1063
398165	33002	33013	GTTCTTAGGAAG	1-10-1 MOE	968
147081	33073	33084	GCTCCTTCCACT	1-10-1 MOE	1006
147082	33074	33085	AGCTCCTTCCAC	1-10-1 MOE	1036
389950	33097	33108	CCCTGAAGGTTC	1-10-1 MOE	1063
147736	33160	33171	AGGTAGGAGAAG	1-10-1 MOE	963
147081	33221	33232	GCTCCTTCCACT	1-10-1 MOE	1006
368360	33221	33234	AAGCTCCTTCCACT	2-10-2 MOE	1035
147082	33222	33233	AGCTCCTTCCAC	1-10-1 MOE	1036
398138	33244	33257	AACATCAAGCTTGA	2-10-2 MOE	931
147746	33250	33261	TAAAAACAACAA	1-10-1 MOE	1073
398138	33392	33405	AACATCAAGCTTGA	2-10-2 MOE	931
401383	33588	33601	GATCACCTTCAGAG	2-10-2 MOE	932
147746	33886	33897	TAAAAACAACAA	1-10-1 MOE	1073
147746	34606	34617	TAAAAACAACAA	1-10-1 MOE	1073
398165	34704	34715	GTTCTTAGGAAG	1-10-1 MOE	968
147717	34745	34756	ATCTTCAGAGAT	1-10-1 MOE	996
147746	34754	34765	TAAAAACAACAA	1-10-1 MOE	1073
398165	34852	34863	GTTCTTAGGAAG	1-10-1 MOE	968
147717	34893	34904	ATCTTCAGAGAT	1-10-1 MOE	996
401384	34905	34918	TGAACACATCACTA	2-10-2 MOE	933
147738	35391	35402	TGGGTGGCCGGG	1-10-1 MOE	1069
147736	35396	35407	AGGTAGGAGAAG	1-10-1 MOE	963
147738	35539	35550	TGGGTGGCCGGG	1-10-1 MOE	1069
147691	35554	35565	GAGGTGGGAAAA	1-10-1 MOE	966
147691	35702	35713	GAGGTGGGAAAA	1-10-1 MOE	966
147746	35814	35825	TAAAAACAACAA	1-10-1 MOE	1073
401385	36109	36122	CCCAGTGGGTTTGA	2-10-2 MOE	890
147691	36360	36371	GAGGTGGGAAAA	1-10-1 MOE	966
147746	36416	36427	TAAAAACAACAA	1-10-1 MOE	1073
147731	36620	36631	TTTCCTCTTGTC	1-10-1 MOE	934
147714	37881	37892	TTCTGCTCCCAC	1-10-1 MOE	986
147714	38029	38040	TTCTGCTCCCAC	1-10-1 MOE	986
147681	38512	38523	ATGTCATTAAAC	1-10-1 MOE	965
401386	38516	38529	TAATTGATGTCAAT	2-10-2 MOE	935
401387	38518	38531	AGTAATTGATGTCA	2-10-2 MOE	936

401388	38520	38533	ACAGTAATTGATGT	2-10-2 MOE	937
401389	38522	38535	TTACAGTAATTGAT	2-10-2 MOE	938
401390	38524	38537	ACTTACAGTAATTG	2-10-2 MOE	939
401391	38526	38539	AGACTTACAGTAAT	2-10-2 MOE	940
401392	38528	38541	TCAGACTTACAGTA	2-10-2 MOE	941
401393	38530	38543	AATCAGACTTACAG	2-10-2 MOE	942
401394	38532	38545	TGAATCAGACTTAC	2-10-2 MOE	943
401395	38534	38547	AATGAATCAGACTT	2-10-2 MOE	944
147738	38909	38920	TGGGTGGCCGGG	1-10-1 MOE	1069
147738	39057	39068	TGGGTGGCCGGG	1-10-1 MOE	1069
390030	39249	39260	TTTATAAAACTG	1-10-1 MOE	1074
390030	39397	39408	TTTATAAAACTG	1-10-1 MOE	1074
401396	39488	39501	TGCAGGATGTTGAG	2-10-2 MOE	945
147717	39545	39556	ATCTTCAGAGAT	1-10-1 MOE	996
147746	39641	39652	TAAAAACAACAA	1-10-1 MOE	1073
147717	39693	39704	ATCTTCAGAGAT	1-10-1 MOE	996
147746	39729	39740	TAAAAACAACAA	1-10-1 MOE	1073
147746	39877	39888	TAAAAACAACAA	1-10-1 MOE	1073
147746	40185	40196	TAAAAACAACAA	1-10-1 MOE	1073
147746	40478	40489	TAAAAACAACAA	1-10-1 MOE	1073
398166	40589	40600	GGGCTTCTTCCA	1-10-1 MOE	1070
147735	40662	40673	GGAGAAGCGCAG	1-10-1 MOE	1016
147746	40706	40717	TAAAAACAACAA	1-10-1 MOE	1073
398166	40737	40748	GGGCTTCTTCCA	1-10-1 MOE	1070
147746	40854	40865	TAAAAACAACAA	1-10-1 MOE	1073
401397	41012	41025	CTGGTCAGCATTGA	2-10-2 MOE	946
147718	41070	41081	TAATATGACTTG	1-10-1 MOE	998
147718	41218	41229	TAATATGACTTG	1-10-1 MOE	998
147717	41221	41232	ATCTTCAGAGAT	1-10-1 MOE	996
147717	41369	41380	ATCTTCAGAGAT	1-10-1 MOE	996
147717	41599	41610	ATCTTCAGAGAT	1-10-1 MOE	996
147717	41747	41758	ATCTTCAGAGAT	1-10-1 MOE	996
401398	41768	41781	CAAAGTCCCTTAGC	2-10-2 MOE	947
390030	42056	42067	TTTATAAAACTG	1-10-1 MOE	1074
398153	42157	42170	ATTTCTCTTACAGG	2-10-2 MOE	948
398153	42305	42318	ATTTCTCTTACAGG	2-10-2 MOE	948
147710	42691	42702	TATAGCTCCTCT	1-10-1 MOE	994
147079	43322	43333	TCCTTCCACTGA	1-10-1 MOE	1001
147080	43323	43334	CTCCTTCCACTG	1-10-1 MOE	1021
147716	43477	43488	TTAACGAGCCTT	1-10-1 MOE	949
147746	43992	44003	TAAAAACAACAA	1-10-1 MOE	1073
147736	44137	44148	AGGTAGGAGAAG	1-10-1 MOE	963
384545	44242	44253	CAAGTAGGATGT	1-10-1 MOE	951
147687	44354	44365	CGACACGGGAAC	1-10-1 MOE	950
384545	44390	44401	CAAGTAGGATGT	1-10-1 MOE	951
398110	44713	44726	GTTCCCTTTGCAGG	2-10-2 MOE	952
147705	45092	45103	CGGTTTTTGTTC	1-10-1 MOE	1002
147705	45240	45251	CGGTTTTTGTTC	1-10-1 MOE	1002
147074	45977	45988	CCACTGATCCTG	1-10-1 MOE	845
147075	45978	45989	TCCACTGATCCT	1-10-1 MOE	1026

147076	45979	45990	TTCCACTGATCC	1-10-1 MOE	1029
147076	46127	46138	TTCCACTGATCC	1-10-1 MOE	1029
401399	46247	46260	ATTAGCCATATCTC	2-10-2 MOE	953
147705	46555	46566	CGGTTTTTGTTC	1-10-1 MOE	1002
147714	46685	46696	TTCTGCTCCCAC	1-10-1 MOE	986
147705	46703	46714	CGGTTTTTGTTC	1-10-1 MOE	1002
390030	46859	46870	TTTATAAAACTG	1-10-1 MOE	1074
390030	46933	46944	TTTATAAAACTG	1-10-1 MOE	1074
147681	46984	46995	ATGTCATTAAAC	1-10-1 MOE	965
390030	47007	47018	TTTATAAAACTG	1-10-1 MOE	1074
147746	47023	47034	TAAAAACAACAA	1-10-1 MOE	1073
390030	47081	47092	TTTATAAAACTG	1-10-1 MOE	1074
147681	47132	47143	ATGTCATTAAAC	1-10-1 MOE	965
147746	47171	47182	TAAAAACAACAA	1-10-1 MOE	1073
401400	47411	47424	AGCATTCAGCAGTG	2-10-2 MOE	954
147746	47461	47472	TAAAAACAACAA	1-10-1 MOE	1073
147086	47608	47619	CTCTACACCAGG	1-10-1 MOE	969
147087	47609	47620	CCTCTACACCAG	1-10-1 MOE	982
147088	47610	47621	CCCTCTACACCA	1-10-1 MOE	1050
147090	47612	47623	TTCCCTCTACAC	1-10-1 MOE	955
147691	47729	47740	GAGGTGGGAAAA	1-10-1 MOE	966
147086	47756	47767	CTCTACACCAGG	1-10-1 MOE	969
147088	47758	47769	CCCTCTACACCA	1-10-1 MOE	1050
147089	47759	47770	TCCCTCTACACC	1-10-1 MOE	956
390030	47847	47858	TTTATAAAACTG	1-10-1 MOE	1074
390030	47995	48006	TTTATAAAACTG	1-10-1 MOE	1074
147691	48393	48404	GAGGTGGGAAAA	1-10-1 MOE	966
398147	48887	48900	CTACAGGACAATAC	2-10-2 MOE	957
147706	49133	49144	GCTGACATCTCG	1-10-1 MOE	1071
147706	49281	49292	GCTGACATCTCG	1-10-1 MOE	1071
398168	49742	49753	TCGGACTTTGAA	1-10-1 MOE	1008
401401	49791	49804	AACTGGGTTAAGTA	2-10-2 MOE	958
147689	49936	49947	CAGAGAAGGTCT	1-10-1 MOE	987
401402	50192	50205	TGAACACGCTATCC	2-10-2 MOE	959
398117	50241	50254	TTTCCACTTGGGTG	2-10-2 MOE	960
147736	50582	50593	AGGTAGGAGAAG	1-10-1 MOE	963
398168	50703	50714	TCGGACTTTGAA	1-10-1 MOE	1008
398168	50849	50860	TCGGACTTTGAA	1-10-1 MOE	1008
147746	51019	51030	TAAAAACAACAA	1-10-1 MOE	1073
147708	51101	51112	TTGATATAGTCA	1-10-1 MOE	997
147746	51178	51189	TAAAAACAACAA	1-10-1 MOE	1073
147708	51247	51258	TTGATATAGTCA	1-10-1 MOE	997
147083	51281	51292	TACACCAGGTCA	1-10-1 MOE	973
147081	51287	51298	GCTCCTTCCACT	1-10-1 MOE	1006
147082	51288	51299	AGCTCCTTCCAC	1-10-1 MOE	1036
147746	51331	51342	TAAAAACAACAA	1-10-1 MOE	1073
147085	51416	51427	TCTACACCAGGT	1-10-1 MOE	961
147083	51427	51438	TACACCAGGTCA	1-10-1 MOE	973
147081	51433	51444	GCTCCTTCCACT	1-10-1 MOE	1006
147082	51434	51445	AGCTCCTTCCAC	1-10-1 MOE	1036

147728	51522	51533	GCCAGACAGAAG	1-10-1 MOE	1013
147085	51562	51573	TCTACACCAGGT	1-10-1 MOE	961
147081	51633	51644	GCTCCTTCCACT	1-10-1 MOE	1006
368360	51633	51646	AAGCTCCTTCCACT	2-10-2 MOE	1035
147082	51634	51645	AGCTCCTTCCAC	1-10-1 MOE	1036
368361	51635	51648	GAAAGCTCCTTCCA	2-10-2 MOE	962
368360	51779	51792	AAGCTCCTTCCACT	2-10-2 MOE	1035
147082	51780	51791	AGCTCCTTCCAC	1-10-1 MOE	1036
147736	51859	51870	AGGTAGGAGAAG	1-10-1 MOE	963
147684	51867	51878	ACCCAGTCAGGG	1-10-1 MOE	964
147746	51918	51929	TAAAAACAACAA	1-10-1 MOE	1073
147077	51988	51999	CTTCCACTGATC	1-10-1 MOE	1047
147746	52064	52075	TAAAAACAACAA	1-10-1 MOE	1073
147084	52125	52136	CTACACCAGGTC	1-10-1 MOE	993
147079	52136	52147	TCCTTCCACTGA	1-10-1 MOE	1001
147681	52231	52242	ATGTCATTAAAC	1-10-1 MOE	965
147084	52271	52282	CTACACCAGGTC	1-10-1 MOE	993
147691	52312	52323	GAGGTGGGAAAA	1-10-1 MOE	966
401403	52318	52331	TTTCCTAGGAGGTG	2-10-2 MOE	967
398167	52527	52538	CAGGCCATGTGG	1-10-1 MOE	1059
147703	52670	52681	TGGCTTCATGTC	1-10-1 MOE	971
398167	52673	52684	CAGGCCATGTGG	1-10-1 MOE	1059
398165	52708	52719	GTTCTTAGGAAG	1-10-1 MOE	968
398090	52708	52721	TTGTTCTTAGGAAG	2-10-2 MOE	972
147705	52716	52727	CGGTTTTTGTTC	1-10-1 MOE	1002
147682	52717	52728	CGGGTACTATGG	1-10-1 MOE	992
398167	52762	52773	CAGGCCATGTGG	1-10-1 MOE	1059
147703	52816	52827	TGGCTTCATGTC	1-10-1 MOE	971
398090	52854	52867	TTGTTCTTAGGAAG	2-10-2 MOE	972
147704	52856	52867	TTGTTCTTAGGA	1-10-1 MOE	1012
147705	52862	52873	CGGTTTTTGTTC	1-10-1 MOE	1002
398167	52908	52919	CAGGCCATGTGG	1-10-1 MOE	1059
147084	53704	53715	CTACACCAGGTC	1-10-1 MOE	993
147088	53708	53719	CCCTCTACACCA	1-10-1 MOE	1050
147083	53849	53860	TACACCAGGTCA	1-10-1 MOE	973
147084	53850	53861	CTACACCAGGTC	1-10-1 MOE	993
147086	53852	53863	CTCTACACCAGG	1-10-1 MOE	969
147088	53854	53865	CCCTCTACACCA	1-10-1 MOE	1050
398167	53870	53881	CAGGCCATGTGG	1-10-1 MOE	1059
147703	54137	54148	TGGCTTCATGTC	1-10-1 MOE	971
398155	54172	54185	TGTTTTTACACAGA	2-10-2 MOE	970
390030	54263	54274	TTTATAAAACTG	1-10-1 MOE	1074
147705	54275	54286	CGGTTTTTGTTC	1-10-1 MOE	1002
147703	54283	54294	TGGCTTCATGTC	1-10-1 MOE	971
390030	54409	54420	TTTATAAAACTG	1-10-1 MOE	1074
147704	54965	54976	TTGTTCTTAGGA	1-10-1 MOE	1012
147705	54971	54982	CGGTTTTTGTTC	1-10-1 MOE	1002
398090	55109	55122	TTGTTCTTAGGAAG	2-10-2 MOE	972
147705	55117	55128	CGGTTTTTGTTC	1-10-1 MOE	1002
147083	55206	55217	TACACCAGGTCA	1-10-1 MOE	973

147084	55207	55218	CTACACCAGGTC	1-10-1 MOE	993
147084	55353	55364	CTACACCAGGTC	1-10-1 MOE	993
147705	55524	55535	CGGTTTTTGTTC	1-10-1 MOE	1002
147685	55602	55613	GGCTGACATTCA	1-10-1 MOE	975
401404	55638	55651	TGAGCTACAGTAGG	2-10-2 MOE	974
147685	55748	55759	GGCTGACATTCA	1-10-1 MOE	975
147712	55819	55830	ACACCATCTCCC	1-10-1 MOE	1005
147712	55965	55976	ACACCATCTCCC	1-10-1 MOE	1005
147707	56300	56311	TAGTCATTATCT	1-10-1 MOE	977
147708	56306	56317	TTGATATAGTCA	1-10-1 MOE	997
390030	56321	56332	TTTATAAAACTG	1-10-1 MOE	1074
147709	56326	56337	CCATTTTTATCA	1-10-1 MOE	978
398091	56333	56346	GGGCTTCTTCCATT	2-10-2 MOE	979
401405	56408	56421	TGGTCAACTGAAAG	2-10-2 MOE	976
147707	56446	56457	TAGTCATTATCT	1-10-1 MOE	977
147708	56452	56463	TTGATATAGTCA	1-10-1 MOE	997
147709	56472	56483	CCATTTTTATCA	1-10-1 MOE	978
398091	56479	56492	GGGCTTCTTCCATT	2-10-2 MOE	979
401406	56570	56583	GGTGTGGATAACAG	2-10-2 MOE	980
368366	56664	56677	CTGATCCTTAGAAG	2-10-2 MOE	1019
398148	57157	57170	TCATAACTATTAAG	2-10-2 MOE	981
147082	57220	57231	AGCTCCTTCCAC	1-10-1 MOE	1036
398148	57303	57316	TCATAACTATTAAG	2-10-2 MOE	981
147082	57366	57377	AGCTCCTTCCAC	1-10-1 MOE	1036
147743	57758	57769	AGGGCTTCCAGT	1-10-1 MOE	1042
398093	57963	57976	TCGGACTTTGAAAA	2-10-2 MOE	1009
398093	58109	58122	TCGGACTTTGAAAA	2-10-2 MOE	1009
147735	58279	58290	GGAGAAGCGCAG	1-10-1 MOE	1016
147087	58821	58832	CCTCTACACCAG	1-10-1 MOE	982
147087	58967	58978	CCTCTACACCAG	1-10-1 MOE	982
390030	59180	59191	TTTATAAAACTG	1-10-1 MOE	1074
390030	59326	59337	TTTATAAAACTG	1-10-1 MOE	1074
147711	59357	59368	AAGGGCCCTGGG	1-10-1 MOE	1040
147743	59382	59393	AGGGCTTCCAGT	1-10-1 MOE	1042
147711	59503	59514	AAGGGCCCTGGG	1-10-1 MOE	1040
147711	59675	59686	AAGGGCCCTGGG	1-10-1 MOE	1040
401407	59710	59723	CAGCTTAGGCAGAG	2-10-2 MOE	983
147712	59711	59722	ACACCATCTCCC	1-10-1 MOE	1005
147713	59716	59727	CTCCCACACCAT	1-10-1 MOE	985
147714	59721	59732	TTCTGCTCCCAC	1-10-1 MOE	986
147695	59722	59733	TCATTCCCCACT	1-10-1 MOE	984
147715	59746	59757	GTTGAGCATGAC	1-10-1 MOE	1077
147711	59821	59832	AAGGGCCCTGGG	1-10-1 MOE	1040
390030	59847	59858	TTTATAAAACTG	1-10-1 MOE	1074
147712	59857	59868	ACACCATCTCCC	1-10-1 MOE	1005
147713	59862	59873	CTCCCACACCAT	1-10-1 MOE	985
147714	59867	59878	TTCTGCTCCCAC	1-10-1 MOE	986
390030	59993	60004	TTTATAAAACTG	1-10-1 MOE	1074
389949	60471	60482	GCGCGAGCCCGA	1-10-1 MOE	1061
147746	60619	60630	TAAAAACAACAA	1-10-1 MOE	1073

147689	61113	61124	CAGAGAAGGTCT	1-10-1 MOE	987
398105	61267	61280	TGCACAGGCAGGTT	2-10-2 MOE	1066
147680	61473	61484	GTATGCACTGCT	1-10-1 MOE	988
147080	61757	61768	CTCCTTCCACTG	1-10-1 MOE	1021
147078	61901	61912	CCTTCCACTGAT	1-10-1 MOE	1044
147079	61902	61913	TCCTTCCACTGA	1-10-1 MOE	1001
147088	62215	62226	CCCTCTACACCA	1-10-1 MOE	1050
401408	62600	62613	CAATGAAGCACAGG	2-10-2 MOE	989
147688	62843	62854	TCCCAAACAAAT	1-10-1 MOE	990
147746	63102	63113	TAAAAACAACAA	1-10-1 MOE	1073
147746	63248	63259	TAAAAACAACAA	1-10-1 MOE	1073
401409	63430	63443	ATTCTTAACACAGA	2-10-2 MOE	991
147682	63483	63494	CGGGTACTATGG	1-10-1 MOE	992
147084	63677	63688	CTACACCAGGTC	1-10-1 MOE	993
147710	64847	64858	TATAGCTCCTCT	1-10-1 MOE	994
147710	64993	65004	TATAGCTCCTCT	1-10-1 MOE	994
147746	65151	65162	TAAAAACAACAA	1-10-1 MOE	1073
401410	65263	65276	CATTTAGGGTCTAA	2-10-2 MOE	995
147717	65862	65873	ATCTTCAGAGAT	1-10-1 MOE	996
147717	65895	65906	ATCTTCAGAGAT	1-10-1 MOE	996
147708	65900	65911	TTGATATAGTCA	1-10-1 MOE	997
147718	65909	65920	TAATATGACTTG	1-10-1 MOE	998
147717	66008	66019	ATCTTCAGAGAT	1-10-1 MOE	996
147717	66041	66052	ATCTTCAGAGAT	1-10-1 MOE	996
147708	66046	66057	TTGATATAGTCA	1-10-1 MOE	997
147718	66055	66066	TAATATGACTTG	1-10-1 MOE	998
401411	66123	66136	AGCCGCCTGAAGTG	2-10-2 MOE	999
147697	66497	66508	CCCCAGCAGCGG	1-10-1 MOE	1000
368377	66562	66577	CTCCTTCCACTGATCC	3-10-3 MOE	1030
147077	66563	66574	CTTCCACTGATC	1-10-1 MOE	1047
368358	66563	66576	TCCTTCCACTGATC	2-10-2 MOE	1031
147078	66564	66575	CCTTCCACTGAT	1-10-1 MOE	1044
147079	66565	66576	TCCTTCCACTGA	1-10-1 MOE	1001
147080	66566	66577	CTCCTTCCACTG	1-10-1 MOE	1021
147697	66643	66654	CCCCAGCAGCGG	1-10-1 MOE	1000
368358	66709	66722	TCCTTCCACTGATC	2-10-2 MOE	1031
147078	66710	66721	CCTTCCACTGAT	1-10-1 MOE	1044
147079	66711	66722	TCCTTCCACTGA	1-10-1 MOE	1001
147075	66999	67010	TCCACTGATCCT	1-10-1 MOE	1026
147705	67067	67078	CGGTTTTTGTTC	1-10-1 MOE	1002
147088	67409	67420	CCCTCTACACCA	1-10-1 MOE	1050
147080	67430	67441	CTCCTTCCACTG	1-10-1 MOE	1021
147082	67432	67443	AGCTCCTTCCAC	1-10-1 MOE	1036
147737	67455	67466	ACAGCCAGGTAG	1-10-1 MOE	1067
147088	67555	67566	CCCTCTACACCA	1-10-1 MOE	1050
147082	67578	67589	AGCTCCTTCCAC	1-10-1 MOE	1036
401412	67637	67650	TAAATCCTCTAGCA	2-10-2 MOE	1003
147091	67729	67740	GTTCCCTCTACA	1-10-1 MOE	1004
147742	67737	67748	AACTTCAGTGTC	1-10-1 MOE	1041
147712	68527	68538	ACACCATCTCCC	1-10-1 MOE	1005

147712	68673	68684	ACACCATCTCCC	1-10-1 MOE	1005
147711	68760	68771	AAGGGCCCTGGG	1-10-1 MOE	1040
147711	68906	68917	AAGGGCCCTGGG	1-10-1 MOE	1040
389965	69271	69282	CTGCAACATGAT	1-10-1 MOE	1018
389965	69417	69428	CTGCAACATGAT	1-10-1 MOE	1018
368353	69519	69532	CACTGATCCTGCAC	2-10-2 MOE	1007
147080	69630	69641	CTCCTTCCACTG	1-10-1 MOE	1021
147081	69631	69642	GCTCCTTCCACT	1-10-1 MOE	1006
368353	69665	69678	CACTGATCCTGCAC	2-10-2 MOE	1007
398167	69757	69768	CAGGCCATGTGG	1-10-1 MOE	1059
398092	69758	69771	AGTCAGGCCATGTG	2-10-2 MOE	1060
398093	69811	69824	TCGGACTTTGAAAA	2-10-2 MOE	1009
398168	69813	69824	TCGGACTTTGAA	1-10-1 MOE	1008
398167	69903	69914	CAGGCCATGTGG	1-10-1 MOE	1059
398093	69957	69970	TCGGACTTTGAAAA	2-10-2 MOE	1009
398094	70047	70060	ATCAGCCAGACAGA	2-10-2 MOE	1010
398095	70065	70078	CATCAGCAAGAGGC	2-10-2 MOE	1011
147704	70137	70148	TTGTTCTTAGGA	1-10-1 MOE	1012
147728	70450	70461	GCCAGACAGAAG	1-10-1 MOE	1013
398164	70464	70475	TTGTCGATCTGC	1-10-1 MOE	1014
398096	70562	70575	GGAGAAGCGCAGCT	2-10-2 MOE	1015
147735	70564	70575	GGAGAAGCGCAG	1-10-1 MOE	1016
147737	70575	70586	ACAGCCAGGTAG	1-10-1 MOE	1067
147735	70710	70721	GGAGAAGCGCAG	1-10-1 MOE	1016
147737	70721	70732	ACAGCCAGGTAG	1-10-1 MOE	1067
404131	70729	70742	ACCTTCGATCACAG	2-10-2 MOE	831
368349	70762	70775	CTGCACTGACGAGT	2-10-2 MOE	1017
389965	70930	70941	CTGCAACATGAT	1-10-1 MOE	1018
368366	70995	71008	CTGATCCTTAGAAG	2-10-2 MOE	1019
368354	70999	71012	TCCACTGATCCTGC	2-10-2 MOE	1024
368375	71000	71015	CCTTCCACTGATCCTG	3-10-3 MOE	1020
368356	71001	71014	CTTCCACTGATCCT	2-10-2 MOE	1027
368376	71001	71016	TCCTTCCACTGATCCT	3-10-3 MOE	1028
368357	71002	71015	CCTTCCACTGATCC	2-10-2 MOE	1046
368377	71002	71017	CTCCTTCCACTGATCC	3-10-3 MOE	1030
147077	71003	71014	CTTCCACTGATC	1-10-1 MOE	1047
368358	71003	71016	TCCTTCCACTGATC	2-10-2 MOE	1031
368378	71003	71018	GCTCCTTCCACTGATC	3-10-3 MOE	1032
147078	71004	71015	CCTTCCACTGAT	1-10-1 MOE	1044
368359	71005	71018	GCTCCTTCCACTGA	2-10-2 MOE	1033
368379	71005	71020	AAGCTCCTTCCACTGA	3-10-3 MOE	1034
147080	71006	71017	CTCCTTCCACTG	1-10-1 MOE	1021
147082	71008	71019	AGCTCCTTCCAC	1-10-1 MOE	1036
401413	71019	71032	TGCAGCCATGTACT	2-10-2 MOE	1022
147738	71067	71078	TGGGTGGCCGGG	1-10-1 MOE	1069
147739	71071	71082	CGTTTGGGTGGC	1-10-1 MOE	1023
147741	71129	71140	CACCCACTGGTG	1-10-1 MOE	1055
368354	71145	71158	TCCACTGATCCTGC	2-10-2 MOE	1024
368355	71146	71159	TTCCACTGATCCTG	2-10-2 MOE	1025
147075	71147	71158	TCCACTGATCCT	1-10-1 MOE	1026

368356	71147	71160	CTTCCACTGATCCT	2-10-2 MOE	1027
368376	71147	71162	TCCTTCCACTGATCCT	3-10-3 MOE	1028
147076	71148	71159	TTCCACTGATCC	1-10-1 MOE	1029
368357	71148	71161	CCTTCCACTGATCC	2-10-2 MOE	1046
368377	71148	71163	CTCCTTCCACTGATCC	3-10-3 MOE	1030
147077	71149	71160	CTTCCACTGATC	1-10-1 MOE	1047
368358	71149	71162	TCCTTCCACTGATC	2-10-2 MOE	1031
368378	71149	71164	GCTCCTTCCACTGATC	3-10-3 MOE	1032
147078	71150	71161	CCTTCCACTGAT	1-10-1 MOE	1044
368359	71151	71164	GCTCCTTCCACTGA	2-10-2 MOE	1033
368379	71151	71166	AAGCTCCTTCCACTGA	3-10-3 MOE	1034
368360	71153	71166	AAGCTCCTTCCACT	2-10-2 MOE	1035
147082	71154	71165	AGCTCCTTCCAC	1-10-1 MOE	1036
368381	71155	71170	GGGAAAGCTCCTTCCA	3-10-3 MOE	1037
390030	71986	71997	TTTATAAAACTG	1-10-1 MOE	1074
390030	72132	72143	TTTATAAAACTG	1-10-1 MOE	1074
147711	72300	72311	AAGGGCCCTGGG	1-10-1 MOE	1040
401414	72347	72360	TTGCAATGTCTGGC	2-10-2 MOE	1038
147741	72400	72411	CACCCACTGGTG	1-10-1 MOE	1055
401415	72415	72428	GATTTATCTGGCTG	2-10-2 MOE	1039
147711	72446	72457	AAGGGCCCTGGG	1-10-1 MOE	1040
147742	72575	72586	AACTTCAGTGTC	1-10-1 MOE	1041
147743	72690	72701	AGGGCTTCCAGT	1-10-1 MOE	1042
147744	72694	72705	AGGAAGGGCTTC	1-10-1 MOE	1043
147745	72700	72711	TTGACCAGGAAG	1-10-1 MOE	1058
147742	72721	72732	AACTTCAGTGTC	1-10-1 MOE	1041
147743	72836	72847	AGGGCTTCCAGT	1-10-1 MOE	1042
147744	72840	72851	AGGAAGGGCTTC	1-10-1 MOE	1043
368357	72898	72911	CCTTCCACTGATCC	2-10-2 MOE	1046
147078	72900	72911	CCTTCCACTGAT	1-10-1 MOE	1044
398157	72903	72916	GGAAACATACCCTG	2-10-2 MOE	1045
368357	73044	73057	CCTTCCACTGATCC	2-10-2 MOE	1046
147077	73045	73056	CTTCCACTGATC	1-10-1 MOE	1047
147746	73052	73063	TAAAAACAACAA	1-10-1 MOE	1073
147746	73101	73112	TAAAAACAACAA	1-10-1 MOE	1073
398160	73139	73152	GAATAGGTTAAGGC	2-10-2 MOE	1048
147746	73198	73209	TAAAAACAACAA	1-10-1 MOE	1073
398161	73238	73251	AACAATGTGTTGTA	2-10-2 MOE	1049
147088	73419	73430	CCCTCTACACCA	1-10-1 MOE	1050
404140	73457	73470	GCACACAGCTGAGG	2-10-2 MOE	1051
404139	73459	73472	GTGCACACAGCTGA	2-10-2 MOE	1052
399301	73461	73474	GTGTGCACACAGCT	2-10-2 MOE	1542
404137	73463	73476	CAGTGTGCACACAG	2-10-2 MOE	1053
404138	73465	73478	CTCAGTGTGCACAC	2-10-2 MOE	1054
147741	73705	73716	CACCCACTGGTG	1-10-1 MOE	1055
404135	73858	73871	CATTTCCATGGCCA	2-10-2 MOE	1056
398167	74008	74019	CAGGCCATGTGG	1-10-1 MOE	1059
398092	74009	74022	AGTCAGGCCATGTG	2-10-2 MOE	1060
398162	74114	74127	ACCAAACAGTTCAG	2-10-2 MOE	1057
147745	74137	74148	TTGACCAGGAAG	1-10-1 MOE	1058

398167	74154	74165	CAGGCCATGTGG	1-10-1 MOE	1059
398092	74155	74168	AGTCAGGCCATGTG	2-10-2 MOE	1060
389949	74310	74321	GCGCGAGCCCGA	1-10-1 MOE	1061
147740	74485	74496	TGTGAGGCTCCA	1-10-1 MOE	1062
389950	74527	74538	CCCTGAAGGTTC	1-10-1 MOE	1063
398101	74656	74669	TTTGATAAAGCCCT	2-10-2 MOE	1064
398104	74805	74818	CAAGAAGACCTTAC	2-10-2 MOE	1065
147737	74893	74904	ACAGCCAGGTAG	1-10-1 MOE	1067
398105	74894	74907	TGCACAGGCAGGTT	2-10-2 MOE	1066
147737	74919	74930	ACAGCCAGGTAG	1-10-1 MOE	1067
398106	74974	74987	TGGAAAACTGCACC	2-10-2 MOE	1068
404199	75045	75058	GGTCATGCACAGGC	2-10-2 MOE	867
404134	75048	75061	TCAGGTCATGCACA	2-10-2 MOE	873
398106	75120	75133	TGGAAAACTGCACC	2-10-2 MOE	1068
147738	75155	75166	TGGGTGGCCGGG	1-10-1 MOE	1069
404132	75227	75240	CCTTGGAATGTCTG	2-10-2 MOE	852
147738	75301	75312	TGGGTGGCCGGG	1-10-1 MOE	1069
398166	75499	75510	GGGCTTCTTCCA	1-10-1 MOE	1070
147746	75617	75628	TAAAAACAACAA	1-10-1 MOE	1073
147706	75686	75697	GCTGACATCTCG	1-10-1 MOE	1071
398112	75730	75743	CAGCCTGGCACCTA	2-10-2 MOE	1072
147746	75763	75774	TAAAAACAACAA	1-10-1 MOE	1073
398115	75786	75799	AGTAAATATTGGCT	2-10-2 MOE	1076
390030	75839	75850	TTTATAAAACTG	1-10-1 MOE	1074
398114	75916	75929	AGGCATATAGCAGA	2-10-2 MOE	1075
398115	75932	75945	AGTAAATATTGGCT	2-10-2 MOE	1076
404133	75968	75981	TATTCCATGGCCAT	2-10-2 MOE	872
147715	77045	77056	GTTGAGCATGAC	1-10-1 MOE	1077
147715	77190	77201	GTTGAGCATGAC	1-10-1 MOE	1077
147693	77385	77396	GTGCGCTCCCAT	1-10-1 MOE	1078
398173	40201	40212	CAGCCTGGGCAC	1-10-1 MOE	1543
398173	72764	72775	CAGCCTGGGCAC	1-10-1 MOE	1543
399096	1986	1999	TGCTCGAACTCCTT	2-10-2 MOE	1544
399102	52822	52835	GAAGTCACTGGCTT	2-10-2 MOE	1545
399103	52824	52837	GGGAAGTCACTGGC	2-10-2 MOE	1546
399113	59827	59840	GTTAGGCAAAGGGC	2-10-2 MOE	1547
399132	69977	69990	GGGCTGAGTGACCC	2-10-2 MOE	1548
399173	74592	74605	ATGCTAGTGCACTA	2-10-2 MOE	1549
399208	75900	75913	AGCTCGCTACCTCT	2-10-2 MOE	1550
399276	27559	27572	GAGGTATCCCATCT	2-10-2 MOE	1551
399315	74039	74052	GGCAACTTCAACCT	2-10-2 MOE	1552

Table 19: Short antisense compounds targeted to SEQ ID NO: 12 and having 1 or 2 mismatches

ISIS NO.	5' Target Site	3' Target Site	Sequence (5'-3')	Gapmer Motif	Seq ID NO
398163	20	31	ATGTCAACCGGC	1-10-1 MOE	908
384545	23	34	CAAGTAGGATGT	1-10-1 MOE	951
147733	26	37	TTCTTGATGTCC	1-10-1 MOE	891
147721	59	70	AATGCAGGATCT	1-10-1 MOE	1118

147700	110	121	GCGCTAGGCCGC	1-10-1 MOE	1110
384545	130	141	CAAGTAGGATGT	1-10-1 MOE	951
147705	159	170	CGGTTTTTGTTC	1-10-1 MOE	1002
147701	167	178	CCATGGCGGGAC	1-10-1 MOE	921
398164	198	209	TTGTCGATCTGC	1-10-1 MOE	1014
147730	199	210	CTTGTCCATCAG	1-10-1 MOE	1121
147702	226	237	CTGGTAAATAGC	1-10-1 MOE	898
147703	245	256	TGGCTTCATGTC	1-10-1 MOE	971
147705	266	277	CGGTTTTTGTTC	1-10-1 MOE	1002
398165	283	294	GTTCTTAGGAAG	1-10-1 MOE	968
147704	285	296	TTGTTCTTAGGA	1-10-1 MOE	1012
147705	291	302	CGGTTTTTGTTC	1-10-1 MOE	1002
147709	311	322	CCATTTTTATCA	1-10-1 MOE	978
147733	349	360	TTCTTGATGTCC	1-10-1 MOE	891
147707	360	371	TAGTCATTATCT	1-10-1 MOE	977
147708	366	377	TTGATATAGTCA	1-10-1 MOE	997
390030	381	392	TTTATAAAACTG	1-10-1 MOE	1074
147709	386	397	CCATTTTTATCA	1-10-1 MOE	978
147081	393	404	GCTCCTTCCACT	1-10-1 MOE	1006
398091	393	406	GGGCTTCTTCCATT	2-10-2 MOE	979
398166	395	406	GGGCTTCTTCCA	1-10-1 MOE	1070
147712	461	472	ACACCATCTCCC	1-10-1 MOE	1005
147713	466	477	CTCCCACACCAT	1-10-1 MOE	985
147714	471	482	TTCTGCTCCCAC	1-10-1 MOE	986
147710	502	513	TATAGCTCCTCT	1-10-1 MOE	994
147736	551	562	AGGTAGGAGAAG	1-10-1 MOE	963
147717	574	585	ATCTTCAGAGAT	1-10-1 MOE	996
147717	607	618	ATCTTCAGAGAT	1-10-1 MOE	996
147710	609	620	TATAGCTCCTCT	1-10-1 MOE	994
147708	612	623	TTGATATAGTCA	1-10-1 MOE	997
147718	621	632	TAATATGACTTG	1-10-1 MOE	998
147746	625	636	TAAAAACAACAA	1-10-1 MOE	1073
147736	658	669	AGGTAGGAGAAG	1-10-1 MOE	963
147720	676	687	GATCTCTCGAGT	1-10-1 MOE	1117
147721	683	694	AATGCAGGATCT	1-10-1 MOE	1118
398167	704	715	CAGGCCATGTGG	1-10-1 MOE	1059
398092	705	718	AGTCAGGCCATGTG	2-10-2 MOE	1060
147722	709	720	AAAGTCAGGCCA	1-10-1 MOE	1130
147723	715	726	GACTCCAAAGTC	1-10-1 MOE	892
147746	733	744	TAAAAACAACAA	1-10-1 MOE	1073
398093	758	771	TCGGACTTTGAAAA	2-10-2 MOE	1009
398168	760	771	TCGGACTTTGAA	1-10-1 MOE	1008
147725	761	772	CTCGGACTTTGA	1-10-1 MOE	1119
147726	766	777	TGACTCTCGGAC	1-10-1 MOE	1120
147738	780	791	TGGGTGGCCGGG	1-10-1 MOE	1069
147727	807	818	CAGTGGACCACA	1-10-1 MOE	1128
147728	846	857	GCCAGACAGAAG	1-10-1 MOE	1013
398094	848	861	ATCAGCCAGACAGA	2-10-2 MOE	1010
398169	849	860	TCAGCCAGACAG	1-10-1 MOE	909
147729	863	874	GTAAGAGGCAGG	1-10-1 MOE	920

398095	866	879	CATCAGCAAGAGGC	2-10-2 MOE	1011
398164	873	884	TTGTCGATCTGC	1-10-1 MOE	1014
147730	874	885	CTTGTCCATCAG	1-10-1 MOE	1121
147731	880	891	TTTCCTCTTGTC	1-10-1 MOE	934
147732	885	896	GGGTCTTTCCTC	1-10-1 MOE	1122
147738	888	899	TGGGTGGCCGGG	1-10-1 MOE	1069
147733	906	917	TTCTTGATGTCC	1-10-1 MOE	891
398096	971	984	GGAGAAGCGCAGCT	2-10-2 MOE	1015
147735	973	984	GGAGAAGCGCAG	1-10-1 MOE	1016
147736	978	989	AGGTAGGAGAAG	1-10-1 MOE	963
147729	979	990	GTAAGAGGCAGG	1-10-1 MOE	920
147737	984	995	ACAGCCAGGTAG	1-10-1 MOE	1067
368349	1025	1038	CTGCACTGACGAGT	2-10-2 MOE	1017
368369	1025	1040	TCCTGCACTGACGAGT	3-10-3 MOE	893
368350	1027	1040	TCCTGCACTGACGA	2-10-2 MOE	1079
368370	1027	1042	GATCCTGCACTGACGA	3-10-3 MOE	1080
368351	1029	1042	GATCCTGCACTGAC	2-10-2 MOE	1081
368371	1029	1044	CTGATCCTGCACTGAC	3-10-3 MOE	1082
368352	1031	1044	CTGATCCTGCACTG	2-10-2 MOE	1105
368372	1031	1046	CACTGATCCTGCACTG	3-10-3 MOE	894
368353	1033	1046	CACTGATCCTGCAC	2-10-2 MOE	1007
368373	1033	1048	TCCACTGATCCTGCAC	3-10-3 MOE	1083
368354	1035	1048	TCCACTGATCCTGC	2-10-2 MOE	1024
368368	1035	1048	TCCACTGATCCTTA	2-10-2 MOE	1127
368374	1035	1050	CTTCCACTGATCCTGC	3-10-3 MOE	1126
368388	1035	1050	CTTCCACTGATCCTTA	3-10-3 MOE	895
147074	1036	1047	CCACTGATCCTG	1-10-1 MOE	845
368355	1036	1049	TTCCACTGATCCTG	2-10-2 MOE	1025
368375	1036	1051	CCTTCCACTGATCCTG	3-10-3 MOE	1020
147075	1037	1048	TCCACTGATCCT	1-10-1 MOE	1026
368356	1037	1050	CTTCCACTGATCCT	2-10-2 MOE	1027
368376	1037	1052	TCCTTCCACTGATCCT	3-10-3 MOE	1028
147076	1038	1049	TTCCACTGATCC	1-10-1 MOE	1029
368357	1038	1051	CCTTCCACTGATCC	2-10-2 MOE	1046
368377	1038	1053	CTCCTTCCACTGATCC	3-10-3 MOE	1030
147077	1039	1050	CTTCCACTGATC	1-10-1 MOE	1047
368358	1039	1052	TCCTTCCACTGATC	2-10-2 MOE	1031
368378	1039	1054	GCTCCTTCCACTGATC	3-10-3 MOE	1032
147078	1040	1051	CCTTCCACTGAT	1-10-1 MOE	1044
147079	1041	1052	TCCTTCCACTGA	1-10-1 MOE	1001
368359	1041	1054	GCTCCTTCCACTGA	2-10-2 MOE	1033
368379	1041	1056	AAGCTCCTTCCACTGA	3-10-3 MOE	1034
147080	1042	1053	CTCCTTCCACTG	1-10-1 MOE	1021
147081	1043	1054	GCTCCTTCCACT	1-10-1 MOE	1006
368360	1043	1056	AAGCTCCTTCCACT	2-10-2 MOE	1035
368380	1043	1058	GAAAGCTCCTTCCACT	3-10-3 MOE	896
147082	1044	1055	AGCTCCTTCCAC	1-10-1 MOE	1036
368361	1045	1058	GAAAGCTCCTTCCA	2-10-2 MOE	962
368381	1045	1060	GGGAAAGCTCCTTCCA	3-10-3 MOE	1037
147729	1087	1098	GTAAGAGGCAGG	1-10-1 MOE	920

147738	1103	1114	TGGGTGGCCGGG	1-10-1 MOE	1069
147739	1107	1118	CGTTTGGGTGGC	1-10-1 MOE	1023
147740	1124	1135	TGTGAGGCTCCA	1-10-1 MOE	1062
398117	1164	1177	TTTCCACTTGGGTG	2-10-2 MOE	960
147741	1165	1176	CACCCACTGGTG	1-10-1 MOE	1055
398097	1194	1207	GGCAGTCTTTATCC	2-10-2 MOE	897
398098	1272	1285	TAACTTCAGTGTCT	2-10-2 MOE	1131
398117	1272	1285	TTTCCACTTGGGTG	2-10-2 MOE	960
147742	1273	1284	AACTTCAGTGTC	1-10-1 MOE	1041
147698	1293	1304	CCCGCCACCACC	1-10-1 MOE	928
147743	1388	1399	AGGGCTTCCAGT	1-10-1 MOE	1042
398099	1388	1401	GAAGGGCTTCCAGT	2-10-2 MOE	1132
147744	1392	1403	AGGAAGGGCTTC	1-10-1 MOE	1043
398100	1395	1408	TGACCAGGAAGGGC	2-10-2 MOE	1133
147745	1398	1409	TTGACCAGGAAG	1-10-1 MOE	1058
398157	1455	1468	GGAAACATACCCTG	2-10-2 MOE	1045
147745	1458	1469	TTGACCAGGAAG	1-10-1 MOE	1058
398167	1475	1486	CAGGCCATGTGG	1-10-1 MOE	1059
398118	1564	1577	CGCGAGATATCTAA	2-10-2 MOE	1084
147697	1575	1586	CCCCAGCAGCGG	1-10-1 MOE	1000
147076	1596	1607	TTCCACTGATCC	1-10-1 MOE	1029
368357	1596	1609	CCTTCCACTGATCC	2-10-2 MOE	1046
147077	1597	1608	CTTCCACTGATC	1-10-1 MOE	1047
147078	1598	1609	CCTTCCACTGAT	1-10-1 MOE	1044
398118	1672	1685	CGCGAGATATCTAA	2-10-2 MOE	1084
398158	1681	1694	AGGCCCTGAGATTA	2-10-2 MOE	1134
147697	1683	1694	CCCCAGCAGCGG	1-10-1 MOE	1000
398159	1686	1699	GGTTAAGGCCCTGA	2-10-2 MOE	1135
398160	1691	1704	GAATAGGTTAAGGC	2-10-2 MOE	1048
398163	1711	1722	ATGTCAACCGGC	1-10-1 MOE	908
147733	1717	1728	TTCTTGATGTCC	1-10-1 MOE	891
147089	1747	1758	TCCCTCTACACC	1-10-1 MOE	956
147090	1748	1759	TTCCCTCTACAC	1-10-1 MOE	955
147746	1750	1761	TAAAAACAACAA	1-10-1 MOE	1073
389949	1777	1788	GCGCGAGCCCGA	1-10-1 MOE	1061
398161	1790	1803	AACAATGTGTTGTA	2-10-2 MOE	1049
147746	1799	1810	TAAAAACAACAA	1-10-1 MOE	1073
147700	1801	1812	GCGCTAGGCCGC	1-10-1 MOE	1110
147740	1806	1817	TGTGAGGCTCCA	1-10-1 MOE	1062
398163	1819	1830	ATGTCAACCGGC	1-10-1 MOE	908
147733	1825	1836	TTCTTGATGTCC	1-10-1 MOE	891
389950	1848	1859	CCCTGAAGGTTC	1-10-1 MOE	1063
147701	1858	1869	CCATGGCGGGAC	1-10-1 MOE	921
398164	1889	1900	TTGTCGATCTGC	1-10-1 MOE	1014
147730	1890	1901	CTTGTCCATCAG	1-10-1 MOE	1121
147700	1909	1920	GCGCTAGGCCGC	1-10-1 MOE	1110
398119	1920	1933	CGCACCTGGTAAAT	2-10-2 MOE	1085
147685	1957	1968	GGCTGACATTCA	1-10-1 MOE	975
147701	1966	1977	CCATGGCGGGAC	1-10-1 MOE	921
398120	1966	1979	GTTCAAGCGGCCTA	2-10-2 MOE	1086

398101	1977	1990	TTTGATAAAGCCCT	2-10-2 MOE	1064
398164	1997	2008	TTGTCGATCTGC	1-10-1 MOE	1014
147730	1998	2009	CTTGTCCATCAG	1-10-1 MOE	1121
147702	2025	2036	CTGGTAAATAGC	1-10-1 MOE	898
398119	2028	2041	CGCACCTGGTAAAT	2-10-2 MOE	1085
398120	2074	2087	GTTCAAGCGGCCTA	2-10-2 MOE	1086
398105	2099	2112	TGCACAGGCAGGTT	2-10-2 MOE	1066
147736	2204	2215	AGGTAGGAGAAG	1-10-1 MOE	963
147741	2257	2268	CACCCACTGGTG	1-10-1 MOE	1055
398104	2272	2285	CAAGAAGACCTTAC	2-10-2 MOE	1065
147737	2360	2371	ACAGCCAGGTAG	1-10-1 MOE	1067
398105	2361	2374	TGCACAGGCAGGTT	2-10-2 MOE	1066
147737	2386	2397	ACAGCCAGGTAG	1-10-1 MOE	1067
398095	2407	2420	CATCAGCAAGAGGC	2-10-2 MOE	1011
398106	2441	2454	TGGAAAACTGCACC	2-10-2 MOE	1068
398107	2447	2460	TATTCCTGGAAAAC	2-10-2 MOE	902
398121	2474	2487	GTGCCTAGCACAGA	2-10-2 MOE	1097
147745	2497	2508	TTGACCAGGAAG	1-10-1 MOE	1058
147712	2499	2510	ACACCATCTCCC	1-10-1 MOE	1005
398108	2544	2557	GGAATGTCTGAGTT	2-10-2 MOE	1136
147691	2575	2586	GAGGTGGGAAAA	1-10-1 MOE	966
398121	2582	2595	GTGCCTAGCACAGA	2-10-2 MOE	1097
147738	2622	2633	TGGGTGGCCGGG	1-10-1 MOE	1069
398162	2666	2679	ACCAAACAGTTCAG	2-10-2 MOE	1057
147745	2689	2700	TTGACCAGGAAG	1-10-1 MOE	1058
398167	2706	2717	CAGGCCATGTGG	1-10-1 MOE	1059
398092	2707	2720	AGTCAGGCCATGTG	2-10-2 MOE	1060
398109	2714	2727	CAAGAAGTGTGGTT	2-10-2 MOE	903
398110	2852	2865	GTTCCCTTTGCAGG	2-10-2 MOE	952
147091	2854	2865	GTTCCCTCTACA	1-10-1 MOE	1004
147723	2924	2935	GACTCCAAAGTC	1-10-1 MOE	892
398111	2937	2950	GTGAAAATGCTGGC	2-10-2 MOE	904
398166	2966	2977	GGGCTTCTTCCA	1-10-1 MOE	1070
147089	2978	2989	TCCCTCTACACC	1-10-1 MOE	956
147090	2979	2990	TTCCCTCTACAC	1-10-1 MOE	955
147706	3007	3018	GCTGACATCTCG	1-10-1 MOE	1071
389949	3008	3019	GCGCGAGCCCGA	1-10-1 MOE	1061
147723	3032	3043	GACTCCAAAGTC	1-10-1 MOE	892
147740	3037	3048	TGTGAGGCTCCA	1-10-1 MOE	1062
398112	3051	3064	CAGCCTGGCACCTA	2-10-2 MOE	1072
389950	3079	3090	CCCTGAAGGTTC	1-10-1 MOE	1063
147746	3084	3095	TAAAAACAACAA	1-10-1 MOE	1073
398122	3148	3161	CCCTTTACACAAGT	2-10-2 MOE	1087
147089	3151	3162	TCCCTCTACACC	1-10-1 MOE	956
147090	3152	3163	TTCCCTCTACAC	1-10-1 MOE	955
398113	3160	3173	AGGAGGTTAAACCA	2-10-2 MOE	905
147685	3188	3199	GGCTGACATTCA	1-10-1 MOE	975
398101	3208	3221	TTTGATAAAGCCCT	2-10-2 MOE	1064
398102	3234	3247	CTACCTGAGGATTT	2-10-2 MOE	899
398123	3235	3248	CTCAAAATAGATTT	2-10-2 MOE	1088

398114	3237	3250	AGGCATATAGCAGA	2-10-2 MOE	1075
398103	3241	3254	CCCAGTACTACCTG	2-10-2 MOE	900
398115	3253	3266	AGTAAATATTGGCT	2-10-2 MOE	1076
398122	3256	3269	CCCTTTACACAAGT	2-10-2 MOE	1087
147089	3259	3270	TCCCTCTACACC	1-10-1 MOE	956
147090	3260	3271	TTCCCTCTACAC	1-10-1 MOE	955
398116	3266	3279	TAATGACCTGATGA	2-10-2 MOE	1137
390030	3306	3317	TTTATAAAACTG	1-10-1 MOE	1074
398123	3343	3356	CTCAAAATAGATTT	2-10-2 MOE	1088
147736	3435	3446	AGGTAGGAGAAG	1-10-1 MOE	963
398104	3503	3516	CAAGAAGACCTTAC	2-10-2 MOE	1065
147737	3591	3602	ACAGCCAGGTAG	1-10-1 MOE	1067
398105	3592	3605	TGCACAGGCAGGTT	2-10-2 MOE	1066
147719	3608	3619	CCAACTCCAACT	1-10-1 MOE	1116
147737	3617	3628	ACAGCCAGGTAG	1-10-1 MOE	1067
401398	3621	3634	CAAAGTCCCTTAGC	2-10-2 MOE	947
147079	3637	3648	TCCTTCCACTGA	1-10-1 MOE	1001
147080	3638	3649	CTCCTTCCACTG	1-10-1 MOE	1021
398095	3638	3651	CATCAGCAAGAGGC	2-10-2 MOE	1011
398106	3672	3685	TGGAAAACTGCACC	2-10-2 MOE	1068
147733	3687	3698	TTCTTGATGTCC	1-10-1 MOE	891
147731	3688	3699	TTTCCTCTTGTC	1-10-1 MOE	934
147719	3716	3727	CCAACTCCAACT	1-10-1 MOE	1116
147745	3728	3739	TTGACCAGGAAG	1-10-1 MOE	1058
147683	3740	3751	GCTTACGATTGT	1-10-1 MOE	922
147079	3745	3756	TCCTTCCACTGA	1-10-1 MOE	1001
147080	3746	3757	CTCCTTCCACTG	1-10-1 MOE	1021
398108	3775	3788	GGAATGTCTGAGTT	2-10-2 MOE	1136
147733	3795	3806	TTCTTGATGTCC	1-10-1 MOE	891
147731	3796	3807	TTTCCTCTTGTC	1-10-1 MOE	934
147691	3806	3817	GAGGTGGGAAAA	1-10-1 MOE	966
147738	3853	3864	TGGGTGGCCGGG	1-10-1 MOE	1069
398167	3926	3937	CAGGCCATGTGG	1-10-1 MOE	1059
147691	3978	3989	GAGGTGGGAAAA	1-10-1 MOE	966
398167	4034	4045	CAGGCCATGTGG	1-10-1 MOE	1059
147091	4085	4096	GTTCCCTCTACA	1-10-1 MOE	1004
147691	4086	4097	GAGGTGGGAAAA	1-10-1 MOE	966
398111	4168	4181	GTGAAAATGCTGGC	2-10-2 MOE	904
398166	4197	4208	GGGCTTCTTCCA	1-10-1 MOE	1070
147091	4223	4234	GTTCCCTCTACA	1-10-1 MOE	1004
147092	4224	4235	TGTTCCCTCTAC	1-10-1 MOE	901
398112	4282	4295	CAGCCTGGCACCTA	2-10-2 MOE	1072
147746	4315	4326	TAAAAACAACAA	1-10-1 MOE	1073
398113	4391	4404	AGGAGGTTAAACCA	2-10-2 MOE	905
147723	4422	4433	GACTCCAAAGTC	1-10-1 MOE	892
398114	4468	4481	AGGCATATAGCAGA	2-10-2 MOE	1075
398115	4484	4497	AGTAAATATTGGCT	2-10-2 MOE	1076
390030	4491	4502	TTTATAAAACTG	1-10-1 MOE	1074
398116	4497	4510	TAATGACCTGATGA	2-10-2 MOE	1137
147723	4530	4541	GACTCCAAAGTC	1-10-1 MOE	892

390030	4599	4610	TTTATAAAACTG	1-10-1 MOE	1074
398124	4761	4774	CACATGAGCTATTC	2-10-2 MOE	1089
398124	4869	4882	CACATGAGCTATTC	2-10-2 MOE	1089
147703	4926	4937	TGGCTTCATGTC	1-10-1 MOE	971
147692	4928	4939	CTCACCTTCATG	1-10-1 MOE	1113
147696	4975	4986	TGGATGATTGGC	1-10-1 MOE	906
147703	5034	5045	TGGCTTCATGTC	1-10-1 MOE	971
147692	5036	5047	CTCACCTTCATG	1-10-1 MOE	1113
147098	5173	5184	AGTTGTTGTTCC	1-10-1 MOE	1112
398125	5183	5196	CAGTAAGGAATTTT	2-10-2 MOE	913
398126	5216	5229	GTGAAGTGAGTCAT	2-10-2 MOE	1090
147098	5281	5292	AGTTGTTGTTCC	1-10-1 MOE	1112
398127	5283	5296	GGTCACTCAAGATG	2-10-2 MOE	1091
398126	5324	5337	GTGAAGTGAGTCAT	2-10-2 MOE	1090
398128	5335	5348	CTAAATTTAGTTCA	2-10-2 MOE	911
398127	5391	5404	GGTCACTCAAGATG	2-10-2 MOE	1091
398128	5443	5456	CTAAATTTAGTTCA	2-10-2 MOE	911
147712	5474	5485	ACACCATCTCCC	1-10-1 MOE	1005
147736	5600	5611	AGGTAGGAGAAG	1-10-1 MOE	963
147746	5606	5617	TAAAAACAACAA	1-10-1 MOE	1073
398129	5628	5641	TTTGAGGAGCTATT	2-10-2 MOE	1106
147085	5654	5665	TCTACACCAGGT	1-10-1 MOE	961
147736	5708	5719	AGGTAGGAGAAG	1-10-1 MOE	963
398129	5736	5749	TTTGAGGAGCTATT	2-10-2 MOE	1106
147679	5934	5945	CAAAAGGATCCC	1-10-1 MOE	907
147723	6229	6240	GACTCCAAAGTC	1-10-1 MOE	892
147723	6338	6349	GACTCCAAAGTC	1-10-1 MOE	892
390030	6803	6814	TTTATAAAACTG	1-10-1 MOE	1074
398142	6885	6898	CCAGCACACTGGAA	2-10-2 MOE	923
390030	6912	6923	TTTATAAAACTG	1-10-1 MOE	1074
398142	6994	7007	CCAGCACACTGGAA	2-10-2 MOE	923
147695	7054	7065	TCATTCCCCACT	1-10-1 MOE	984
147695	7163	7174	TCATTCCCCACT	1-10-1 MOE	984
398166	7197	7208	GGGCTTCTTCCA	1-10-1 MOE	1070
398166	7306	7317	GGGCTTCTTCCA	1-10-1 MOE	1070
147684	7442	7453	ACCCAGTCAGGG	1-10-1 MOE	964
398130	7694	7707	TTAGTATGACAGCT	2-10-2 MOE	925
398131	7711	7724	GGACTCACTCAGCA	2-10-2 MOE	1092
398130	7802	7815	TTAGTATGACAGCT	2-10-2 MOE	925
398125	7804	7817	CAGTAAGGAATTTT	2-10-2 MOE	913
398131	7819	7832	GGACTCACTCAGCA	2-10-2 MOE	1092
390030	7877	7888	TTTATAAAACTG	1-10-1 MOE	1074
398125	7912	7925	CAGTAAGGAATTTT	2-10-2 MOE	913
390030	7985	7996	TTTATAAAACTG	1-10-1 MOE	1074
398132	8031	8044	TCAGGGCTACTCAT	2-10-2 MOE	1093
398132	8139	8152	TCAGGGCTACTCAT	2-10-2 MOE	1093
147684	8148	8159	ACCCAGTCAGGG	1-10-1 MOE	964
147684	8256	8267	ACCCAGTCAGGG	1-10-1 MOE	964
398163	8365	8376	ATGTCAACCGGC	1-10-1 MOE	908
398166	8447	8458	GGGCTTCTTCCA	1-10-1 MOE	1070

398163	8473	8484	ATGTCAACCGGC	1-10-1 MOE	908
398166	8555	8566	GGGCTTCTTCCA	1-10-1 MOE	1070
147718	8631	8642	TAATATGACTTG	1-10-1 MOE	998
147691	8698	8709	GAGGTGGGAAAA	1-10-1 MOE	966
147691	8806	8817	GAGGTGGGAAAA	1-10-1 MOE	966
147728	8835	8846	GCCAGACAGAAG	1-10-1 MOE	1013
147727	8876	8887	CAGTGGACCACA	1-10-1 MOE	1128
147728	8943	8954	GCCAGACAGAAG	1-10-1 MOE	1013
398169	8946	8957	TCAGCCAGACAG	1-10-1 MOE	909
147727	8984	8995	CAGTGGACCACA	1-10-1 MOE	1128
147742	9060	9071	AACTTCAGTGTC	1-10-1 MOE	1041
398133	9112	9125	CAGCACTAGATTCA	2-10-2 MOE	1094
384545	9135	9146	CAAGTAGGATGT	1-10-1 MOE	951
147742	9168	9179	AACTTCAGTGTC	1-10-1 MOE	1041
398133	9220	9233	CAGCACTAGATTCA	2-10-2 MOE	1094
384545	9243	9254	CAAGTAGGATGT	1-10-1 MOE	951
398125	9368	9381	CAGTAAGGAATTTT	2-10-2 MOE	913
398125	9476	9489	CAGTAAGGAATTTT	2-10-2 MOE	913
401409	9516	9529	ATTCTTAACACAGA	2-10-2 MOE	991
147096	9594	9605	TTGTTGTTCCCT	1-10-1 MOE	1107
147733	9597	9608	TTCTTGATGTCC	1-10-1 MOE	891
147720	9689	9700	GATCTCTCGAGT	1-10-1 MOE	1117
147096	9702	9713	TTGTTGTTCCCT	1-10-1 MOE	1107
147733	9705	9716	TTCTTGATGTCC	1-10-1 MOE	891
147720	9797	9808	GATCTCTCGAGT	1-10-1 MOE	1117
147746	9963	9974	TAAAAACAACAA	1-10-1 MOE	1073
147746	9966	9977	TAAAAACAACAA	1-10-1 MOE	1073
147746	9969	9980	TAAAAACAACAA	1-10-1 MOE	1073
147746	9991	10002	TAAAAACAACAA	1-10-1 MOE	1073
147746	10071	10082	TAAAAACAACAA	1-10-1 MOE	1073
147746	10074	10085	TAAAAACAACAA	1-10-1 MOE	1073
147746	10077	10088	TAAAAACAACAA	1-10-1 MOE	1073
147746	10099	10110	TAAAAACAACAA	1-10-1 MOE	1073
398134	10153	10166	TAGCTTAATGTAAC	2-10-2 MOE	1095
147085	10221	10232	TCTACACCAGGT	1-10-1 MOE	961
398134	10261	10274	TAGCTTAATGTAAC	2-10-2 MOE	1095
390030	10278	10289	TTTATAAAACTG	1-10-1 MOE	1074
147084	10328	10339	CTACACCAGGTC	1-10-1 MOE	993
147711	10684	10695	AAGGGCCCTGGG	1-10-1 MOE	1040
398128	11333	11346	CTAAATTTAGTTCA	2-10-2 MOE	911
398128	11340	11353	CTAAATTTAGTTCA	2-10-2 MOE	911
147730	11783	11794	CTTGTCCATCAG	1-10-1 MOE	1121
147731	11789	11800	TTTCCTCTTGTC	1-10-1 MOE	934
147730	11790	11801	CTTGTCCATCAG	1-10-1 MOE	1121
147731	11796	11807	TTTCCTCTTGTC	1-10-1 MOE	934
147707	11960	11971	TAGTCATTATCT	1-10-1 MOE	977
147090	12008	12019	TTCCCTCTACAC	1-10-1 MOE	955
147091	12009	12020	GTTCCCTCTACA	1-10-1 MOE	1004
147091	12014	12025	GTTCCCTCTACA	1-10-1 MOE	1004
398096	12141	12154	GGAGAAGCGCAGCT	2-10-2 MOE	1015

147735	12143	12154	GGAGAAGCGCAG	1-10-1 MOE	1016
398096	12146	12159	GGAGAAGCGCAGCT	2-10-2 MOE	1015
147735	12148	12159	GGAGAAGCGCAG	1-10-1 MOE	1016
398166	12209	12220	GGGCTTCTTCCA	1-10-1 MOE	1070
398166	12214	12225	GGGCTTCTTCCA	1-10-1 MOE	1070
398135	12303	12316	GACTACATTTTACA	2-10-2 MOE	912
147741	12389	12400	CACCCACTGGTG	1-10-1 MOE	1055
147741	12394	12405	CACCCACTGGTG	1-10-1 MOE	1055
398125	12431	12444	CAGTAAGGAATTTT	2-10-2 MOE	913
147714	12585	12596	TTCTGCTCCCAC	1-10-1 MOE	986
147718	12594	12605	TAATATGACTTG	1-10-1 MOE	998
398125	12612	12625	CAGTAAGGAATTTT	2-10-2 MOE	913
147737	12803	12814	ACAGCCAGGTAG	1-10-1 MOE	1067
147746	12876	12887	TAAAAACAACAA	1-10-1 MOE	1073
147691	12900	12911	GAGGTGGGAAAA	1-10-1 MOE	966
398136	12915	12928	TTGTGACATCTAGG	2-10-2 MOE	1096
147737	12984	12995	ACAGCCAGGTAG	1-10-1 MOE	1067
147746	13057	13068	TAAAAACAACAA	1-10-1 MOE	1073
147691	13081	13092	GAGGTGGGAAAA	1-10-1 MOE	966
398136	13096	13109	TTGTGACATCTAGG	2-10-2 MOE	1096
398138	13254	13267	AACATCAAGCTTGA	2-10-2 MOE	931
398138	13435	13448	AACATCAAGCTTGA	2-10-2 MOE	931
147691	13488	13499	GAGGTGGGAAAA	1-10-1 MOE	966
147681	13659	13670	ATGTCATTAAAC	1-10-1 MOE	965
147691	13669	13680	GAGGTGGGAAAA	1-10-1 MOE	966
389965	13839	13850	CTGCAACATGAT	1-10-1 MOE	1018
389764	13839	13850	CTGCAACATGAT	1-9-2 MOE	1018
147681	13840	13851	ATGTCATTAAAC	1-10-1 MOE	965
389965	14020	14031	CTGCAACATGAT	1-10-1 MOE	1018
389764	14020	14031	CTGCAACATGAT	1-9-2 MOE	1018
389948	14067	14078	CCGTTGGACCCC	1-10-1 MOE	915
147736	14123	14134	AGGTAGGAGAAG	1-10-1 MOE	963
389948	14248	14259	CCGTTGGACCCC	1-10-1 MOE	915
147738	14279	14290	TGGGTGGCCGGG	1-10-1 MOE	1069
147736	14304	14315	AGGTAGGAGAAG	1-10-1 MOE	963
147731	14411	14422	TTTCCTCTTGTC	1-10-1 MOE	934
147738	14461	14472	TGGGTGGCCGGG	1-10-1 MOE	1069
147692	14475	14486	CTCACCTTCATG	1-10-1 MOE	1113
147731	14593	14604	TTTCCTCTTGTC	1-10-1 MOE	934
389950	14614	14625	CCCTGAAGGTTC	1-10-1 MOE	1063
147692	14657	14668	CTCACCTTCATG	1-10-1 MOE	1113
147717	14750	14761	ATCTTCAGAGAT	1-10-1 MOE	996
147698	14754	14765	CCCGCCACCACC	1-10-1 MOE	928
389950	14796	14807	CCCTGAAGGTTC	1-10-1 MOE	1063
398112	14863	14876	CAGCCTGGCACCTA	2-10-2 MOE	1072
398121	14875	14888	GTGCCTAGCACAGA	2-10-2 MOE	1097
147717	14932	14943	ATCTTCAGAGAT	1-10-1 MOE	996
398112	15045	15058	CAGCCTGGCACCTA	2-10-2 MOE	1072
398121	15057	15070	GTGCCTAGCACAGA	2-10-2 MOE	1097
147730	15117	15128	CTTGTCCATCAG	1-10-1 MOE	1121

147730	15299	15310	CTTGTCCATCAG	1-10-1 MOE	1121
401407	15339	15352	CAGCTTAGGCAGAG	2-10-2 MOE	983
398167	15556	15567	CAGGCCATGTGG	1-10-1 MOE	1059
147736	16444	16455	AGGTAGGAGAAG	1-10-1 MOE	963
147746	16510	16521	TAAAAACAACAA	1-10-1 MOE	1073
147738	16590	16601	TGGGTGGCCGGG	1-10-1 MOE	1069
147736	16610	16621	AGGTAGGAGAAG	1-10-1 MOE	963
398167	16631	16642	CAGGCCATGTGG	1-10-1 MOE	1059
401411	16657	16670	AGCCGCCTGAAGTG	2-10-2 MOE	999
147746	16676	16687	TAAAAACAACAA	1-10-1 MOE	1073
398144	16745	16758	GACAGCTTCTATAA	2-10-2 MOE	916
147738	16756	16767	TGGGTGGCCGGG	1-10-1 MOE	1069
398167	16797	16808	CAGGCCATGTGG	1-10-1 MOE	1059
398144	16911	16924	GACAGCTTCTATAA	2-10-2 MOE	916
389965	17096	17107	CTGCAACATGAT	1-10-1 MOE	1018
389764	17096	17107	CTGCAACATGAT	1-9-2 MOE	1018
389965	17264	17275	CTGCAACATGAT	1-10-1 MOE	1018
389764	17264	17275	CTGCAACATGAT	1-9-2 MOE	1018
147709	17406	17417	CCATTTTTATCA	1-10-1 MOE	978
147745	17443	17454	TTGACCAGGAAG	1-10-1 MOE	1058
147746	17497	17508	TAAAAACAACAA	1-10-1 MOE	1073
147720	17589	17600	GATCTCTCGAGT	1-10-1 MOE	1117
147745	17611	17622	TTGACCAGGAAG	1-10-1 MOE	1058
147695	17634	17645	TCATTCCCCACT	1-10-1 MOE	984
147746	17665	17676	TAAAAACAACAA	1-10-1 MOE	1073
147088	17707	17718	CCCTCTACACCA	1-10-1 MOE	1050
147720	17757	17768	GATCTCTCGAGT	1-10-1 MOE	1117
147711	17808	17819	AAGGGCCCTGGG	1-10-1 MOE	1040
147711	17976	17987	AAGGGCCCTGGG	1-10-1 MOE	1040
398139	18049	18062	AGTGACTGACCACA	2-10-2 MOE	917
398139	18217	18230	AGTGACTGACCACA	2-10-2 MOE	917
398140	18596	18609	GTAGCATAGAGCCT	2-10-2 MOE	918
398140	18764	18777	GTAGCATAGAGCCT	2-10-2 MOE	918
398167	18927	18938	CAGGCCATGTGG	1-10-1 MOE	1059
398167	19095	19106	CAGGCCATGTGG	1-10-1 MOE	1059
147724	19147	19158	GAAATTGAGGAA	1-10-1 MOE	1139
147746	19207	19218	TAAAAACAACAA	1-10-1 MOE	1073
147724	19315	19326	GAAATTGAGGAA	1-10-1 MOE	1139
147740	19348	19359	TGTGAGGCTCCA	1-10-1 MOE	1062
147746	19375	19386	TAAAAACAACAA	1-10-1 MOE	1073
147729	19386	19397	GTAAGAGGCAGG	1-10-1 MOE	920
147701	19503	19514	CCATGGCGGGAC	1-10-1 MOE	921
147711	19508	19519	AAGGGCCCTGGG	1-10-1 MOE	1040
147740	19516	19527	TGTGAGGCTCCA	1-10-1 MOE	1062
147718	19617	19628	TAATATGACTTG	1-10-1 MOE	998
390030	19618	19629	TTTATAAAACTG	1-10-1 MOE	1074
147679	19635	19646	CAAAAGGATCCC	1-10-1 MOE	907
147711	19676	19687	AAGGGCCCTGGG	1-10-1 MOE	1040
147694	19747	19758	CAGCCTACCAGT	1-10-1 MOE	1098
147718	19785	19796	TAATATGACTTG	1-10-1 MOE	998

390030	19786	19797	TTTATAAAACTG	1-10-1 MOE	1074
147679	19803	19814	CAAAAGGATCCC	1-10-1 MOE	907
147698	19852	19863	CCCGCCACCACC	1-10-1 MOE	928
147694	19915	19926	CAGCCTACCAGT	1-10-1 MOE	1098
147704	20011	20022	TTGTTCTTAGGA	1-10-1 MOE	1012
147698	20020	20031	CCCGCCACCACC	1-10-1 MOE	928
398142	20485	20498	CCAGCACACTGGAA	2-10-2 MOE	923
147078	20514	20525	CCTTCCACTGAT	1-10-1 MOE	1044
147079	20515	20526	TCCTTCCACTGA	1-10-1 MOE	1001
147080	20516	20527	CTCCTTCCACTG	1-10-1 MOE	1021
398143	20561	20574	GTCAGTCCCAGCTA	2-10-2 MOE	924
389965	20620	20631	CTGCAACATGAT	1-10-1 MOE	1018
389764	20620	20631	CTGCAACATGAT	1-9-2 MOE	1018
398142	20653	20666	CCAGCACACTGGAA	2-10-2 MOE	923
147078	20682	20693	CCTTCCACTGAT	1-10-1 MOE	1044
147079	20683	20694	TCCTTCCACTGA	1-10-1 MOE	1001
147080	20684	20695	CTCCTTCCACTG	1-10-1 MOE	1021
147080	20704	20715	CTCCTTCCACTG	1-10-1 MOE	1021
147081	20705	20716	GCTCCTTCCACT	1-10-1 MOE	1006
398143	20729	20742	GTCAGTCCCAGCTA	2-10-2 MOE	924
389965	20788	20799	CTGCAACATGAT	1-10-1 MOE	1018
389764	20788	20799	CTGCAACATGAT	1-9-2 MOE	1018
147746	20870	20881	TAAAAACAACAA	1-10-1 MOE	1073
147080	20872	20883	CTCCTTCCACTG	1-10-1 MOE	1021
147081	20873	20884	GCTCCTTCCACT	1-10-1 MOE	1006
147746	21038	21049	TAAAAACAACAA	1-10-1 MOE	1073
147717	21080	21091	ATCTTCAGAGAT	1-10-1 MOE	996
147076	21222	21233	TTCCACTGATCC	1-10-1 MOE	1029
147076	21390	21401	TTCCACTGATCC	1-10-1 MOE	1029
398094	21441	21454	ATCAGCCAGACAGA	2-10-2 MOE	1010
147746	21465	21476	TAAAAACAACAA	1-10-1 MOE	1073
398094	21609	21622	ATCAGCCAGACAGA	2-10-2 MOE	1010
398169	21610	21621	TCAGCCAGACAG	1-10-1 MOE	909
147746	21633	21644	TAAAAACAACAA	1-10-1 MOE	1073
147738	21884	21895	TGGGTGGCCGGG	1-10-1 MOE	1069
147743	22045	22056	AGGGCTTCCAGT	1-10-1 MOE	1042
147738	22052	22063	TGGGTGGCCGGG	1-10-1 MOE	1069
147683	22107	22118	GCTTACGATTGT	1-10-1 MOE	922
147743	22213	22224	AGGGCTTCCAGT	1-10-1 MOE	1042
147681	22566	22577	ATGTCATTAAAC	1-10-1 MOE	965
389950	22619	22630	CCCTGAAGGTTC	1-10-1 MOE	1063
147681	22734	22745	ATGTCATTAAAC	1-10-1 MOE	965
147736	22759	22770	AGGTAGGAGAAG	1-10-1 MOE	963
389950	22787	22798	CCCTGAAGGTTC	1-10-1 MOE	1063
389949	22794	22805	GCGCGAGCCCGA	1-10-1 MOE	1061
147736	22927	22938	AGGTAGGAGAAG	1-10-1 MOE	963
389949	22962	22973	GCGCGAGCCCGA	1-10-1 MOE	1061
398144	22962	22975	GACAGCTTCTATAA	2-10-2 MOE	916
398142	23008	23021	CCAGCACACTGGAA	2-10-2 MOE	923
147727	23019	23030	CAGTGGACCACA	1-10-1 MOE	1128

398169	23064	23075	TCAGCCAGACAG	1-10-1 MOE	909
398144	23130	23143	GACAGCTTCTATAA	2-10-2 MOE	916
398145	23154	23167	ACATGTCAGTAATT	2-10-2 MOE	1099
398142	23176	23189	CCAGCACACTGGAA	2-10-2 MOE	923
147727	23187	23198	CAGTGGACCACA	1-10-1 MOE	1128
147735	23243	23254	GGAGAAGCGCAG	1-10-1 MOE	1016
398145	23322	23335	ACATGTCAGTAATT	2-10-2 MOE	1099
147735	23411	23422	GGAGAAGCGCAG	1-10-1 MOE	1016
398146	23478	23491	CTCATGGACACAAA	2-10-2 MOE	1100
398146	23646	23659	CTCATGGACACAAA	2-10-2 MOE	1100
398147	23784	23797	CTACAGGACAATAC	2-10-2 MOE	957
398114	23853	23866	AGGCATATAGCAGA	2-10-2 MOE	1075
398147	23952	23965	CTACAGGACAATAC	2-10-2 MOE	957
398114	24021	24034	AGGCATATAGCAGA	2-10-2 MOE	1075
147702	24319	24330	CTGGTAAATAGC	1-10-1 MOE	898
147702	24487	24498	CTGGTAAATAGC	1-10-1 MOE	898
389965	24543	24554	CTGCAACATGAT	1-10-1 MOE	1018
389764	24543	24554	CTGCAACATGAT	1-9-2 MOE	1018
147713	24602	24613	CTCCCACACCAT	1-10-1 MOE	985
389965	24711	24722	CTGCAACATGAT	1-10-1 MOE	1018
389764	24711	24722	CTGCAACATGAT	1-9-2 MOE	1018
147684	24918	24929	ACCCAGTCAGGG	1-10-1 MOE	964
147684	25086	25097	ACCCAGTCAGGG	1-10-1 MOE	964
398148	25152	25165	TCATAACTATTAAG	2-10-2 MOE	981
398144	25192	25205	GACAGCTTCTATAA	2-10-2 MOE	916
147746	25216	25227	TAAAAACAACAA	1-10-1 MOE	1073
147736	25313	25324	AGGTAGGAGAAG	1-10-1 MOE	963
398148	25320	25333	TCATAACTATTAAG	2-10-2 MOE	981
398143	25337	25350	GTCAGTCCCAGCTA	2-10-2 MOE	924
398144	25360	25373	GACAGCTTCTATAA	2-10-2 MOE	916
147746	25384	25395	TAAAAACAACAA	1-10-1 MOE	1073
147691	25442	25453	GAGGTGGGAAAA	1-10-1 MOE	966
147736	25481	25492	AGGTAGGAGAAG	1-10-1 MOE	963
398130	25504	25517	TTAGTATGACAGCT	2-10-2 MOE	925
147691	25610	25621	GAGGTGGGAAAA	1-10-1 MOE	966
147721	25662	25673	AATGCAGGATCT	1-10-1 MOE	1118
398130	25672	25685	TTAGTATGACAGCT	2-10-2 MOE	925
147688	25750	25761	TCCCAAACAAAT	1-10-1 MOE	990
147746	25810	25821	TAAAAACAACAA	1-10-1 MOE	1073
147721	25830	25841	AATGCAGGATCT	1-10-1 MOE	1118
147688	25918	25929	TCCCAAACAAAT	1-10-1 MOE	990
147746	25978	25989	TAAAAACAACAA	1-10-1 MOE	1073
147746	26172	26183	TAAAAACAACAA	1-10-1 MOE	1073
147746	26340	26351	TAAAAACAACAA	1-10-1 MOE	1073
398149	26492	26505	GGAAGTTTTCAAGT	2-10-2 MOE	1101
398150	26526	26539	GAATCTGGAGGTAA	2-10-2 MOE	1102
398149	26641	26654	GGAAGTTTTCAAGT	2-10-2 MOE	1101
398150	26675	26688	GAATCTGGAGGTAA	2-10-2 MOE	1102
147729	26712	26723	GTAAGAGGCAGG	1-10-1 MOE	920
398151	26718	26731	TCAGTGTAGGAAGA	2-10-2 MOE	926

147729	26861	26872	GTAAGAGGCAGG	1-10-1 MOE	920
398151	26867	26880	TCAGTGTAGGAAGA	2-10-2 MOE	926
147728	26917	26928	GCCAGACAGAAG	1-10-1 MOE	1013
147728	27066	27077	GCCAGACAGAAG	1-10-1 MOE	1013
147076	27258	27269	TTCCACTGATCC	1-10-1 MOE	1029
147731	27267	27278	TTTCCTCTTGTC	1-10-1 MOE	934
147076	27407	27418	TTCCACTGATCC	1-10-1 MOE	1029
147731	27416	27427	TTTCCTCTTGTC	1-10-1 MOE	934
398152	27559	27572	TGAATATACAGATG	2-10-2 MOE	927
398152	27708	27721	TGAATATACAGATG	2-10-2 MOE	927
147696	28265	28276	TGGATGATTGGC	1-10-1 MOE	906
147696	28414	28425	TGGATGATTGGC	1-10-1 MOE	906
147698	28481	28492	CCCGCCACCACC	1-10-1 MOE	928
147720	28662	28673	GATCTCTCGAGT	1-10-1 MOE	1117
389965	28714	28725	CTGCAACATGAT	1-10-1 MOE	1018
389764	28714	28725	CTGCAACATGAT	1-9-2 MOE	1018
389965	28861	28872	CTGCAACATGAT	1-10-1 MOE	1018
389764	28861	28872	CTGCAACATGAT	1-9-2 MOE	1018
398153	28980	28993	ATTTCTCTTACAGG	2-10-2 MOE	948
398153	29126	29139	ATTTCTCTTACAGG	2-10-2 MOE	948
147719	29570	29581	CCAACTCCAACT	1-10-1 MOE	1116
398154	29692	29705	AGCCCCTTGGCCGT	2-10-2 MOE	1103
147719	29715	29726	CCAACTCCAACT	1-10-1 MOE	1116
398155	29785	29798	TGTTTTTACACAGA	2-10-2 MOE	970
398154	29837	29850	AGCCCCTTGGCCGT	2-10-2 MOE	1103
401384	29905	29918	TGAACACATCACTA	2-10-2 MOE	933
398155	29930	29943	TGTTTTTACACAGA	2-10-2 MOE	970
390030	29945	29956	TTTATAAAACTG	1-10-1 MOE	1074
390030	30090	30101	TTTATAAAACTG	1-10-1 MOE	1074
398156	30141	30154	GAATACTTCAAATC	2-10-2 MOE	1104
398156	30286	30299	GAATACTTCAAATC	2-10-2 MOE	1104
389948	30384	30395	CCGTTGGACCCC	1-10-1 MOE	915
389948	30530	30541	CCGTTGGACCCC	1-10-1 MOE	915
398142	30591	30604	CCAGCACACTGGAA	2-10-2 MOE	923
147744	30654	30665	AGGAAGGGCTTC	1-10-1 MOE	1043
147093	30689	30700	TTGTTCCCTCTA	1-10-1 MOE	929
398142	30738	30751	CCAGCACACTGGAA	2-10-2 MOE	923
147744	30801	30812	AGGAAGGGCTTC	1-10-1 MOE	1043
398168	31082	31093	TCGGACTTTGAA	1-10-1 MOE	1008
147746	31105	31116	TAAAAACAACAA	1-10-1 MOE	1073
398168	31230	31241	TCGGACTTTGAA	1-10-1 MOE	1008
390030	31329	31340	TTTATAAAACTG	1-10-1 MOE	1074
147736	31458	31469	AGGTAGGAGAAG	1-10-1 MOE	963
390030	31477	31488	TTTATAAAACTG	1-10-1 MOE	1074
147736	31606	31617	AGGTAGGAGAAG	1-10-1 MOE	963
147698	31713	31724	CCCGCCACCACC	1-10-1 MOE	928
384545	31829	31840	CAAGTAGGATGT	1-10-1 MOE	951
147698	31861	31872	CCCGCCACCACC	1-10-1 MOE	928
147723	31941	31952	GACTCCAAAGTC	1-10-1 MOE	892
384545	31977	31988	CAAGTAGGATGT	1-10-1 MOE	951

147692	32061	32072	CTCACCTTCATG	1-10-1 MOE	1113
147723	32089	32100	GACTCCAAAGTC	1-10-1 MOE	892
147692	32209	32220	CTCACCTTCATG	1-10-1 MOE	1113
147089	32535	32546	TCCCTCTACACC	1-10-1 MOE	956
401396	32569	32582	TGCAGGATGTTGAG	2-10-2 MOE	945
147730	32714	32725	CTTGTCCATCAG	1-10-1 MOE	1121
398165	32854	32865	GTTCTTAGGAAG	1-10-1 MOE	968
147730	32862	32873	CTTGTCCATCAG	1-10-1 MOE	1121
389950	32949	32960	CCCTGAAGGTTC	1-10-1 MOE	1063
398165	33002	33013	GTTCTTAGGAAG	1-10-1 MOE	968
147736	33012	33023	AGGTAGGAGAAG	1-10-1 MOE	963
368352	33056	33069	CTGATCCTGCACTG	2-10-2 MOE	1105
147081	33073	33084	GCTCCTTCCACT	1-10-1 MOE	1006
368360	33073	33086	AAGCTCCTTCCACT	2-10-2 MOE	1035
147082	33074	33085	AGCTCCTTCCAC	1-10-1 MOE	1036
389950	33097	33108	CCCTGAAGGTTC	1-10-1 MOE	1063
147736	33160	33171	AGGTAGGAGAAG	1-10-1 MOE	963
368352	33204	33217	CTGATCCTGCACTG	2-10-2 MOE	1105
147081	33221	33232	GCTCCTTCCACT	1-10-1 MOE	1006
147082	33222	33233	AGCTCCTTCCAC	1-10-1 MOE	1036
398138	33244	33257	AACATCAAGCTTGA	2-10-2 MOE	931
147746	33250	33261	TAAAAACAACAA	1-10-1 MOE	1073
398138	33392	33405	AACATCAAGCTTGA	2-10-2 MOE	931
147746	33398	33409	TAAAAACAACAA	1-10-1 MOE	1073
147732	33652	33663	GGGTCTTTCCTC	1-10-1 MOE	1122
147724	33733	33744	GAAATTGAGGAA	1-10-1 MOE	1139
147732	33800	33811	GGGTCTTTCCTC	1-10-1 MOE	1122
147724	33881	33892	GAAATTGAGGAA	1-10-1 MOE	1139
147719	33976	33987	CCAACTCCAACT	1-10-1 MOE	1116
147746	34034	34045	TAAAAACAACAA	1-10-1 MOE	1073
398129	34045	34058	TTTGAGGAGCTATT	2-10-2 MOE	1106
147719	34124	34135	CCAACTCCAACT	1-10-1 MOE	1116
147721	34156	34167	AATGCAGGATCT	1-10-1 MOE	1118
398129	34193	34206	TTTGAGGAGCTATT	2-10-2 MOE	1106
147721	34304	34315	AATGCAGGATCT	1-10-1 MOE	1118
147746	34606	34617	TAAAAACAACAA	1-10-1 MOE	1073
398165	34704	34715	GTTCTTAGGAAG	1-10-1 MOE	968
147746	34754	34765	TAAAAACAACAA	1-10-1 MOE	1073
398165	34852	34863	GTTCTTAGGAAG	1-10-1 MOE	968
147717	34893	34904	ATCTTCAGAGAT	1-10-1 MOE	996
147719	34976	34987	CCAACTCCAACT	1-10-1 MOE	1116
147092	34987	34998	TGTTCCCTCTAC	1-10-1 MOE	901
147719	35124	35135	CCAACTCCAACT	1-10-1 MOE	1116
147092	35135	35146	TGTTCCCTCTAC	1-10-1 MOE	901
147736	35248	35259	AGGTAGGAGAAG	1-10-1 MOE	963
147738	35391	35402	TGGGTGGCCGGG	1-10-1 MOE	1069
147736	35396	35407	AGGTAGGAGAAG	1-10-1 MOE	963
147738	35539	35550	TGGGTGGCCGGG	1-10-1 MOE	1069
147691	35554	35565	GAGGTGGGAAAA	1-10-1 MOE	966
147691	35702	35713	GAGGTGGGAAAA	1-10-1 MOE	966

147746	35814	35825	TAAAAACAACAA	1-10-1 MOE	1073
147733	35889	35900	TTCTTGATGTCC	1-10-1 MOE	891
147733	35923	35934	TTCTTGATGTCC	1-10-1 MOE	891
147746	35962	35973	TAAAAACAACAA	1-10-1 MOE	1073
147726	35978	35989	TGACTCTCGGAC	1-10-1 MOE	1120
147733	36037	36048	TTCTTGATGTCC	1-10-1 MOE	891
147733	36071	36082	TTCTTGATGTCC	1-10-1 MOE	891
147726	36126	36137	TGACTCTCGGAC	1-10-1 MOE	1120
147736	36359	36370	AGGTAGGAGAAG	1-10-1 MOE	963
147691	36360	36371	GAGGTGGGAAAA	1-10-1 MOE	966
147736	36507	36518	AGGTAGGAGAAG	1-10-1 MOE	963
147691	36508	36519	GAGGTGGGAAAA	1-10-1 MOE	966
147746	36564	36575	TAAAAACAACAA	1-10-1 MOE	1073
147723	36575	36586	GACTCCAAAGTC	1-10-1 MOE	892
147731	36620	36631	TTTCCTCTTGTC	1-10-1 MOE	934
147723	36723	36734	GACTCCAAAGTC	1-10-1 MOE	892
147731	36768	36779	TTTCCTCTTGTC	1-10-1 MOE	934
398169	37174	37185	TCAGCCAGACAG	1-10-1 MOE	909
147688	37380	37391	TCCCAAACAAAT	1-10-1 MOE	990
147688	37528	37539	TCCCAAACAAAT	1-10-1 MOE	990
147714	37881	37892	TTCTGCTCCCAC	1-10-1 MOE	986
147714	38029	38040	TTCTGCTCCCAC	1-10-1 MOE	986
147681	38364	38375	ATGTCATTAAAC	1-10-1 MOE	965
147736	38766	38777	AGGTAGGAGAAG	1-10-1 MOE	963
147738	38909	38920	TGGGTGGCCGGG	1-10-1 MOE	1069
147736	38914	38925	AGGTAGGAGAAG	1-10-1 MOE	963
147738	39057	39068	TGGGTGGCCGGG	1-10-1 MOE	1069
390030	39249	39260	TTTATAAAACTG	1-10-1 MOE	1074
390030	39397	39408	TTTATAAAACTG	1-10-1 MOE	1074
147717	39545	39556	ATCTTCAGAGAT	1-10-1 MOE	996
147717	39693	39704	ATCTTCAGAGAT	1-10-1 MOE	996
147746	39729	39740	TAAAAACAACAA	1-10-1 MOE	1073
147746	39789	39800	TAAAAACAACAA	1-10-1 MOE	1073
147691	39829	39840	GAGGTGGGAAAA	1-10-1 MOE	966
147746	39877	39888	TAAAAACAACAA	1-10-1 MOE	1073
147691	39977	39988	GAGGTGGGAAAA	1-10-1 MOE	966
147727	39983	39994	CAGTGGACCACA	1-10-1 MOE	1128
147727	40131	40142	CAGTGGACCACA	1-10-1 MOE	1128
147746	40333	40344	TAAAAACAACAA	1-10-1 MOE	1073
147719	40457	40468	CCAACTCCAACT	1-10-1 MOE	1116
147679	40467	40478	CAAAAGGATCCC	1-10-1 MOE	907
147746	40478	40489	TAAAAACAACAA	1-10-1 MOE	1073
147741	40565	40576	CACCCACTGGTG	1-10-1 MOE	1055
398166	40589	40600	GGGCTTCTTCCA	1-10-1 MOE	1070
147719	40605	40616	CCAACTCCAACT	1-10-1 MOE	1116
147679	40615	40626	CAAAAGGATCCC	1-10-1 MOE	907
147746	40626	40637	TAAAAACAACAA	1-10-1 MOE	1073
147735	40662	40673	GGAGAAGCGCAG	1-10-1 MOE	1016
147746	40706	40717	TAAAAACAACAA	1-10-1 MOE	1073
147741	40713	40724	CACCCACTGGTG	1-10-1 MOE	1055

398166	40737	40748	GGGCTTCTTCCA	1-10-1 MOE	1070
147735	40810	40821	GGAGAAGCGCAG	1-10-1 MOE	1016
147746	40854	40865	TAAAAACAACAA	1-10-1 MOE	1073
147718	41218	41229	TAATATGACTTG	1-10-1 MOE	998
147717	41221	41232	ATCTTCAGAGAT	1-10-1 MOE	996
147717	41369	41380	ATCTTCAGAGAT	1-10-1 MOE	996
147723	41627	41638	GACTCCAAAGTC	1-10-1 MOE	892
147717	41747	41758	ATCTTCAGAGAT	1-10-1 MOE	996
147723	41775	41786	GACTCCAAAGTC	1-10-1 MOE	892
390030	41908	41919	TTTATAAAACTG	1-10-1 MOE	1074
390030	42056	42067	TTTATAAAACTG	1-10-1 MOE	1074
398153	42157	42170	ATTTCTCTTACAGG	2-10-2 MOE	948
398153	42305	42318	ATTTCTCTTACAGG	2-10-2 MOE	948
147690	42423	42434	TGAAGTTAATTC	1-10-1 MOE	1138
147695	42521	42532	TCATTCCCCACT	1-10-1 MOE	984
147710	42543	42554	TATAGCTCCTCT	1-10-1 MOE	994
147690	42571	42582	TGAAGTTAATTC	1-10-1 MOE	1138
147695	42669	42680	TCATTCCCCACT	1-10-1 MOE	984
147078	43321	43332	CCTTCCACTGAT	1-10-1 MOE	1044
147079	43322	43333	TCCTTCCACTGA	1-10-1 MOE	1001
147716	43329	43340	TTAACGAGCCTT	1-10-1 MOE	949
147078	43469	43480	CCTTCCACTGAT	1-10-1 MOE	1044
147079	43470	43481	TCCTTCCACTGA	1-10-1 MOE	1001
147080	43471	43482	CTCCTTCCACTG	1-10-1 MOE	1021
398102	43837	43850	CTACCTGAGGATTT	2-10-2 MOE	899
147074	43848	43859	CCACTGATCCTG	1-10-1 MOE	845
401408	43871	43884	CAATGAAGCACAGG	2-10-2 MOE	989
398102	43985	43998	CTACCTGAGGATTT	2-10-2 MOE	899
147736	44137	44148	AGGTAGGAGAAG	1-10-1 MOE	963
147746	44140	44151	TAAAAACAACAA	1-10-1 MOE	1073
147687	44206	44217	CGACACGGGAAC	1-10-1 MOE	950
147743	44223	44234	AGGGCTTCCAGT	1-10-1 MOE	1042
384545	44242	44253	CAAGTAGGATGT	1-10-1 MOE	951
147736	44285	44296	AGGTAGGAGAAG	1-10-1 MOE	963
147743	44371	44382	AGGGCTTCCAGT	1-10-1 MOE	1042
384545	44390	44401	CAAGTAGGATGT	1-10-1 MOE	951
147728	44589	44600	GCCAGACAGAAG	1-10-1 MOE	1013
389948	44628	44639	CCGTTGGACCCC	1-10-1 MOE	915
147720	44703	44714	GATCTCTCGAGT	1-10-1 MOE	1117
147728	44729	44740	GCCAGACAGAAG	1-10-1 MOE	1013
147728	44737	44748	GCCAGACAGAAG	1-10-1 MOE	1013
389948	44776	44787	CCGTTGGACCCC	1-10-1 MOE	915
147720	44851	44862	GATCTCTCGAGT	1-10-1 MOE	1117
398110	44861	44874	GTTCCCTTTGCAGG	2-10-2 MOE	952
147728	44877	44888	GCCAGACAGAAG	1-10-1 MOE	1013
147705	45092	45103	CGGTTTTTGTTC	1-10-1 MOE	1002
147705	45240	45251	CGGTTTTTGTTC	1-10-1 MOE	1002
147681	45337	45348	ATGTCATTAAAC	1-10-1 MOE	965
147681	45485	45496	ATGTCATTAAAC	1-10-1 MOE	965
147096	45660	45671	TTGTTGTTCCCT	1-10-1 MOE	1107

147096	45808	45819	TTGTTGTTCCCT	1-10-1 MOE	1107
368368	45976	45989	TCCACTGATCCTTA	2-10-2 MOE	1127
147074	45977	45988	CCACTGATCCTG	1-10-1 MOE	845
147075	45978	45989	TCCACTGATCCT	1-10-1 MOE	1026
147076	45979	45990	TTCCACTGATCC	1-10-1 MOE	1029
368368	46124	46137	TCCACTGATCCTTA	2-10-2 MOE	1127
147075	46126	46137	TCCACTGATCCT	1-10-1 MOE	1026
147076	46127	46138	TTCCACTGATCC	1-10-1 MOE	1029
147705	46555	46566	CGGTTTTTGTTC	1-10-1 MOE	1002
147714	46685	46696	TTCTGCTCCCAC	1-10-1 MOE	986
147705	46703	46714	CGGTTTTTGTTC	1-10-1 MOE	1002
147714	46833	46844	TTCTGCTCCCAC	1-10-1 MOE	986
390030	47007	47018	TTTATAAAACTG	1-10-1 MOE	1074
147746	47023	47034	TAAAAACAACAA	1-10-1 MOE	1073
147746	47171	47182	TAAAAACAACAA	1-10-1 MOE	1073
147085	47607	47618	TCTACACCAGGT	1-10-1 MOE	961
147746	47609	47620	TAAAAACAACAA	1-10-1 MOE	1073
147089	47611	47622	TCCCTCTACACC	1-10-1 MOE	956
147091	47613	47624	GTTCCCTCTACA	1-10-1 MOE	1004
401384	47689	47702	TGAACACATCACTA	2-10-2 MOE	933
147691	47729	47740	GAGGTGGGAAAA	1-10-1 MOE	966
147085	47755	47766	TCTACACCAGGT	1-10-1 MOE	961
147087	47757	47768	CCTCTACACCAG	1-10-1 MOE	982
147090	47760	47771	TTCCCTCTACAC	1-10-1 MOE	955
147091	47761	47772	GTTCCCTCTACA	1-10-1 MOE	1004
147099	47770	47781	GAGTTGTTGTTC	1-10-1 MOE	1108
147100	47771	47782	CGAGTTGTTGTT	1-10-1 MOE	1109
390030	47847	47858	TTTATAAAACTG	1-10-1 MOE	1074
147691	47877	47888	GAGGTGGGAAAA	1-10-1 MOE	966
147099	47918	47929	GAGTTGTTGTTC	1-10-1 MOE	1108
147100	47919	47930	CGAGTTGTTGTT	1-10-1 MOE	1109
390030	47995	48006	TTTATAAAACTG	1-10-1 MOE	1074
147074	48222	48233	CCACTGATCCTG	1-10-1 MOE	845
147731	48340	48351	TTTCCTCTTGTC	1-10-1 MOE	934
147691	48393	48404	GAGGTGGGAAAA	1-10-1 MOE	966
147731	48488	48499	TTTCCTCTTGTC	1-10-1 MOE	934
147691	48541	48552	GAGGTGGGAAAA	1-10-1 MOE	966
398147	48887	48900	CTACAGGACAATAC	2-10-2 MOE	957
398147	49035	49048	CTACAGGACAATAC	2-10-2 MOE	957
147074	49525	49536	CCACTGATCCTG	1-10-1 MOE	845
398168	49742	49753	TCGGACTTTGAA	1-10-1 MOE	1008
384545	49858	49869	CAAGTAGGATGT	1-10-1 MOE	951
398168	49890	49901	TCGGACTTTGAA	1-10-1 MOE	1008
147724	49974	49985	GAAATTGAGGAA	1-10-1 MOE	1139
384545	50006	50017	CAAGTAGGATGT	1-10-1 MOE	951
147689	50084	50095	CAGAGAAGGTCT	1-10-1 MOE	987
147687	50102	50113	CGACACGGGAAC	1-10-1 MOE	950
147724	50122	50133	GAAATTGAGGAA	1-10-1 MOE	1139
147687	50250	50261	CGACACGGGAAC	1-10-1 MOE	950
398117	50389	50402	TTTCCACTTGGGTG	2-10-2 MOE	960

147736	50436	50447	AGGTAGGAGAAG	1-10-1 MOE	963
147736	50582	50593	AGGTAGGAGAAG	1-10-1 MOE	963
398168	50703	50714	TCGGACTTTGAA	1-10-1 MOE	1008
401397	50822	50835	CTGGTCAGCATTGA	2-10-2 MOE	946
147746	51019	51030	TAAAAACAACAA	1-10-1 MOE	1073
147708	51101	51112	TTGATATAGTCA	1-10-1 MOE	997
147746	51165	51176	TAAAAACAACAA	1-10-1 MOE	1073
147746	51185	51196	TAAAAACAACAA	1-10-1 MOE	1073
147708	51247	51258	TTGATATAGTCA	1-10-1 MOE	997
147081	51287	51298	GCTCCTTCCACT	1-10-1 MOE	1006
147082	51288	51299	AGCTCCTTCCAC	1-10-1 MOE	1036
147746	51324	51335	TAAAAACAACAA	1-10-1 MOE	1073
147746	51331	51342	TAAAAACAACAA	1-10-1 MOE	1073
147728	51376	51387	GCCAGACAGAAG	1-10-1 MOE	1013
147729	51406	51417	GTAAGAGGCAGG	1-10-1 MOE	920
147081	51433	51444	GCTCCTTCCACT	1-10-1 MOE	1006
147082	51434	51445	AGCTCCTTCCAC	1-10-1 MOE	1036
147728	51492	51503	GCCAGACAGAAG	1-10-1 MOE	1013
147728	51522	51533	GCCAGACAGAAG	1-10-1 MOE	1013
147729	51552	51563	GTAAGAGGCAGG	1-10-1 MOE	920
368360	51633	51646	AAGCTCCTTCCACT	2-10-2 MOE	1035
147082	51634	51645	AGCTCCTTCCAC	1-10-1 MOE	1036
368361	51635	51648	GAAAGCTCCTTCCA	2-10-2 MOE	962
147728	51638	51649	GCCAGACAGAAG	1-10-1 MOE	1013
147695	51644	51655	TCATTCCCCACT	1-10-1 MOE	984
147736	51713	51724	AGGTAGGAGAAG	1-10-1 MOE	963
147684	51721	51732	ACCCAGTCAGGG	1-10-1 MOE	964
147081	51779	51790	GCTCCTTCCACT	1-10-1 MOE	1006
368360	51779	51792	AAGCTCCTTCCACT	2-10-2 MOE	1035
147082	51780	51791	AGCTCCTTCCAC	1-10-1 MOE	1036
368361	51781	51794	GAAAGCTCCTTCCA	2-10-2 MOE	962
147695	51790	51801	TCATTCCCCACT	1-10-1 MOE	984
147736	51859	51870	AGGTAGGAGAAG	1-10-1 MOE	963
147077	51988	51999	CTTCCACTGATC	1-10-1 MOE	1047
147079	51990	52001	TCCTTCCACTGA	1-10-1 MOE	1001
147746	52064	52075	TAAAAACAACAA	1-10-1 MOE	1073
147681	52085	52096	ATGTCATTAAAC	1-10-1 MOE	965
147077	52134	52145	CTTCCACTGATC	1-10-1 MOE	1047
147079	52136	52147	TCCTTCCACTGA	1-10-1 MOE	1001
147691	52166	52177	GAGGTGGGAAAA	1-10-1 MOE	966
147719	52252	52263	CCAACTCCAACT	1-10-1 MOE	1116
147691	52312	52323	GAGGTGGGAAAA	1-10-1 MOE	966
147719	52398	52409	CCAACTCCAACT	1-10-1 MOE	1116
147728	52428	52439	GCCAGACAGAAG	1-10-1 MOE	1013
147729	52483	52494	GTAAGAGGCAGG	1-10-1 MOE	920
398167	52527	52538	CAGGCCATGTGG	1-10-1 MOE	1059
147682	52571	52582	CGGGTACTATGG	1-10-1 MOE	992
147728	52574	52585	GCCAGACAGAAG	1-10-1 MOE	1013
147724	52615	52626	GAAATTGAGGAA	1-10-1 MOE	1139
147729	52629	52640	GTAAGAGGCAGG	1-10-1 MOE	920

147703	52670	52681	TGGCTTCATGTC	1-10-1 MOE	971
398167	52673	52684	CAGGCCATGTGG	1-10-1 MOE	1059
398165	52708	52719	GTTCTTAGGAAG	1-10-1 MOE	968
147704	52710	52721	TTGTTCTTAGGA	1-10-1 MOE	1012
147705	52716	52727	CGGTTTTTGTTC	1-10-1 MOE	1002
147724	52761	52772	GAAATTGAGGAA	1-10-1 MOE	1139
398167	52762	52773	CAGGCCATGTGG	1-10-1 MOE	1059
147703	52816	52827	TGGCTTCATGTC	1-10-1 MOE	971
398165	52854	52865	GTTCTTAGGAAG	1-10-1 MOE	968
147704	52856	52867	TTGTTCTTAGGA	1-10-1 MOE	1012
147705	52862	52873	CGGTTTTTGTTC	1-10-1 MOE	1002
398167	52908	52919	CAGGCCATGTGG	1-10-1 MOE	1059
147689	53063	53074	CAGAGAAGGTCT	1-10-1 MOE	987
147727	53111	53122	CAGTGGACCACA	1-10-1 MOE	1128
147727	53158	53169	CAGTGGACCACA	1-10-1 MOE	1128
147689	53209	53220	CAGAGAAGGTCT	1-10-1 MOE	987
147727	53257	53268	CAGTGGACCACA	1-10-1 MOE	1128
147727	53304	53315	CAGTGGACCACA	1-10-1 MOE	1128
147680	53638	53649	GTATGCACTGCT	1-10-1 MOE	988
147722	53650	53661	AAAGTCAGGCCA	1-10-1 MOE	1130
147083	53703	53714	TACACCAGGTCA	1-10-1 MOE	973
147085	53705	53716	TCTACACCAGGT	1-10-1 MOE	961
147086	53706	53717	CTCTACACCAGG	1-10-1 MOE	969
398167	53724	53735	CAGGCCATGTGG	1-10-1 MOE	1059
147684	53747	53758	ACCCAGTCAGGG	1-10-1 MOE	964
147680	53784	53795	GTATGCACTGCT	1-10-1 MOE	988
147722	53796	53807	AAAGTCAGGCCA	1-10-1 MOE	1130
147085	53851	53862	TCTACACCAGGT	1-10-1 MOE	961
398167	53870	53881	CAGGCCATGTGG	1-10-1 MOE	1059
147684	53893	53904	ACCCAGTCAGGG	1-10-1 MOE	964
398155	54026	54039	TGTTTTTACACAGA	2-10-2 MOE	970
147703	54137	54148	TGGCTTCATGTC	1-10-1 MOE	971
398155	54172	54185	TGTTTTTACACAGA	2-10-2 MOE	970
147705	54275	54286	CGGTTTTTGTTC	1-10-1 MOE	1002
147703	54283	54294	TGGCTTCATGTC	1-10-1 MOE	971
147705	54421	54432	CGGTTTTTGTTC	1-10-1 MOE	1002
147727	54853	54864	CAGTGGACCACA	1-10-1 MOE	1128
398165	54963	54974	GTTCTTAGGAAG	1-10-1 MOE	968
398090	54963	54976	TTGTTCTTAGGAAG	2-10-2 MOE	972
147704	54965	54976	TTGTTCTTAGGA	1-10-1 MOE	1012
147705	54971	54982	CGGTTTTTGTTC	1-10-1 MOE	1002
147727	54999	55010	CAGTGGACCACA	1-10-1 MOE	1128
398165	55109	55120	GTTCTTAGGAAG	1-10-1 MOE	968
147704	55111	55122	TTGTTCTTAGGA	1-10-1 MOE	1012
147705	55117	55128	CGGTTTTTGTTC	1-10-1 MOE	1002
147083	55352	55363	TACACCAGGTCA	1-10-1 MOE	973
147705	55378	55389	CGGTTTTTGTTC	1-10-1 MOE	1002
147705	55524	55535	CGGTTTTTGTTC	1-10-1 MOE	1002
147712	55819	55830	ACACCATCTCCC	1-10-1 MOE	1005
147712	55965	55976	ACACCATCTCCC	1-10-1 MOE	1005

147733	56289	56300	TTCTTGATGTCC	1-10-1 MOE	891
147707	56300	56311	TAGTCATTATCT	1-10-1 MOE	977
147708	56306	56317	TTGATATAGTCA	1-10-1 MOE	997
390030	56321	56332	TTTATAAAACTG	1-10-1 MOE	1074
147081	56333	56344	GCTCCTTCCACT	1-10-1 MOE	1006
398166	56335	56346	GGGCTTCTTCCA	1-10-1 MOE	1070
147733	56435	56446	TTCTTGATGTCC	1-10-1 MOE	891
147707	56446	56457	TAGTCATTATCT	1-10-1 MOE	977
147708	56452	56463	TTGATATAGTCA	1-10-1 MOE	997
390030	56467	56478	TTTATAAAACTG	1-10-1 MOE	1074
147081	56479	56490	GCTCCTTCCACT	1-10-1 MOE	1006
398091	56479	56492	GGGCTTCTTCCATT	2-10-2 MOE	979
398166	56481	56492	GGGCTTCTTCCA	1-10-1 MOE	1070
368366	56518	56531	CTGATCCTTAGAAG	2-10-2 MOE	1019
147743	57612	57623	AGGGCTTCCAGT	1-10-1 MOE	1042
147700	57709	57720	GCGCTAGGCCGC	1-10-1 MOE	1110
147743	57758	57769	AGGGCTTCCAGT	1-10-1 MOE	1042
147700	57855	57866	GCGCTAGGCCGC	1-10-1 MOE	1110
398093	57963	57976	TCGGACTTTGAAAA	2-10-2 MOE	1009
398168	57965	57976	TCGGACTTTGAA	1-10-1 MOE	1008
147698	58105	58116	CCCGCCACCACC	1-10-1 MOE	928
398093	58109	58122	TCGGACTTTGAAAA	2-10-2 MOE	1009
398168	58111	58122	TCGGACTTTGAA	1-10-1 MOE	1008
147698	58251	58262	CCCGCCACCACC	1-10-1 MOE	928
147735	58279	58290	GGAGAAGCGCAG	1-10-1 MOE	1016
147735	58425	58436	GGAGAAGCGCAG	1-10-1 MOE	1016
404135	58946	58959	CATTTCCATGGCCA	2-10-2 MOE	1056
390030	59326	59337	TTTATAAAACTG	1-10-1 MOE	1074
147711	59357	59368	AAGGGCCCTGGG	1-10-1 MOE	1040
147743	59382	59393	AGGGCTTCCAGT	1-10-1 MOE	1042
147711	59503	59514	AAGGGCCCTGGG	1-10-1 MOE	1040
147743	59528	59539	AGGGCTTCCAGT	1-10-1 MOE	1042
147695	59576	59587	TCATTCCCCACT	1-10-1 MOE	984
147713	59716	59727	CTCCCACACCAT	1-10-1 MOE	985
147714	59721	59732	TTCTGCTCCCAC	1-10-1 MOE	986
147715	59746	59757	GTTGAGCATGAC	1-10-1 MOE	1077
147716	59771	59782	TTAACGAGCCTT	1-10-1 MOE	949
147712	59857	59868	ACACCATCTCCC	1-10-1 MOE	1005
147714	59867	59878	TTCTGCTCCCAC	1-10-1 MOE	986
147715	59892	59903	GTTGAGCATGAC	1-10-1 MOE	1077
147716	59917	59928	TTAACGAGCCTT	1-10-1 MOE	949
390030	59993	60004	TTTATAAAACTG	1-10-1 MOE	1074
147690	60270	60281	TGAAGTTAATTC	1-10-1 MOE	1138
389949	60325	60336	GCGCGAGCCCGA	1-10-1 MOE	1061
147690	60416	60427	TGAAGTTAATTC	1-10-1 MOE	1138
389949	60471	60482	GCGCGAGCCCGA	1-10-1 MOE	1061
147746	60619	60630	TAAAAACAACAA	1-10-1 MOE	1073
384545	60676	60687	CAAGTAGGATGT	1-10-1 MOE	951
147746	60765	60776	TAAAAACAACAA	1-10-1 MOE	1073
384545	60822	60833	CAAGTAGGATGT	1-10-1 MOE	951

147689	60967	60978	CAGAGAAGGTCT	1-10-1 MOE	987
147689	61008	61019	CAGAGAAGGTCT	1-10-1 MOE	987
147689	61049	61060	CAGAGAAGGTCT	1-10-1 MOE	987
398105	61121	61134	TGCACAGGCAGGTT	2-10-2 MOE	1066
147689	61154	61165	CAGAGAAGGTCT	1-10-1 MOE	987
147689	61195	61206	CAGAGAAGGTCT	1-10-1 MOE	987
398105	61267	61280	TGCACAGGCAGGTT	2-10-2 MOE	1066
147692	61365	61376	CTCACCTTCATG	1-10-1 MOE	1113
147692	61511	61522	CTCACCTTCATG	1-10-1 MOE	1113
147680	61619	61630	GTATGCACTGCT	1-10-1 MOE	988
147078	61755	61766	CCTTCCACTGAT	1-10-1 MOE	1044
147079	61756	61767	TCCTTCCACTGA	1-10-1 MOE	1001
147080	61757	61768	CTCCTTCCACTG	1-10-1 MOE	1021
147078	61901	61912	CCTTCCACTGAT	1-10-1 MOE	1044
147079	61902	61913	TCCTTCCACTGA	1-10-1 MOE	1001
147080	61903	61914	CTCCTTCCACTG	1-10-1 MOE	1021
147088	62361	62372	CCCTCTACACCA	1-10-1 MOE	1050
401384	62573	62586	TGAACACATCACTA	2-10-2 MOE	933
147688	62697	62708	TCCCAAACAAAT	1-10-1 MOE	990
147746	63102	63113	TAAAAACAACAA	1-10-1 MOE	1073
147721	63225	63236	AATGCAGGATCT	1-10-1 MOE	1118
147742	63226	63237	AACTTCAGTGTC	1-10-1 MOE	1041
147746	63248	63259	TAAAAACAACAA	1-10-1 MOE	1073
147682	63337	63348	CGGGTACTATGG	1-10-1 MOE	992
147721	63371	63382	AATGCAGGATCT	1-10-1 MOE	1118
147742	63372	63383	AACTTCAGTGTC	1-10-1 MOE	1041
147688	63401	63412	TCCCAAACAAAT	1-10-1 MOE	990
147097	63449	63460	GTTGTTGTTCCC	1-10-1 MOE	1111
147098	63450	63461	AGTTGTTGTTCC	1-10-1 MOE	1112
401409	63458	63471	ATTCTTAACACAGA	2-10-2 MOE	991
147084	63531	63542	CTACACCAGGTC	1-10-1 MOE	993
147688	63547	63558	TCCCAAACAAAT	1-10-1 MOE	990
147097	63595	63606	GTTGTTGTTCCC	1-10-1 MOE	1111
147098	63596	63607	AGTTGTTGTTCC	1-10-1 MOE	1112
147721	64086	64097	AATGCAGGATCT	1-10-1 MOE	1118
147721	64232	64243	AATGCAGGATCT	1-10-1 MOE	1118
147692	64233	64244	CTCACCTTCATG	1-10-1 MOE	1113
147692	64379	64390	CTCACCTTCATG	1-10-1 MOE	1113
147729	64633	64644	GTAAGAGGCAGG	1-10-1 MOE	920
401403	64746	64759	TTTCCTAGGAGGTG	2-10-2 MOE	967
147729	64779	64790	GTAAGAGGCAGG	1-10-1 MOE	920
147746	65151	65162	TAAAAACAACAA	1-10-1 MOE	1073
147746	65297	65308	TAAAAACAACAA	1-10-1 MOE	1073
147689	65302	65313	CAGAGAAGGTCT	1-10-1 MOE	987
147689	65448	65459	CAGAGAAGGTCT	1-10-1 MOE	987
147717	65862	65873	ATCTTCAGAGAT	1-10-1 MOE	996
147717	65895	65906	ATCTTCAGAGAT	1-10-1 MOE	996
147729	66000	66011	GTAAGAGGCAGG	1-10-1 MOE	920
147717	66008	66019	ATCTTCAGAGAT	1-10-1 MOE	996
147717	66041	66052	ATCTTCAGAGAT	1-10-1 MOE	996

147708	66046	66057	TTGATATAGTCA	1-10-1 MOE	997
147718	66055	66066	TAATATGACTTG	1-10-1 MOE	998
147729	66146	66157	GTAAGAGGCAGG	1-10-1 MOE	920
147089	66236	66247	TCCCTCTACACC	1-10-1 MOE	956
368363	66281	66294	CTTAGAAGGCAGCA	2-10-2 MOE	1114
147727	66293	66304	CAGTGGACCACA	1-10-1 MOE	1128
147093	66319	66330	TTGTTCCCTCTA	1-10-1 MOE	929
147094	66320	66331	GTTGTTCCCTCT	1-10-1 MOE	1115
147089	66382	66393	TCCCTCTACACC	1-10-1 MOE	956
368363	66427	66440	CTTAGAAGGCAGCA	2-10-2 MOE	1114
147727	66439	66450	CAGTGGACCACA	1-10-1 MOE	1128
147719	66441	66452	CCAACTCCAACT	1-10-1 MOE	1116
147093	66465	66476	TTGTTCCCTCTA	1-10-1 MOE	929
147094	66466	66477	GTTGTTCCCTCT	1-10-1 MOE	1115
147075	66561	66572	TCCACTGATCCT	1-10-1 MOE	1026
368357	66562	66575	CCTTCCACTGATCC	2-10-2 MOE	1046
147076	66562	66573	TTCCACTGATCC	1-10-1 MOE	1029
368377	66562	66577	CTCCTTCCACTGATCC	3-10-3 MOE	1030
147077	66563	66574	CTTCCACTGATC	1-10-1 MOE	1047
368358	66563	66576	TCCTTCCACTGATC	2-10-2 MOE	1031
147078	66564	66575	CCTTCCACTGAT	1-10-1 MOE	1044
147079	66565	66576	TCCTTCCACTGA	1-10-1 MOE	1001
147080	66566	66577	CTCCTTCCACTG	1-10-1 MOE	1021
147081	66567	66578	GCTCCTTCCACT	1-10-1 MOE	1006
147719	66587	66598	CCAACTCCAACT	1-10-1 MOE	1116
147075	66707	66718	TCCACTGATCCT	1-10-1 MOE	1026
368377	66708	66723	CTCCTTCCACTGATCC	3-10-3 MOE	1030
147076	66708	66719	TTCCACTGATCC	1-10-1 MOE	1029
368357	66708	66721	CCTTCCACTGATCC	2-10-2 MOE	1046
147077	66709	66720	CTTCCACTGATC	1-10-1 MOE	1047
147078	66710	66721	CCTTCCACTGAT	1-10-1 MOE	1044
147079	66711	66722	TCCTTCCACTGA	1-10-1 MOE	1001
147080	66712	66723	CTCCTTCCACTG	1-10-1 MOE	1021
147081	66713	66724	GCTCCTTCCACT	1-10-1 MOE	1006
147089	66842	66853	TCCCTCTACACC	1-10-1 MOE	956
147089	66988	66999	TCCCTCTACACC	1-10-1 MOE	956
147075	66999	67010	TCCACTGATCCT	1-10-1 MOE	1026
147075	67145	67156	TCCACTGATCCT	1-10-1 MOE	1026
147705	67213	67224	CGGTTTTTGTTC	1-10-1 MOE	1002
401413	67301	67314	TGCAGCCATGTACT	2-10-2 MOE	1022
147737	67309	67320	ACAGCCAGGTAG	1-10-1 MOE	1067
147080	67430	67441	CTCCTTCCACTG	1-10-1 MOE	1021
147737	67455	67466	ACAGCCAGGTAG	1-10-1 MOE	1067
147080	67576	67587	CTCCTTCCACTG	1-10-1 MOE	1021
147082	67578	67589	AGCTCCTTCCAC	1-10-1 MOE	1036
147090	67582	67593	TTCCCTCTACAC	1-10-1 MOE	955
147091	67583	67594	GTTCCCTCTACA	1-10-1 MOE	1004
147742	67591	67602	AACTTCAGTGTC	1-10-1 MOE	1041
147090	67728	67739	TTCCCTCTACAC	1-10-1 MOE	955
147698	68036	68047	CCCGCCACCACC	1-10-1 MOE	928

147698	68182	68193	CCCGCCACCACC	1-10-1 MOE	928
147681	68267	68278	ATGTCATTAAAC	1-10-1 MOE	965
147721	68386	68397	AATGCAGGATCT	1-10-1 MOE	1118
147681	68413	68424	ATGTCATTAAAC	1-10-1 MOE	965
147712	68527	68538	ACACCATCTCCC	1-10-1 MOE	1005
147721	68532	68543	AATGCAGGATCT	1-10-1 MOE	1118
147711	68760	68771	AAGGGCCCTGGG	1-10-1 MOE	1040
147711	68906	68917	AAGGGCCCTGGG	1-10-1 MOE	1040
147696	69045	69056	TGGATGATTGGC	1-10-1 MOE	906
147696	69191	69202	TGGATGATTGGC	1-10-1 MOE	906
147723	69194	69205	GACTCCAAAGTC	1-10-1 MOE	892
147723	69210	69221	GACTCCAAAGTC	1-10-1 MOE	892
389965	69271	69282	CTGCAACATGAT	1-10-1 MOE	1018
389764	69271	69282	CTGCAACATGAT	1-9-2 MOE	1018
147723	69340	69351	GACTCCAAAGTC	1-10-1 MOE	892
147723	69356	69367	GACTCCAAAGTC	1-10-1 MOE	892
398101	69357	69370	TTTGATAAAGCCCT	2-10-2 MOE	1064
389965	69417	69428	CTGCAACATGAT	1-10-1 MOE	1018
389764	69417	69428	CTGCAACATGAT	1-9-2 MOE	1018
398101	69503	69516	TTTGATAAAGCCCT	2-10-2 MOE	1064
368353	69519	69532	CACTGATCCTGCAC	2-10-2 MOE	1007
147074	69522	69533	CCACTGATCCTG	1-10-1 MOE	845
147081	69631	69642	GCTCCTTCCACT	1-10-1 MOE	1006
368353	69665	69678	CACTGATCCTGCAC	2-10-2 MOE	1007
147720	69729	69740	GATCTCTCGAGT	1-10-1 MOE	1117
147721	69736	69747	AATGCAGGATCT	1-10-1 MOE	1118
398167	69757	69768	CAGGCCATGTGG	1-10-1 MOE	1059
147722	69762	69773	AAAGTCAGGCCA	1-10-1 MOE	1130
147723	69768	69779	GACTCCAAAGTC	1-10-1 MOE	892
147080	69776	69787	CTCCTTCCACTG	1-10-1 MOE	1021
147081	69777	69788	GCTCCTTCCACT	1-10-1 MOE	1006
398093	69811	69824	TCGGACTTTGAAAA	2-10-2 MOE	1009
398168	69813	69824	TCGGACTTTGAA	1-10-1 MOE	1008
147725	69814	69825	CTCGGACTTTGA	1-10-1 MOE	1119
147726	69819	69830	TGACTCTCGGAC	1-10-1 MOE	1120
147727	69860	69871	CAGTGGACCACA	1-10-1 MOE	1128
147720	69875	69886	GATCTCTCGAGT	1-10-1 MOE	1117
147721	69882	69893	AATGCAGGATCT	1-10-1 MOE	1118
147728	69899	69910	GCCAGACAGAAG	1-10-1 MOE	1013
398094	69901	69914	ATCAGCCAGACAGA	2-10-2 MOE	1010
398167	69903	69914	CAGGCCATGTGG	1-10-1 MOE	1059
398092	69904	69917	AGTCAGGCCATGTG	2-10-2 MOE	1060
147722	69908	69919	AAAGTCAGGCCA	1-10-1 MOE	1130
147723	69914	69925	GACTCCAAAGTC	1-10-1 MOE	892
147729	69916	69927	GTAAGAGGCAGG	1-10-1 MOE	920
398095	69919	69932	CATCAGCAAGAGGC	2-10-2 MOE	1011
398093	69957	69970	TCGGACTTTGAAAA	2-10-2 MOE	1009
398168	69959	69970	TCGGACTTTGAA	1-10-1 MOE	1008
147725	69960	69971	CTCGGACTTTGA	1-10-1 MOE	1119
147726	69965	69976	TGACTCTCGGAC	1-10-1 MOE	1120

147704	69991	70002	TTGTTCTTAGGA	1-10-1 MOE	1012
147727	70006	70017	CAGTGGACCACA	1-10-1 MOE	1128
147728	70045	70056	GCCAGACAGAAG	1-10-1 MOE	1013
398094	70047	70060	ATCAGCCAGACAGA	2-10-2 MOE	1010
398169	70048	70059	TCAGCCAGACAG	1-10-1 MOE	909
147729	70062	70073	GTAAGAGGCAGG	1-10-1 MOE	920
398095	70065	70078	CATCAGCAAGAGGC	2-10-2 MOE	1011
147704	70137	70148	TTGTTCTTAGGA	1-10-1 MOE	1012
147697	70161	70172	CCCCAGCAGCGG	1-10-1 MOE	1000
147697	70307	70318	CCCCAGCAGCGG	1-10-1 MOE	1000
147728	70450	70461	GCCAGACAGAAG	1-10-1 MOE	1013
398164	70464	70475	TTGTCGATCTGC	1-10-1 MOE	1014
147730	70465	70476	CTTGTCCATCAG	1-10-1 MOE	1121
147731	70471	70482	TTTCCTCTTGTC	1-10-1 MOE	934
147732	70476	70487	GGGTCTTTCCTC	1-10-1 MOE	1122
147733	70497	70508	TTCTTGATGTCC	1-10-1 MOE	891
398096	70562	70575	GGAGAAGCGCAGCT	2-10-2 MOE	1015
147735	70564	70575	GGAGAAGCGCAG	1-10-1 MOE	1016
147736	70569	70580	AGGTAGGAGAAG	1-10-1 MOE	963
147737	70575	70586	ACAGCCAGGTAG	1-10-1 MOE	1067
147728	70596	70607	GCCAGACAGAAG	1-10-1 MOE	1013
398164	70610	70621	TTGTCGATCTGC	1-10-1 MOE	1014
147730	70611	70622	CTTGTCCATCAG	1-10-1 MOE	1121
368349	70616	70629	CTGCACTGACGAGT	2-10-2 MOE	1017
147731	70617	70628	TTTCCTCTTGTC	1-10-1 MOE	934
147732	70622	70633	GGGTCTTTCCTC	1-10-1 MOE	1122
147733	70643	70654	TTCTTGATGTCC	1-10-1 MOE	891
398096	70708	70721	GGAGAAGCGCAGCT	2-10-2 MOE	1015
147735	70710	70721	GGAGAAGCGCAG	1-10-1 MOE	1016
147736	70715	70726	AGGTAGGAGAAG	1-10-1 MOE	963
147737	70721	70732	ACAGCCAGGTAG	1-10-1 MOE	1067
389764	70784	70795	CTGCAACATGAT	1-9-2 MOE	1018
389965	70784	70795	CTGCAACATGAT	1-10-1 MOE	1018
389965	70930	70941	CTGCAACATGAT	1-10-1 MOE	1018
389764	70930	70941	CTGCAACATGAT	1-9-2 MOE	1018
368386	70995	71010	CACTGATCCTTAGAAG	3-10-3 MOE	1123
368367	70997	71010	CACTGATCCTTAGA	2-10-2 MOE	1124
368387	70997	71012	TCCACTGATCCTTAGA	3-10-3 MOE	1125
368354	70999	71012	TCCACTGATCCTGC	2-10-2 MOE	1024
368374	70999	71014	CTTCCACTGATCCTGC	3-10-3 MOE	1126
368368	70999	71012	TCCACTGATCCTTA	2-10-2 MOE	1127
368388	70999	71014	CTTCCACTGATCCTTA	3-10-3 MOE	895
368355	71000	71013	TTCCACTGATCCTG	2-10-2 MOE	1025
147074	71000	71011	CCACTGATCCTG	1-10-1 MOE	845
368375	71000	71015	CCTTCCACTGATCCTG	3-10-3 MOE	1020
147075	71001	71012	TCCACTGATCCT	1-10-1 MOE	1026
368376	71001	71016	TCCTTCCACTGATCCT	3-10-3 MOE	1028
147076	71002	71013	TTCCACTGATCC	1-10-1 MOE	1029
368357	71002	71015	CCTTCCACTGATCC	2-10-2 MOE	1046
368377	71002	71017	CTCCTTCCACTGATCC	3-10-3 MOE	1030

147077	71003	71014	CTTCCACTGATC	1-10-1 MOE	1047
368378	71003	71018	GCTCCTTCCACTGATC	3-10-3 MOE	1032
147078	71004	71015	CCTTCCACTGAT	1-10-1 MOE	1044
368359	71005	71018	GCTCCTTCCACTGA	2-10-2 MOE	1033
368379	71005	71020	AAGCTCCTTCCACTGA	3-10-3 MOE	1034
147079	71005	71016	TCCTTCCACTGA	1-10-1 MOE	1001
147080	71006	71017	CTCCTTCCACTG	1-10-1 MOE	1021
368360	71007	71020	AAGCTCCTTCCACT	2-10-2 MOE	1035
368380	71007	71022	GAAAGCTCCTTCCACT	3-10-3 MOE	896
147081	71007	71018	GCTCCTTCCACT	1-10-1 MOE	1006
147082	71008	71019	AGCTCCTTCCAC	1-10-1 MOE	1036
368361	71009	71022	GAAAGCTCCTTCCA	2-10-2 MOE	962
368381	71009	71024	GGGAAAGCTCCTTCCA	3-10-3 MOE	1037
147738	71067	71078	TGGGTGGCCGGG	1-10-1 MOE	1069
147739	71071	71082	CGTTTGGGTGGC	1-10-1 MOE	1023
147740	71088	71099	TGTGAGGCTCCA	1-10-1 MOE	1062
147741	71129	71140	CACCCACTGGTG	1-10-1 MOE	1055
368366	71141	71154	CTGATCCTTAGAAG	2-10-2 MOE	1019
368386	71141	71156	CACTGATCCTTAGAAG	3-10-3 MOE	1123
368367	71143	71156	CACTGATCCTTAGA	2-10-2 MOE	1124
368387	71143	71158	TCCACTGATCCTTAGA	3-10-3 MOE	1125
368374	71145	71160	CTTCCACTGATCCTGC	3-10-3 MOE	1126
368354	71145	71158	TCCACTGATCCTGC	2-10-2 MOE	1024
368368	71145	71158	TCCACTGATCCTTA	2-10-2 MOE	1127
368388	71145	71160	CTTCCACTGATCCTTA	3-10-3 MOE	895
368355	71146	71159	TTCCACTGATCCTG	2-10-2 MOE	1025
368375	71146	71161	CCTTCCACTGATCCTG	3-10-3 MOE	1020
147075	71147	71158	TCCACTGATCCT	1-10-1 MOE	1026
368356	71147	71160	CTTCCACTGATCCT	2-10-2 MOE	1027
368376	71147	71162	TCCTTCCACTGATCCT	3-10-3 MOE	1028
147076	71148	71159	TTCCACTGATCC	1-10-1 MOE	1029
368357	71148	71161	CCTTCCACTGATCC	2-10-2 MOE	1046
368377	71148	71163	CTCCTTCCACTGATCC	3-10-3 MOE	1030
147077	71149	71160	CTTCCACTGATC	1-10-1 MOE	1047
368358	71149	71162	TCCTTCCACTGATC	2-10-2 MOE	1031
368378	71149	71164	GCTCCTTCCACTGATC	3-10-3 MOE	1032
147078	71150	71161	CCTTCCACTGAT	1-10-1 MOE	1044
368359	71151	71164	GCTCCTTCCACTGA	2-10-2 MOE	1033
147079	71151	71162	TCCTTCCACTGA	1-10-1 MOE	1001
368379	71151	71166	AAGCTCCTTCCACTGA	3-10-3 MOE	1034
147080	71152	71163	CTCCTTCCACTG	1-10-1 MOE	1021
368380	71153	71168	GAAAGCTCCTTCCACT	3-10-3 MOE	896
147081	71153	71164	GCTCCTTCCACT	1-10-1 MOE	1006
368360	71153	71166	AAGCTCCTTCCACT	2-10-2 MOE	1035
147082	71154	71165	AGCTCCTTCCAC	1-10-1 MOE	1036
368381	71155	71170	GGGAAAGCTCCTTCCA	3-10-3 MOE	1037
368361	71155	71168	GAAAGCTCCTTCCA	2-10-2 MOE	962
398097	71158	71171	GGCAGTCTTTATCC	2-10-2 MOE	897
147738	71213	71224	TGGGTGGCCGGG	1-10-1 MOE	1069
147739	71217	71228	CGTTTGGGTGGC	1-10-1 MOE	1023

147740	71234	71245	TGTGAGGCTCCA	1-10-1 MOE	1062
147741	71275	71286	CACCCACTGGTG	1-10-1 MOE	1055
398097	71304	71317	GGCAGTCTTTATCC	2-10-2 MOE	897
147727	71702	71713	CAGTGGACCACA	1-10-1 MOE	1128
147727	71848	71859	CAGTGGACCACA	1-10-1 MOE	1128
390030	71986	71997	TTTATAAAACTG	1-10-1 MOE	1074
147102	72015	72026	TGCGAGTTGTTG	1-10-1 MOE	1129
390030	72132	72143	TTTATAAAACTG	1-10-1 MOE	1074
147102	72161	72172	TGCGAGTTGTTG	1-10-1 MOE	1129
147722	72199	72210	AAAGTCAGGCCA	1-10-1 MOE	1130
147696	72232	72243	TGGATGATTGGC	1-10-1 MOE	906
147741	72254	72265	CACCCACTGGTG	1-10-1 MOE	1055
147722	72345	72356	AAAGTCAGGCCA	1-10-1 MOE	1130
147696	72378	72389	TGGATGATTGGC	1-10-1 MOE	906
147741	72400	72411	CACCCACTGGTG	1-10-1 MOE	1055
147711	72446	72457	AAGGGCCCTGGG	1-10-1 MOE	1040
398098	72574	72587	TAACTTCAGTGTCT	2-10-2 MOE	1131
147742	72575	72586	AACTTCAGTGTC	1-10-1 MOE	1041
147698	72595	72606	CCCGCCACCACC	1-10-1 MOE	928
147743	72690	72701	AGGGCTTCCAGT	1-10-1 MOE	1042
398099	72690	72703	GAAGGGCTTCCAGT	2-10-2 MOE	1132
147744	72694	72705	AGGAAGGGCTTC	1-10-1 MOE	1043
398100	72697	72710	TGACCAGGAAGGGC	2-10-2 MOE	1133
147745	72700	72711	TTGACCAGGAAG	1-10-1 MOE	1058
398098	72720	72733	TAACTTCAGTGTCT	2-10-2 MOE	1131
147742	72721	72732	AACTTCAGTGTC	1-10-1 MOE	1041
147698	72741	72752	CCCGCCACCACC	1-10-1 MOE	928
398157	72757	72770	GGAAACATACCCTG	2-10-2 MOE	1045
147743	72836	72847	AGGGCTTCCAGT	1-10-1 MOE	1042
398099	72836	72849	GAAGGGCTTCCAGT	2-10-2 MOE	1132
147744	72840	72851	AGGAAGGGCTTC	1-10-1 MOE	1043
398100	72843	72856	TGACCAGGAAGGGC	2-10-2 MOE	1133
147745	72846	72857	TTGACCAGGAAG	1-10-1 MOE	1058
147076	72898	72909	TTCCACTGATCC	1-10-1 MOE	1029
368357	72898	72911	CCTTCCACTGATCC	2-10-2 MOE	1046
147077	72899	72910	CTTCCACTGATC	1-10-1 MOE	1047
147078	72900	72911	CCTTCCACTGAT	1-10-1 MOE	1044
398157	72903	72916	GGAAACATACCCTG	2-10-2 MOE	1045
398158	72983	72996	AGGCCCTGAGATTA	2-10-2 MOE	1134
398159	72988	73001	GGTTAAGGCCCTGA	2-10-2 MOE	1135
398160	72993	73006	GAATAGGTTAAGGC	2-10-2 MOE	1048
147076	73044	73055	TTCCACTGATCC	1-10-1 MOE	1029
368357	73044	73057	CCTTCCACTGATCC	2-10-2 MOE	1046
147077	73045	73056	CTTCCACTGATC	1-10-1 MOE	1047
147078	73046	73057	CCTTCCACTGAT	1-10-1 MOE	1044
147746	73052	73063	TAAAAACAACAA	1-10-1 MOE	1073
398161	73092	73105	AACAATGTGTTGTA	2-10-2 MOE	1049
147746	73101	73112	TAAAAACAACAA	1-10-1 MOE	1073
398158	73129	73142	AGGCCCTGAGATTA	2-10-2 MOE	1134
398159	73134	73147	GGTTAAGGCCCTGA	2-10-2 MOE	1135

398160	73139	73152	GAATAGGTTAAGGC	2-10-2 MOE	1048
147746	73198	73209	TAAAAACAACAA	1-10-1 MOE	1073
398161	73238	73251	AACAATGTGTTGTA	2-10-2 MOE	1049
147746	73247	73258	TAAAAACAACAA	1-10-1 MOE	1073
147088	73273	73284	CCCTCTACACCA	1-10-1 MOE	1050
398105	73401	73414	TGCACAGGCAGGTT	2-10-2 MOE	1066
398105	73547	73560	TGCACAGGCAGGTT	2-10-2 MOE	1066
147741	73559	73570	CACCCACTGGTG	1-10-1 MOE	1055
147741	73705	73716	CACCCACTGGTG	1-10-1 MOE	1055
398162	73968	73981	ACCAAACAGTTCAG	2-10-2 MOE	1057
147745	73991	74002	TTGACCAGGAAG	1-10-1 MOE	1058
398167	74008	74019	CAGGCCATGTGG	1-10-1 MOE	1059
398092	74009	74022	AGTCAGGCCATGTG	2-10-2 MOE	1060
398162	74114	74127	ACCAAACAGTTCAG	2-10-2 MOE	1057
147745	74137	74148	TTGACCAGGAAG	1-10-1 MOE	1058
398167	74154	74165	CAGGCCATGTGG	1-10-1 MOE	1059
147089	74280	74291	TCCCTCTACACC	1-10-1 MOE	956
147090	74281	74292	TTCCCTCTACAC	1-10-1 MOE	955
389949	74310	74321	GCGCGAGCCCGA	1-10-1 MOE	1061
147740	74339	74350	TGTGAGGCTCCA	1-10-1 MOE	1062
389950	74381	74392	CCCTGAAGGTTC	1-10-1 MOE	1063
147089	74426	74437	TCCCTCTACACC	1-10-1 MOE	956
147090	74427	74438	TTCCCTCTACAC	1-10-1 MOE	955
389949	74456	74467	GCGCGAGCCCGA	1-10-1 MOE	1061
147685	74490	74501	GGCTGACATTCA	1-10-1 MOE	975
398101	74510	74523	TTTGATAAAGCCCT	2-10-2 MOE	1064
398102	74536	74549	CTACCTGAGGATTT	2-10-2 MOE	899
398103	74543	74556	CCCAGTACTACCTG	2-10-2 MOE	900
147685	74636	74647	GGCTGACATTCA	1-10-1 MOE	975
398102	74682	74695	CTACCTGAGGATTT	2-10-2 MOE	899
398103	74689	74702	CCCAGTACTACCTG	2-10-2 MOE	900
147736	74737	74748	AGGTAGGAGAAG	1-10-1 MOE	963
398104	74805	74818	CAAGAAGACCTTAC	2-10-2 MOE	1065
147736	74883	74894	AGGTAGGAGAAG	1-10-1 MOE	963
147737	74893	74904	ACAGCCAGGTAG	1-10-1 MOE	1067
398105	74894	74907	TGCACAGGCAGGTT	2-10-2 MOE	1066
147737	74919	74930	ACAGCCAGGTAG	1-10-1 MOE	1067
398095	74940	74953	CATCAGCAAGAGGC	2-10-2 MOE	1011
398104	74951	74964	CAAGAAGACCTTAC	2-10-2 MOE	1065
398106	74974	74987	TGGAAAACTGCACC	2-10-2 MOE	1068
398107	74980	74993	TATTCCTGGAAAAC	2-10-2 MOE	902
147745	75030	75041	TTGACCAGGAAG	1-10-1 MOE	1058
147737	75039	75050	ACAGCCAGGTAG	1-10-1 MOE	1067
398105	75040	75053	TGCACAGGCAGGTT	2-10-2 MOE	1066
147737	75065	75076	ACAGCCAGGTAG	1-10-1 MOE	1067
398108	75077	75090	GGAATGTCTGAGTT	2-10-2 MOE	1136
398095	75086	75099	CATCAGCAAGAGGC	2-10-2 MOE	1011
147691	75108	75119	GAGGTGGGAAAA	1-10-1 MOE	966
398106	75120	75133	TGGAAAACTGCACC	2-10-2 MOE	1068
398107	75126	75139	TATTCCTGGAAAAC	2-10-2 MOE	902

147738	75155	75166	TGGGTGGCCGGG	1-10-1 MOE	1069
147745	75176	75187	TTGACCAGGAAG	1-10-1 MOE	1058
398108	75223	75236	GGAATGTCTGAGTT	2-10-2 MOE	1136
398109	75247	75260	CAAGAAGTGTGGTT	2-10-2 MOE	903
147691	75254	75265	GAGGTGGGAAAA	1-10-1 MOE	966
147738	75301	75312	TGGGTGGCCGGG	1-10-1 MOE	1069
398110	75385	75398	GTTCCCTTTGCAGG	2-10-2 MOE	952
147091	75387	75398	GTTCCCTCTACA	1-10-1 MOE	1004
398109	75393	75406	CAAGAAGTGTGGTT	2-10-2 MOE	903
398111	75470	75483	GTGAAAATGCTGGC	2-10-2 MOE	904
401385	75494	75507	CCCAGTGGGTTTGA	2-10-2 MOE	890
398166	75499	75510	GGGCTTCTTCCA	1-10-1 MOE	1070
147091	75525	75536	GTTCCCTCTACA	1-10-1 MOE	1004
147092	75526	75537	TGTTCCCTCTAC	1-10-1 MOE	901
398110	75531	75544	GTTCCCTTTGCAGG	2-10-2 MOE	952
147091	75533	75544	GTTCCCTCTACA	1-10-1 MOE	1004
147706	75540	75551	GCTGACATCTCG	1-10-1 MOE	1071
398112	75584	75597	CAGCCTGGCACCTA	2-10-2 MOE	1072
398111	75616	75629	GTGAAAATGCTGGC	2-10-2 MOE	904
147746	75617	75628	TAAAAACAACAA	1-10-1 MOE	1073
398166	75645	75656	GGGCTTCTTCCA	1-10-1 MOE	1070
147091	75671	75682	GTTCCCTCTACA	1-10-1 MOE	1004
147092	75672	75683	TGTTCCCTCTAC	1-10-1 MOE	901
398113	75693	75706	AGGAGGTTAAACCA	2-10-2 MOE	905
398112	75730	75743	CAGCCTGGCACCTA	2-10-2 MOE	1072
147746	75763	75774	TAAAAACAACAA	1-10-1 MOE	1073
398114	75770	75783	AGGCATATAGCAGA	2-10-2 MOE	1075
398115	75786	75799	AGTAAATATTGGCT	2-10-2 MOE	1076
398116	75799	75812	TAATGACCTGATGA	2-10-2 MOE	1137
398113	75839	75852	AGGAGGTTAAACCA	2-10-2 MOE	905
390030	75839	75850	TTTATAAAACTG	1-10-1 MOE	1074
398115	75932	75945	AGTAAATATTGGCT	2-10-2 MOE	1076
398116	75945	75958	TAATGACCTGATGA	2-10-2 MOE	1137
398106	75982	75995	TGGAAAACTGCACC	2-10-2 MOE	1068
390030	75985	75996	TTTATAAAACTG	1-10-1 MOE	1074
398106	76127	76140	TGGAAAACTGCACC	2-10-2 MOE	1068
147690	76196	76207	TGAAGTTAATTC	1-10-1 MOE	1138
147690	76341	76352	TGAAGTTAATTC	1-10-1 MOE	1138
147724	76740	76751	GAAATTGAGGAA	1-10-1 MOE	1139
147089	76873	76884	TCCCTCTACACC	1-10-1 MOE	956
147679	76881	76892	CAAAAGGATCCC	1-10-1 MOE	907
147724	76885	76896	GAAATTGAGGAA	1-10-1 MOE	1139
147089	77018	77029	TCCCTCTACACC	1-10-1 MOE	956
147679	77026	77037	CAAAAGGATCCC	1-10-1 MOE	907
147693	77240	77251	GTGCGCTCCCAT	1-10-1 MOE	1078
147697	77759	77770	CCCCAGCAGCGG	1-10-1 MOE	1000

In certain embodiments, a target region is nucleotides 177-190 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 177-190 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted to nucleotides 177-190 comprises a nucleotide

sequence selected from SEQ ID NO 886, 859, or 853. In certain such embodiments, a short antisense compound targeted to nucleotides 177-190 of SEQ ID NO: 11 is selected from Isis No 147022, 147023, or 147024.

In certain embodiments, a target region is nucleotides 195-228 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 195-228 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted to nucleotides 195-228 comprises a nucleotide sequence selected from SEQ ID NO 877, 868, 882, 886, 859, 853, 865, 835, 843, 846, 842, 848, 874, 849, 863, 855, 850, 864, or 834. In certain such embodiments, a short antisense compound targeted to nucleotides 195-228 of SEQ ID NO: 11 is selected from Isis No 147019, 147020, 147021, 147022, 147023, 147024, 147025, 147026, 147027, 147028, 147073, 147029, 147030, 147036, 147037, 147038, 147039, 147040, or 147041.

In certain embodiments, a target region is nucleotides 323-353 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 323-353 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted to nucleotides 323-353 comprises a nucleotide sequence selected from SEQ ID NO 866, 881, 869, 883, 858, 833, 875, 837, 829, 871, 884, 887, 839, 830, 840, 861, or 879. In certain such embodiments, a short antisense compound targeted to nucleotides 323-353 of SEQ ID NO: 11 is selected from Isis No 147042, 147043, 147044, 147045, 147046, 147047, 147051, 147052, 147053, 147054, 147055, 147056, 147057, 147058, 147059, 147060, or 147061.

In certain embodiments, a target region is nucleotides 322-353 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 322-353 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted to nucleotides 322-353 comprises a nucleotide sequence selected from SEQ ID NO 842, 866, 881, 869, 883, 858, 833, 875, 837, 829, 871, 884, 887, 839, 830, 840, 861, or 879. In certain such embodiments, a short antisense compound targeted to nucleotides 322-353 of SEQ ID NO: 11 is selected from Isis No 147073, 147042, 147043, 147044, 147045, 147046, 147047, 147051, 147052, 147053, 147054, 147055, 147056, 147057, 147058, 147059, 147060, or 147061.

In certain embodiments, a target region is nucleotides 679-799 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 679-799 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted to nucleotides 679-799 comprises a nucleotide sequence selected from SEQ ID NO 883, 858, 883, or 858. In certain such embodiments, a short antisense compound targeted to nucleotides 679-799 of SEQ ID NO: 11 is selected from Isis No 147045, 147046, 147045, or 147046.

In certain embodiments, a target region is nucleotides 679-827 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 679-827 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted to nucleotides 679-827 comprises a nucleotide sequence selected from SEQ ID NO 883, 858, 883, 858, or 851. In certain such embodiments, a short antisense compound targeted to nucleotides 679-827 of SEQ ID NO: 11 is selected from Isis No 147045, 147046, 147045, 147046, or 147066.

In certain embodiments, a target region is nucleotides 1024-1046 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 1024-1046 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted to nucleotides 1024-1046 comprises a nucleotide sequence selected from SEQ ID NO 841, 862, 880, 857, 851, 876, 838, 860, 878, 856, 832, or 842. In certain such embodiments, a short antisense compound targeted to nucleotides 1024-1046 of SEQ ID NO: 11 is selected from Isis No 147062, 147063, 147064, 147065, 147066, 147067, 147068, 147069, 147070, 147071, 147072, or 147073.

In certain embodiments, a target region is nucleotides 992-1046 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 992-1046 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted to nucleotides 992-1046 comprises a nucleotide sequence selected from SEQ ID NO 831, 841, 862, 880, 857, 851, 876, 838, 860, 878, 856, 832, or 842. In certain such embodiments, a short antisense compound targeted to nucleotides 992-1046 of SEQ ID NO: 11 is selected from Isis No 404131, 147062, 147063, 147064, 147065, 147066, 147067, 147068, 147069, 147070, 147071, 147072, or 147073.

In certain embodiments, a target region is nucleotides 1868-1881 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 1868-1881 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted to nucleotides 1868-1881 comprises a nucleotide sequence selected from SEQ ID NO 886, 859, or 853. In certain such embodiments, a short antisense compound targeted to nucleotides 1868-1881 of SEQ ID NO: 11 is selected from Isis No 147022, 147023, or 147024.

In certain embodiments, a target region is nucleotides 1886-1919 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 1886-1919 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted to nucleotides 1886-1919 comprises a nucleotide sequence selected from SEQ ID NO 877, 868, 882, 886, 859, 865, 843, 846, 874, 863, 855, 864, or 834. In certain such embodiments, a short antisense compound targeted to nucleotides 1886-1919 of SEQ ID NO: 11 is selected from Isis No 147019, 147020, 147021, 147022, 147023, 147025, 147027, 147028, 147030, 147037, 147038, 147040, or 147041.

In certain embodiments, a target region is nucleotides 1869-1919 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 1869-1919 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted to nucleotides 1869-1919 comprises a nucleotide sequence selected from SEQ ID NO 859, 853, 877, 868, 882, 886, 859, 865, 843, 846, 874, 863, 855, 864, or 834. In certain such embodiments, a short antisense compound targeted to nucleotides 1869-1919 of SEQ ID NO: 11 is selected from Isis No 147023, 147024, 147019, 147020, 147021, 147022, 147023, 147025, 147027, 147028, 147030, 147037, 147038, 147040, or 147041.

In certain embodiments, a target region is nucleotides 1976-1989 of SEQ ID NO: 11. In certain

embodiments, a short antisense compound is targeted to nucleotides 1976-1989 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted to nucleotides 1976-1989 comprises a nucleotide sequence selected from SEQ ID NO 886, 859, or 853. In certain such embodiments, a short antisense compound targeted to nucleotides 1976-1989 of SEQ ID NO: 11 is selected from Isis No 147022, 147023, or 147024.

In certain embodiments, a target region is nucleotides 1995-2027 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 1995-2027 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted to nucleotides 1995-2027 comprises a nucleotide sequence selected from SEQ ID NO 868, 882, 886, 859, 853, 865, 835, 843, 846, 848, 874, 849, 863, 855, 850, 864, or 834. In certain such embodiments, a short antisense compound targeted to nucleotides 1995-2027 of SEQ ID NO: 11 is selected from Isis No 147020, 147021, 147022, 147023, 147024, 147025, 147026, 147027, 147028, 147029, 147030, 147036, 147037, 147038, 147039, 147040, or 147041.

In certain embodiments, a target region is nucleotides 2366-2382 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 2366-2382 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted to nucleotides 2366-2382 comprises a nucleotide sequence selected from SEQ ID NO 867 or 873. In certain such embodiments, a short antisense compound targeted to nucleotides 2366-2382 of SEQ ID NO: 11 is selected from Isis No 404199 or 404134.

In certain embodiments, a target region is nucleotides 6220-6233 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 6220-6233 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted to nucleotides 6220-6233 comprises a nucleotide sequence selected from SEQ ID NO 870, 836, or 844. In certain such embodiments, a short antisense compound targeted to nucleotides 6220-6233 of SEQ ID NO: 11 is selected from Isis No 147032, 147033, or 147034.

In certain embodiments, a target region is nucleotides 6288-6300 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 6288-6300 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted to nucleotides 6288-6300 comprises a nucleotide sequence selected from SEQ ID NO 869 or 883. In certain such embodiments, a short antisense compound targeted to nucleotides 6288-6300 of SEQ ID NO: 11 is selected from Isis No 147044 or 147045.

In certain embodiments, a target region is nucleotides 6329-6342 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 6329-6342 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted to nucleotides 6329-6342 comprises a nucleotide sequence selected from SEQ ID NO 870, 836, or 844. In certain such embodiments, a short antisense compound targeted to nucleotides 6329-6342 of SEQ ID NO: 11 is selected from Isis No 147032, 147033, or 147034.

In certain embodiments, a target region is nucleotides 6397-6409 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 6397-6409 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted to nucleotides 6397-6409 comprises a nucleotide sequence selected from SEQ ID NO 869 or 883. In certain such embodiments, a short antisense compound targeted to nucleotides 6397-6409 of SEQ ID NO: 11 is selected from Isis No 147044 or 147045.

In certain embodiments, a target region is nucleotides 7057-7178 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 7057-7178 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted to 7057-7178 comprises a nucleotide sequence selected from SEQ ID NO 830, 840, 861, 830, or 840. In certain such embodiments, a short antisense compound targeted to nucleotides 7057-7178 of SEQ ID NO: 11 is selected from Isis No 147058, 147059, 147060, 147058, or 147059.

In certain embodiments, a target region is nucleotides 8630-8750 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 8630-8750 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted to 8630-8750 comprises a nucleotide sequence selected from SEQ ID NO 843, 846, 843, or 846. In certain such embodiments, a short antisense compound targeted to nucleotides 8630-8750 of SEQ ID NO: 11 is selected from Isis No 147027, 147028, 147027, or 147028.

In certain embodiments, a target region is nucleotides 10957-11077 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 10957-11077 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted to 10957-11077 comprises a nucleotide sequence selected from SEQ ID NO 881, 869, 881, or 869. In certain such embodiments, a short antisense compound targeted to nucleotides 10957-11077 of SEQ ID NO: 11 is selected from Isis No 147043, 147044, 147043, or 147044.

In certain embodiments, a target region is nucleotides 11605-11623 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 11605-11623 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted to 11605-11623 comprises a nucleotide sequence selected from SEQ ID NO 856, 878, or 856. In certain such embodiments, a short antisense compound targeted to nucleotides 11605-11623 of SEQ ID NO: 11 is selected from Isis No 147071, 147070, or 147071.

In certain embodiments, a target region is nucleotides 12805-12817 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 12805-12817 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted to 12805-12817 comprises a nucleotide sequence selected from SEQ ID NO 874 or 885. In certain such embodiments, a short antisense compound targeted to nucleotides 12805-12817 of SEQ ID NO: 11 is selected from Isis No 147030 or 147031.

In certain embodiments, a target region is nucleotides 12986-12998 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 12986-12998 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted to 12986-12998 comprises a nucleotide sequence selected from SEQ ID NO 874 or 885. In certain such embodiments, a short antisense compound targeted to nucleotides 12986-12998 of SEQ ID NO: 11 is selected from Isis No 147030 or 147031.

In certain embodiments, a target region is nucleotides 15560-15572 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 15560-15572 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted to 15560-15572 comprises a nucleotide sequence selected from SEQ ID NO 876 or 838. In certain such embodiments, a short antisense compound targeted to nucleotides 15560-15572 of SEQ ID NO: 11 is selected from Isis No 147067 or 147068.

In certain embodiments, a target region is nucleotides 17787-17941 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 17787-17941 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted to 17787-17941 comprises a nucleotide sequence selected from SEQ ID NO 874 or 880. In certain such embodiments, a short antisense compound targeted to nucleotides 17787-17941 of SEQ ID NO: 11 is selected from Isis No 147030 or 147064.

In certain embodiments, a target region is nucleotides 21190-21202 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 21190-21202 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted to 21190-21202 comprises a nucleotide sequence selected from SEQ ID NO 843 or 846. In certain such embodiments, a short antisense compound targeted to nucleotides 21190-21202 of SEQ ID NO: 11 is selected from Isis No 147027 or 147028.

In certain embodiments, a target region is nucleotides 21358-21370 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 21358-21370 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted to 21358-21370 comprises a nucleotide sequence selected from SEQ ID NO 843 or 846. In certain such embodiments, a short antisense compound targeted to nucleotides 21358-21370 of SEQ ID NO: 11 is selected from Isis No 017027 or 147028.

In certain embodiments, a target region is nucleotides 24318-24332 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 24318-24332 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted to 24318-24332 comprises a nucleotide sequence selected from SEQ ID NO 881, 869, 883, or 858. In certain such embodiments, a short antisense compound targeted to nucleotides 24318-24332 of SEQ ID NO: 11 is selected from Isis No 147043, 147044, 147045, or 147046.

In certain embodiments, a target region is nucleotides 24486-24501 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 24486-24501 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted to 24486-24501 comprises a nucleotide sequence selected from SEQ ID NO 881, 869, 858, or 833. In certain such embodiments, a short antisense compound targeted to nucleotides 24486-24501 of SEQ ID NO: 11 is selected from Isis No 147043, 147044, 147046, or 147047.

In certain embodiments, a target region is nucleotides 25065-25077 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 25065-25077 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted to 25065-25077 comprises a nucleotide sequence selected from SEQ ID NO 864 or 834. In certain such embodiments, a short antisense compound targeted to nucleotides 25065-25077 of SEQ ID NO: 11 is selected from Isis No 147040 or 147041.

In certain embodiments, a target region is nucleotides 25232-25245 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 25232-25245 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted to 25232-25245 comprises a nucleotide sequence selected from SEQ ID NO 850, 864, or 834. In certain such embodiments, a short antisense compound targeted to nucleotides 25232-25245 of SEQ ID NO: 11 is selected from Isis No 147039, 147040, or 147041.

In certain embodiments, a target region is nucleotides 25508-25523 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 25508-25523 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted to 25508-25523 comprises a nucleotide sequence selected from SEQ ID NO 839 or 879. In certain such embodiments, a short antisense compound targeted to nucleotides 25508-25523 of SEQ ID NO: 11 is selected from Isis No 147057 or 147061.

In certain embodiments, a target region is nucleotides 25676-28890 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 25676-28890 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted to 25676-28890 comprises a nucleotide sequence selected from SEQ ID NO 839, 860, or 878. In certain such embodiments, a short antisense compound targeted to nucleotides 25676-28890 of SEQ ID NO: 11 is selected from Isis No 147057, 147069, or 147070.

In certain embodiments, a target region is nucleotides 33056-33069 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 33056-33069 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted to 33056-33069 comprises a nucleotide sequence selected from SEQ ID NO 860, 878, or 856. In certain such embodiments, a short antisense compound targeted to nucleotides 33056-33069 of SEQ ID NO: 11 is selected from Isis No 147069, 147070, or 147071.

In certain embodiments, a target region is nucleotides 33205-33217 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 33205-33217 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted to 33205-33217 comprises a nucleotide sequence selected from SEQ ID NO 878 or 856. In certain such embodiments, a short antisense compound targeted to nucleotides 33205-33217 of SEQ ID NO: 11 is selected from Isis No 14707 or 147071.

In certain embodiments, a target region is nucleotides 33318-33334 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 33318-33334 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted to 33318-33334 comprises a nucleotide sequence selected from SEQ ID NO 858, 854, or 875. In certain such embodiments, a short antisense compound targeted to nucleotides 33318-33334 of SEQ ID NO: 11 is selected from Isis No 147046, 147049, or 147051.

In certain embodiments, a target region is nucleotides 33466-33482 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 33466-33482 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 33466-33482 comprises a nucleotide sequence selected from SEQ ID NO 858, 833, or 875. In certain such embodiments, a short antisense compound targeted to nucleotides 33466-33482 of SEQ ID NO: 11 is selected from Isis No 147046, 147047, or 147051.

In certain embodiments, a target region is nucleotides 33640-33656 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 33640-33656 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 33640-33656 comprises a nucleotide sequence selected from SEQ ID NO 858 or 875. In certain such embodiments, a short antisense compound targeted to nucleotides 33640-33656 of SEQ ID NO: 11 is selected from Isis No 147046 or 147051.

In certain embodiments, a target region is nucleotides 33788-33804 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 33788-33804 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 33788-33804 comprises a nucleotide sequence selected from SEQ ID NO 858 or 875. In certain such embodiments, a short antisense compound targeted to nucleotides 33788-33804 of SEQ ID NO: 11 is selected from Isis No 147046 or 147051.

In certain embodiments, a target region is nucleotides 35437-35449 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 35437-35449 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 35437-35449 comprises a nucleotide sequence selected from SEQ ID NO 840 or 861. In certain such embodiments, a short antisense compound targeted to nucleotides 35437-35449 of SEQ ID NO: 11 is selected from Isis No 147059 or 147060.

In certain embodiments, a target region is nucleotides 40353-40373 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 40353-40373 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 40353-40373 comprises a nucleotide sequence selected from SEQ ID NO 879 or 881. In certain such embodiments, a short antisense compound targeted to nucleotides 40353-40373 of SEQ ID NO: 11 is selected from Isis No 147061 or 147043.

In certain embodiments, a target region is nucleotides 42527-42541 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 42527-42541 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 42527-42541 comprises a nucleotide sequence selected from SEQ ID NO 885, 870, or 844. In certain such embodiments, a short antisense compound targeted to nucleotides 42527-42541 of SEQ ID NO: 11 is selected from Isis No 147031, 147032, or 147034.

In certain embodiments, a target region is nucleotides 42675-42689 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 42675-42689 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 42675-42689 comprises a nucleotide sequence selected from SEQ ID NO 885, 870, 836, or 844. In certain such embodiments, a short antisense compound targeted to nucleotides 42675-42689 of SEQ ID NO: 11 is selected from Isis No 147031, 147032, 147033, or 147034.

In certain embodiments, a target region is nucleotides 46313-46328 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 46313-46328 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 46313-46328 comprises a nucleotide sequence selected from SEQ ID NO 839, 830, 840, or 879. In certain such embodiments, a short antisense compound targeted to nucleotides 46313-46328 of SEQ ID NO: 11 is selected from Isis No 147057, 147058, 147059, or 147061.

In certain embodiments, a target region is nucleotides 46461-46476 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 46461-46476 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 46461-46476 comprises a nucleotide sequence selected from SEQ ID NO 839, 840, or 879. In certain such embodiments, a short antisense compound targeted to nucleotides 46461-46476 of SEQ ID NO: 11 is selected from Isis No 147057, 147059, or 147061.

In certain embodiments, a target region is nucleotides 48369-48381 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 48369-48381 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 48369-48381 comprises a nucleotide sequence selected from SEQ ID NO 842 or 845. In certain such embodiments, a short antisense compound targeted to nucleotides 48369-48381 of SEQ ID NO: 11 is selected from Isis No 147073 or 147074.

In certain embodiments, a target region is nucleotides 48714-48726 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 48714-48726 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 48714-48726 comprises a nucleotide sequence selected from SEQ ID NO 843 or 846. In certain such embodiments, a short antisense compound targeted to nucleotides 48714-48726 of SEQ ID NO: 11 is selected from Isis No 147027 or 147028.

In certain embodiments, a target region is nucleotides 49050-49062 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 49050-49062 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 49050-49062 of comprises a nucleotide sequence selected from SEQ ID NO 876 or 838. In certain such embodiments, a short antisense compound targeted to nucleotides 49050-49062 of SEQ ID NO: 11 is selected from Isis No 147067 or 147068.

In certain embodiments, a target region is nucleotides 49672-49684 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 49672-49684 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 49672-49684 of comprises a nucleotide sequence selected from SEQ ID NO 842 or 845. In certain such embodiments, a short antisense compound targeted to nucleotides 49672-49684 of SEQ ID NO: 11 is selected from Isis No 147073 or 147074.

In certain embodiments, a target region is nucleotides 52292-52304 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 52292-52304 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 52292-52304 of comprises a nucleotide sequence selected from SEQ ID NO 849 or 863. In certain such embodiments, a short antisense compound targeted to nucleotides 52292-52304 of SEQ ID NO: 11 is selected from Isis No 147036 or 147037.

In certain embodiments, a target region is nucleotides 52438-52450 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 52438-52450 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 52438-52450 of comprises a nucleotide sequence selected from SEQ ID NO 849 or 863. In certain such embodiments, a short antisense compound targeted to nucleotides 52438-52450 of SEQ ID NO: 11 is selected from Isis No 147036 or 147037.

In certain embodiments, a target region is nucleotides 53445-53458 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 53445-53458 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 53445-53458 of comprises a nucleotide sequence selected from SEQ ID NO 866, 881, or 869. In certain such embodiments, a short antisense compound targeted to nucleotides 53445-53458 of SEQ ID NO: 11 is selected from Isis No 147042, 147043, or 147044.

In certain embodiments, a target region is nucleotides 53591-53604 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 53591-53604 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 53591-53604 of comprises a nucleotide sequence selected from SEQ ID NO 866, 874, 881, 885, or 869. In certain such embodiments, a short antisense compound targeted to nucleotides 53591-53604 of SEQ ID NO: 11 is selected from Isis No 147042, 147030, 147043, 147031, or 147044.

In certain embodiments, a target region is nucleotides 53738-53750 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 53738-53750 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 53738-53750 of comprises a nucleotide sequence selected from SEQ ID NO 874 or 885. In certain such embodiments, a short antisense compound targeted to nucleotides 53738-53750 of SEQ ID NO: 11 is selected from Isis No 147030 or 147031.

In certain embodiments, a target region is nucleotides 53783-53795 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 53783-53795 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 53783-53795 of comprises a nucleotide sequence selected from SEQ ID NO 864 or 834. In certain such embodiments, a short antisense compound targeted to nucleotides 53783-53795 of SEQ ID NO: 11 is selected from Isis No 147040 or 147041.

In certain embodiments, a target region is nucleotides 55008-55020 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 55008-55020 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 55008-55020 of comprises a nucleotide sequence selected from SEQ ID NO 866 or 881. In certain such embodiments, a short antisense compound targeted to nucleotides 55008-55020 of SEQ ID NO: 11 is selected from Isis No 147042 or 147043.

In certain embodiments, a target region is nucleotides 55154-55166 of SEQ ID NO: 11. In certain

embodiments, a short antisense compound is targeted to nucleotides 55154-55166 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 55154-55166 of comprises a nucleotide sequence selected from SEQ ID NO 866 or 881. In certain such embodiments, a short antisense compound targeted to nucleotides 55154-55166 of SEQ ID NO: 11 is selected from Isis No 147042 or 147043.

In certain embodiments, a target region is nucleotides 55682-55695 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 55682-55695 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 55682-55695 of comprises a nucleotide sequence selected from SEQ ID NO 877 or 882. In certain such embodiments, a short antisense compound targeted to nucleotides 55682-55695 of SEQ ID NO: 11 is selected from Isis No 147019 or 147021.

In certain embodiments, a target region is nucleotides 56275-56293 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 56275-56293 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 56275-56293 of comprises a nucleotide sequence selected from SEQ ID NO 871, 884, 887, 830, 840, 861, or 879. In certain such embodiments, a short antisense compound targeted to nucleotides 56275-56293 of SEQ ID NO: 11 is selected from Isis No 147054, 147055, 147056, 147058, 147059, 147060, or 147061.

In certain embodiments, a target region is nucleotides 56418-56439 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 56418-56439 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 56418-56439 of comprises a nucleotide sequence selected from SEQ ID NO 875, 829, 871, 884, 887, 839, 830, or 879. In certain such embodiments, a short antisense compound targeted to nucleotides 56418-56439 of SEQ ID NO: 11 is selected from Isis No 147051, 147053, 147054, 147055, 147056, 147057, 147058, or 147061.

In certain embodiments, a target region is nucleotides 57264-57276 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 57264-57276 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 57264-57276 of comprises a nucleotide sequence selected from SEQ ID NO 883 or 858. In certain such embodiments, a short antisense compound targeted to nucleotides 57264-57276 of SEQ ID NO: 11 is selected from Isis No 147045 or 147046.

In certain embodiments, a target region is nucleotides 61276-61293 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 61276-61293 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 61276-61293 of comprises a nucleotide sequence selected from SEQ ID NO 856, 847, 849, 863, 855, 850, or 864. In certain such embodiments, a short antisense compound targeted to nucleotides 61276-61293 of SEQ ID NO: 11 is selected from Isis No 147071, 147035, 147036, 147037, 147038, 147039, or 147040.

In certain embodiments, a target region is nucleotides 61257-61320 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 61257-61320 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 61257-61320 of comprises a nucleotide sequence selected from SEQ ID NO 881, 856, 847, 849, 863, 855, 850, 864, or 886. In certain such embodiments, a short antisense compound targeted to nucleotides 61257-61320 of SEQ ID NO: 11 is selected from Isis No 147043, 147071, 147035, 147036, 147037, 147038, 147039, 147040, or 147071.

In certain embodiments, a target region is nucleotides 61422-61439 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 61422-61439 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 61422-61439 of comprises a nucleotide sequence selected from SEQ ID NO 844, 847, 849, 863, 855, or 864. In certain such embodiments, a short antisense compound targeted to nucleotides 61422-61439 of SEQ ID NO: 11 is selected from Isis No 147034, 147035, 147036, 147037, 147038, or 147040.

In certain embodiments, a target region is nucleotides 61422-61466 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 61422-61466 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 61422-61466 of comprises a nucleotide sequence selected from SEQ ID NO 844, 847, 849, 863, 855, 864, or 856. In certain such embodiments, a short antisense compound targeted to nucleotides 61422-61466 of SEQ ID NO: 11 is selected from Isis No 147034, 147035, 147036, 147037, 147038, 147040, or 147071.

In certain embodiments, a target region is nucleotides 63065-63078 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 63065-63078 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 63065-63078 of comprises a nucleotide sequence selected from SEQ ID NO 851 or 838. In certain such embodiments, a short antisense compound targeted to nucleotides 63065-63078 of SEQ ID NO: 11 is selected from Isis No 147066 or 147068.

In certain embodiments, a target region is nucleotides 63207-63222 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 63207-63222 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 63207-63222 of comprises a nucleotide sequence selected from SEQ ID NO 841 or 851. In certain such embodiments, a short antisense compound targeted to nucleotides 63207-63222 of SEQ ID NO: 11 is selected from Isis No 147062 or 147066.

In certain embodiments, a target region is nucleotides 64538-64550 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 64538-64550 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 64538-64550 of comprises a nucleotide sequence selected from SEQ ID NO 849 or 863. In certain such embodiments, a short antisense compound targeted to nucleotides 64538-64550 of SEQ ID NO: 11 is selected from Isis No 147036 or 147037.

In certain embodiments, a target region is nucleotides 64864-64876 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 64864-64876 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 64864-64876 of comprises a nucleotide sequence selected from SEQ ID NO 851 or 876. In certain such embodiments, a short antisense compound targeted to nucleotides 64864-64876 of SEQ ID NO: 11 is selected from Isis No 147066 or 147067.

In certain embodiments, a target region is nucleotides 65010-65028 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 65010-65028 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 65010-65028 of comprises a nucleotide sequence selected from SEQ ID NO 851, 876, or 883. In certain such embodiments, a short antisense compound targeted to nucleotides 65010-65028 of SEQ ID NO: 11 is selected from Isis No 147066, 147067, or 147045.

In certain embodiments, a target region is nucleotides 65163-65175 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 65163-65175 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 65163-65175 of comprises a nucleotide sequence selected from SEQ ID NO 883 or 858. In certain such embodiments, a short antisense compound targeted to nucleotides 65163-65175 of SEQ ID NO: 11 is selected from Isis No 147045 or 147046.

In certain embodiments, a target region is nucleotides 65408-65422 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 65408-65422 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 65408-65422 of comprises a nucleotide sequence selected from SEQ ID NO 883 or 856. In certain such embodiments, a short antisense compound targeted to nucleotides 65408-65422 of SEQ ID NO: 11 is selected from Isis No 147068 or 147071.

In certain embodiments, a target region is nucleotides 65549-65568 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 65549-65568 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 65549-65568 of comprises a nucleotide sequence selected from SEQ ID NO 860, 838, or 856. In certain such embodiments, a short antisense compound targeted to nucleotides 65549-65568 of SEQ ID NO: 11 is selected from Isis No 147069, 147068, or 147071.

In certain embodiments, a target region is nucleotides 67741-67754 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 67741-67754 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 67741-67754 of comprises a nucleotide sequence selected from SEQ ID NO 848, 874, or 885. In certain such embodiments, a short antisense compound targeted to nucleotides 67741-67754 of SEQ ID NO: 11 is selected from Isis No 147029, 147030, or 147031.

In certain embodiments, a target region is nucleotides 67886-67900 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 67886-67900 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 67886-67900 of comprises a nucleotide sequence selected from SEQ ID NO 846, 848, 874, or 885. In certain such embodiments, a short antisense compound targeted to nucleotides 67886-67900 of SEQ ID NO: 11 is selected from Isis No 147028, 147029, 147030, or 147031.

In certain embodiments, a target region is nucleotides 68867-68880 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 68867-68880 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 68867-68880 of comprises a nucleotide sequence selected from SEQ ID NO 881, 869, or 883. In certain such embodiments, a short antisense compound targeted to nucleotides 68867-68880 of SEQ ID NO: 11 is selected from Isis No 147043, 147044, or 147045.

In certain embodiments, a target region is nucleotides 69013-69532 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 69013-69532 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 69013-69532 of comprises a nucleotide sequence selected from SEQ ID NO 881, 869, 883, 858, 856, 832, or 842. In certain such embodiments, a short antisense compound targeted to nucleotides 69013-69532 of SEQ ID NO: 11 is selected from Isis No 147043, 147044, 147045, 147046, 147071, 147072, or 147073.

In certain embodiments, a target region is nucleotides 69665-69880 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 69665-69880 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 69665-69880 of comprises a nucleotide sequence selected from SEQ ID NO 856, 832, 842, 845, or 851. In certain such embodiments, a short antisense compound targeted to nucleotides 69665-69880 of SEQ ID NO: 11 is selected from Isis No 147071, 147072, 147073, 147074, or 147066.

In certain embodiments, a target region is nucleotides 70611-70630 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 70611-70630 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 70611-70630 of comprises a nucleotide sequence selected from SEQ ID NO 859, 841, 862, 880, 857, or 851. In certain such embodiments, a short antisense compound targeted to nucleotides 70611-70630 of SEQ ID NO: 11 is selected from Isis No 147023, 147062, 147063, 147064, 147065, or 147066.

In certain embodiments, a target region is nucleotides 70762-70776 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 70762-70776 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 70762-70776 of comprises a nucleotide sequence selected from SEQ ID NO 862, 880, 857, or 851. In certain such embodiments, a short antisense compound targeted to nucleotides 70762-70776 of SEQ ID NO: 11 is selected from Isis No 147063, 147064, 147065, or 147066.

In certain embodiments, a target region is nucleotides 70998-71010 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 70998-71010 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 70998-71010 of comprises a nucleotide sequence selected from SEQ ID NO 832 or 842. In certain such embodiments, a short antisense compound targeted to nucleotides 70998-71010 of SEQ ID NO: 11 is selected from Isis No 147072 or 147073.

In certain embodiments, a target region is nucleotides 71144-714364 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 71144-714364 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 71144-714364 of comprises a nucleotide sequence selected from SEQ ID NO 832, 842, 845, 863, 855, or 850. In certain such embodiments, a short antisense compound targeted to nucleotides 71144-714364 of SEQ ID NO: 11 is selected from Isis No

147072, 147073, 147074, 147037, 147038, or 147039.

In certain embodiments, a target region is nucleotides 71497-71652 of SEQ ID NO: 11. In certain embodiments, a short antisense compound is targeted to nucleotides 71497-71652 of SEQ ID NO: 11. In certain such embodiments, a short antisense compound targeted 71497-71652 of comprises a nucleotide sequence selected from SEQ ID NO 863, 855, 850, or 879. In certain such embodiments, a short antisense compound targeted to nucleotides 71497-71652 of SEQ ID NO: 11 is selected from Isis No 147037, 147038, 147039, or 147061.

In certain embodiments, short antisense compounds targeted to a PTP1B nucleic acid are 8 to 16, preferably 9 to 15, more preferably 9 to 14, more preferably 10 to 14 nucleotides in length. In certain embodiments, short antisense compounds targeted to a PTP1B nucleic acid are 9 to 14 nucleotides in length. In certain embodiments, short antisense compounds targeted to a PTP1B nucleic acid are 10 to 14 nucleotides in length. In certain embodiments, such short antisense compounds are short antisense oligonucleotides.

In certain embodiments, short antisense compounds targeted to a PTP1B nucleic acid are short gapmers. In certain such embodiments, short gapmers targeted to a PTP1B nucleic acid comprise at least one high affinity modification in one or more wings of the compound. In certain embodiments, short antisense compounds targeted to a PTP1B nucleic acid comprise 1 to 3 high-affinity modifications in each wing. In certain such embodiments, the nucleosides or nucleotides of the wing comprise a 2' modification. In certain such embodiments, the monomers of the wing are BNA's. In certain such embodiments, the monomers of the wing are selected from α-L-Methyleneoxy (4'-CH_2-O-2') BNA , β-D-Methyleneoxy (4'-CH_2-O-2') BNA , Ethyleneoxy (4'-$(CH_2)_2$-O-2') BNA , Aminooxy (4'-CH_2-O-N(R)-2') BNA and Oxyamino (4'-CH_2-N(R)-O-2') BNA. In certain embodiments, the monomers of a wing comprise a substituent at the 2' position selected from allyl, amino, azido, thio, O-allyl, O-C_1-C_{10} alkyl, -OCF_3, O-$(CH_2)_2$-O-CH_3, 2'-$O(CH_2)_2SCH_3$, O-$(CH_2)_2$-O-N(R_m)(R_n), and O-CH_2-C(=O)-N(R_m)(R_n), where each R_m and R_n is, independently, H or substituted or unsubstituted C_1-C_{10} alkyl. In certain embodiments, the monomers of a wing are 2'MOE nucleotides.

In certain embodiments, short antisense compounds targeted to a PTP1B nucleic acid comprise a gap between the 5' wing and the 3' wing. In certain embodiments the gap comprises five, six, seven, eight, nine, ten, eleven, twelve, thirteen, or fourteen monomers. In certain embodiments, the monomers of the gap are unmodified deoxyribonucleotides. In certain embodiments, the monomers of the gap are unmodified ribonucleotides. In certain embodiments, gap modifications (if any) gap result in an antisense compound that, when bound to its target nucleic acid, supports cleavage by an RNase, including, but not limited to, RNase H.

In certain embodiments, short antisense compounds targeted to a PTP1B nucleic acid have uniform monomeric linkages. In certain such embodiments, those linkages are all phosphorothioate linkages. In certain embodiments, the linkages are all phosphodiester linkages. In certain embodiments, short antisense compounds targeted to a PTP1B nucleic acid have mixed backbones.

In certain embodiments, short antisense compounds targeted to a PTP1B nucleic acid are 8 monomers in length. In certain embodiments, short antisense compounds targeted to a PTP1B nucleic acid are 9 monomers in length. In certain embodiments, short antisense compounds targeted to a PTP1B nucleic acid are 10 monomers in length. In certain embodiments, short antisense compounds targeted to a PTP1B nucleic acid are 11 monomers in length. In certain embodiments, short antisense compounds targeted to a PTP1B nucleic acid are monomers in length. In certain embodiments, short antisense compounds targeted to a PTP1B nucleic acid are 13 monomers in length. In certain embodiments, short antisense compounds targeted to a PTP1B nucleic acid are 14 monomers in length. In certain embodiments, short antisense compounds targeted to a PTP1B nucleic acid are 15 monomers in length. In certain embodiments, short antisense compounds targeted to a PTP1B nucleic acid are 16 monomers in length. In certain embodiments, short antisense compounds targeted to a PTP1B nucleic acid comprise 9 to 15 monomers. In certain embodiments, short antisense compounds targeted to a PTP1B nucleic acid comprise 10 to 15 monomers. In certain embodiments, short antisense compounds targeted to a PTP1B nucleic acid comprise 12 to 14 monomers. In certain embodiments, short antisense compounds targeted to a PTP1B nucleic acid comprise 12 to 14 nucleotides or nucleosides.

In certain embodiments, the invention provides methods of modulating expression of PTP1B. In certain embodiments, such methods comprise use of one or more short antisense compound targeted to a PTP1B nucleic acid, wherein the short antisense compound targeted to a PTP1B nucleic acid is from about 8 to about 16, preferably 9 to 15, more preferably 9 to 14, more preferably 10 to 14 monomers (i.e. from about 8 to about 16 linked monomers). One of ordinary skill in the art will appreciate that this comprehends methods of modulating expression of PTP1B using one or more short antisense compounds targeted to a PTP1B nucleic acid of 8, 9, 10, 11, 12, 13, 14, 15 or 16 monomers.

In certain embodiments, methods of modulating PTP1B comprise use of a short antisense compound targeted to a PTP1B nucleic acid that is 8 monomers in length. In certain embodiments, methods of modulating PTP1B comprise use of a short antisense compound targeted to a PTP1B nucleic acid that is 9 monomers in length. In certain embodiments, methods of modulating PTP1B comprise use of a short antisense compound targeted to a PTP1B nucleic acid that is 10 monomers in length. In certain embodiments, methods of modulating PTP1B comprise use of a short antisense compound targeted to a PTP1B nucleic acid that is 11 monomers in length. In certain embodiments, methods of modulating PTP1B comprise use of a short antisense compound targeted to a PTP1B nucleic acid that is 12 monomers in length. In certain embodiments, methods of modulating PTP1B comprise use of a short antisense compound targeted to a PTP1B nucleic acid that is 13 monomers in length. In certain embodiments, methods of modulating

PTP1B comprise use of a short antisense compound targeted to a PTP1B nucleic acid that is 14 monomers in length. In certain embodiments, methods of modulating PTP1B comprise use of a short antisense compound targeted to a PTP1B nucleic acid that is 15 monomers in length. In certain embodiments, methods of modulating PTP1B comprise use of a short antisense compound targeted to a PTP1B nucleic acid that is 16 monomers in length.

In certain embodiments, methods of modulating expression of PTP1B comprise use of a short antisense compound targeted to a PTP1B nucleic acid comprising 9 to 15 monomers. In certain embodiments, methods of modulating expression of PTP1B comprise use of a short antisense compound targeted to a PTP1B nucleic acid comprising 10 to 15 monomers. In certain embodiments, methods of modulating expression of PTP1B comprise use of a short antisense compound targeted to a PTP1B nucleic acid comprising 12 to 14 monomers. In certain embodiments, methods of modulating expression of PTP1B comprise use of a short antisense compound targeted to a PTP1B nucleic acid comprising 12 or 14 nucleotides or nucleosides.

10. PTEN

In certain embodiments, the invention provides short antisense compounds targeted to a nucleic acid encoding PTEN. In certain embodiments, such compounds are used to modulate PTEN expression if cells. In certain such embodiments, short antisense compounds targeted to a PTEN nucleic acid are administered to an animal. In certain embodiments, short antisense compounds targeted to a PTEN nucleic acid are useful for studying PTEN, for studying certain nucleases and/or for assessing antisense activity. In certain such embodiments, short antisense compounds targeted to PTEN nucleic acids are useful for assessing certain motifs and/or chemical modifications. In certain embodiments, administration of a short antisense compound targeted to PTEN nucleic acid to an animal results in a measurable phenotypic change.

The short antisense compounds targeting PTEN may have any one or more properties or characteristics of the short antisense compounds generally described herein. In certain embodiments, short antisense compounds targeting a PTP1B nucleic acid have a motif (wing – deoxy gap –wing) selected from 1-12-1, 1-1-10-2, 2-10-1-1, 3-10-3, 2-10-3, 2-10-2, 1-10-1,1-10-2, 3-8-3, 2-8-2, 1-8-1, 3-6-3 or 1-6-1, more preferably 1-10-1, 2-10-2, 3-10-3, and 1-9-2.

Certain Short Antisense Compounds Targeted to a PTEN Nucleic Acid

In certain embodiments, short antisense compounds are targeted to a PTEN nucleic acid having the sequence of GENBANK® Accession No. NM_000314.4, incorporated herein as SEQ ID NO: 14. In certain embodiments, short antisense compounds are targeted to a PTEN nucleic acid having the sequence of nucleotides 8063255 to 8167140 of the sequence of GENBANK® Accession No. NT_033890.3, incorporated herein as SEQ ID NO: 15. In certain such embodiments, a short antisense compound targeted to SEQ ID NO:

14 is at least 90% complementary to SEQ ID NO: 14. In certain such embodiments, a short antisense compound targeted to SEQ ID NO: 14 is at least 95% complementary to SEQ ID NO: 14. In certain such embodiments, a short antisense compound targeted to SEQ ID NO: 15 is 100% complementary to SEQ ID NO: 15. In certain such embodiments, a short antisense compound targeted to SEQ ID NO: 15 is at least 90% complementary to SEQ ID NO: 15. In certain such embodiments, a short antisense compound targeted to SEQ ID NO: 15 is at least 95% complementary to SEQ ID NO: 15. In certain such embodiments, a short antisense compound targeted to SEQ ID NO: 15 is 100% complementary to SEQ ID NO: 15.

In certain embodiments, a short antisense compound targeted to SEQ ID NO: 14 comprises a nucleotide sequence selected from the nucleotide sequences set forth in Tables 20 and 21. In certain embodiments, a short antisense compound targeted to SEQ ID NO: 15 comprises a nucleotide sequence selected from the nucleotide sequences set forth in Tables 22 and 23.

Each nucleotide sequence set forth in Tables 20, 21, 22, and 23 is independent of any modification to a sugar moiety, an internucleoside linkage, or a nucleobase. As such, short antisense compounds comprising a nucleotide sequence as set forth in Tables 20, 21, 22, and 23 may comprise, independently, one or more modifications to a sugar moiety, an internucleoside linkage, or a nucleobase. Antisense compounds described by Isis Number (Isis NO.) indicate a combination of nucleobase sequence and one or more modifications to a sugar moiety, an internucleoside linkage, or a nucleobase.

Table 20 illustrates short antisense compounds that are 100% complementary to SEQ ID NO: 14. Table 22 illustrates short antisense compounds that are 100% complementary to SEQ ID NO: 15. The column labeled 'gapmer motif' indicates the wing-gap-wing motif of each short antisense compounds. The gap segment comprises 2'-deoxynucleotides and each nucleotide of each wing segment comprises a 2'-modified sugar. The particular 2'-modified sugar is also indicated in the 'gapmer motif' column. For example, '2-10-2 MOE' means a 2-10-2 gapmer motif, where a gap segment of ten 2'-deoxynucleotides is flanked by wing segments of two nucleotides, where the nucleotides of the wing segments are 2'-MOE nucleotides. Internucleoside linkages are phosphorothioate. The short antisense compounds comprise 5-methylcytidine in place of unmodified cytosine, unless "unmodified cytosine" is listed in the gapmer motif column, in which case the indicated cytosines are unmodified cytosines. For example, "5-mC in gap only" indicates that the gap segment has 5-methylcytosines, while the wing segments have unmodified cytosines.

The 2'-modified nucleotides and abbreviations include: 2'-O-methoxyethyl (MOE); 2'-O-methyl (OMe); 2'-O-(2,2,3,3,3-pentafluoropropyl) (PentaF); 2'-O-[(2-methoxy)ethyl]-4'-thio (2'-MOE-4'-thio);. (R)-CMOE-BNA. As illustrated in Tables 20 and 22, a wing may comprise monomers comprising more than type of 2' substituent. For example, 1-2-10-2 MOE/PentaF/MOE indicates one MOE-modified nucleotide, followed by two PentaF-modified nucleotides, followed by a gap of ten deoxynucleotides, followed by two PentaF-modified nucleotides. For example, 1-1-10-2 2'-(butylacetomido)-palmitamide Methyleneoxy BNA/Methyleneoxy BNA indicates that the 5'-most nucleotide is 2'-(butylacetomide)-palmitamide, the second nucleotide is a methyleneoxy BNA nucleotide, and the 3' wing is methyleneoxy BNA. Unless otherwise indicated, cytosines are 5-methylcytosines and internucleoside linkages are phosphorothioate.

Table 20: Short Antisense Compounds Targeted to SEQ ID NO: 14

ISIS No	5' Target Site	3' Target Site	Sequence (5'-3')	Gapmer Motif	SEQ ID NO
390092	5530	5541	AGAATGAGACTT	1-10-1 MOE	1514
390091	5435	5446	TGAGGCATTATC	1-10-1 MOE	1522
390090	5346	5357	AGAGTATCTGAA	1-10-1 MOE	1227
390088	5162	5173	CACATTAACAGT	1-10-1 MOE	1511
390087	5126	5137	GTGGCAACCACA	1-10-1 MOE	1501
390085	5031	5042	ATTTGATGCTGC	1-10-1 MOE	1505
390084	4982	4993	CAAAGAATGGTG	1-10-1 MOE	1215
390082	4910	4921	AGGACTTGGGAT	1-10-1 MOE	1503
390080	4833	4844	TGCTGCACATCC	1-10-1 MOE	1150
392067	4832	4845	CTGCTGCACATCCA	2-10-2 Methyleneoxy BNA Unmodified cytosines in gap	1510
390078	4714	4725	CTTTCAGTCATA	1-10-1 MOE	1520
390077	4693	4704	GTCAAATTCTAT	1-10-1 MOE	1252
390076	4599	4610	TTCCAATGACTA	1-10-1 MOE	1506
390075	4576	4587	GTAAGCAAGGCT	1-10-1 MOE	#N/A
390074	4533	4544	ACCCTCATTCAG	1-10-1 MOE	1513
390068	4191	4202	GTAAATCCTAAG	1-10-1 MOE	1515
390064	4001	4012	ACCACAGCTAGT	1-10-1 MOE	1498
390063	3977	3988	CACCAATAAGTT	1-10-1 MOE	1219
390058	3828	3839	AGTAGTTGTACT	1-10-1 MOE	1192
390056	3793	3804	GGGCATATCAAA	1-10-1 MOE	1521
390054	3705	3716	AACACTGCACAT	1-10-1 MOE	1493
390052	3623	3634	GACAATTTCTAC	1-10-1 MOE	1492
390050	3503	3514	GTATTCAAGTAA	1-10-1 MOE	1140
390049	3479	3490	GTTAATGACATT	1-10-1 MOE	1491
390047	3428	3439	TGTGTAAGGTCA	1-10-1 MOE	1490
390041	3175	3186	TTAGCACTGGCC	1-10-1 MOE	1489
398076	3171	3182	CACTGGCCTTGA	1-10-1 MOE	1488
398009	3170	3183	GCACTGGCCTTGAT	2-10-2 MOE	1487
398075	3111	3122	AAATCATTGTCA	1-10-1 MOE	1233
398008	3110	3123	TAAATCATTGTCAA	2-10-2 MOE	1486
398074	2913	2924	GCACCAATATGC	1-10-1 MOE	1248
398007	2912	2925	AGCACCAATATGCT	2-10-2 MOE	1247
398073	2681	2692	TTAGCCAACTGC	1-10-1 MOE	1485
398006	2680	2693	CTTAGCCAACTGCA	2-10-2 MOE	1484
390033	2679	2690	AGCCAACTGCAA	1-10-1 MOE	1483
398072	2671	2682	GCAAACTTATCT	1-10-1 MOE	1482
398005	2670	2683	TGCAAACTTATCTG	2-10-2 MOE	1481
390030	2534	2545	TTTATAAAACTG	1-10-1 MOE	1074
398071	2533	2544	TTATAAAACTGG	1-10-1 MOE	1480

398004	2532	2545	TTTATAAAACTGGA	2-10-2 MOE	1479
390029	2510	2521	AAAGTGCCATCT	1-10-1 MOE	1478
390028	2491	2502	TCCTAATTGAAT	1-10-1 MOE	1477
398070	2481	2492	ATTTTAAATGTC	1-10-1 MOE	1476
398003	2480	2493	AATTTTAAATGTCC	2-10-2 MOE	1475
390027	2455	2466	AGGTATATACAT	1-10-1 MOE	1206
398069	2451	2462	ATATACATGACA	1-10-1 MOE	1474
398002	2450	2463	TATATACATGACAC	2-10-2 MOE	1473
398068	2440	2451	ACAGCTACACAA	1-10-1 MOE	1472
398001	2439	2452	CACAGCTACACAAC	2-10-2 MOE	1471
390026	2438	2449	AGCTACACAACC	1-10-1 MOE	1470
390025	2406	2417	GTGTCAAAACCC	1-10-1 MOE	1211
398067	2405	2416	TGTCAAAACCCT	1-10-1 MOE	1210
398000	2404	2417	GTGTCAAAACCCTG	2-10-2 MOE	1469
398066	2372	2383	AGATTGGTCAGG	1-10-1 MOE	1468
397999	2371	2384	AAGATTGGTCAGGA	2-10-2 MOE	1467
398065	2349	2360	GTTCCTATAACT	1-10-1 MOE	1466
397998	2348	2361	TGTTCCTATAACTG	2-10-2 MOE	1465
398064	2331	2342	CTGACACAATGT	1-10-1 MOE	1464
397997	2330	2343	TCTGACACAATGTC	2-10-2 MOE	1463
398063	2321	2332	GTCCTATTGCCA	1-10-1 MOE	1205
397996	2320	2333	TGTCCTATTGCCAT	2-10-2 MOE	1462
390022	2286	2297	CAGTTTATTCAA	1-10-1 MOE	1142
336221	2230	2243	TCAGACTTTTGTAA	3-8-3 MOE	1461
336220	2224	2237	TTTTGTAATTTGTG	3-8-3 MOE	1460
336219	2209	2222	ATGCTGATCTTCAT	3-8-3 MOE	1459
390021	2203	2214	CTTCATCAAAAG	1-10-1 MOE	1458
336218	2201	2214	CTTCATCAAAAGGT	3-8-3 MOE	1457
389779	2201	2212	TCATCAAAAGGT	1-9-2 MOE	1176
389979	2201	2212	TCATCAAAAGGT	1-10-1 MOE	1176
397995	2200	2213	TTCATCAAAAGGTT	2-10-2 MOE	1456
336217	2192	2205	AAGGTTCATTCTCT	3-8-3 MOE	1455
390020	2183	2194	TCTGGATCAGAG	1-10-1 MOE	1149
336216	2182	2195	CTCTGGATCAGAGT	3-8-3 MOE	1454
336215	2169	2182	TCAGTGGTGTCAGA	3-8-3 MOE	1453
398062	2166	2177	GGTGTCAGAATA	1-10-1 MOE	1255
397994	2165	2178	TGGTGTCAGAATAT	2-10-2 MOE	1452
390019	2163	2174	GTCAGAATATCT	1-10-1 MOE	1173
336214	2157	2170	GAATATCTATAATG	3-8-3 MOE	1573
398061	2151	2162	ATAATGATCAGG	1-10-1 MOE	1451
397993	2150	2163	TATAATGATCAGGT	2-10-2 MOE	1450
336213	2146	2159	ATGATCAGGTTCAT	3-8-3 MOE	1449
389778	2144	2155	TCAGGTTCATTG	1-9-2 MOE	1448
389978	2144	2155	TCAGGTTCATTG	1-10-1 MOE	1448
398060	2137	2148	CATTGTCACTAA	1-10-1 MOE	1447
336212	2136	2149	TCATTGTCACTAAC	3-8-3 MOE	1446
397992	2136	2149	TCATTGTCACTAAC	2-10-2 MOE	1446
336211	2112	2125	ACAGAAGTTGAACT	3-8-3 MOE	1445
390017	2111	2122	GAAGTTGAACTG	1-10-1 MOE	1444
398059	2108	2119	GTTGAACTGCTA	1-10-1 MOE	1443

397991	2107	2120	AGTTGAACTGCTAG	2-10-2 MOE	1442
336210	2104	2117	TGAACTGCTAGCCT	3-8-3 MOE	1441
335340	2104	2118	TTGAACTGCTAGCCT	1-10-4 MOE	1440
335339	2103	2117	TGAACTGCTAGCCTC	1-10-4 MOE	1439
335338	2102	2116	GAACTGCTAGCCTCT	1-10-4 MOE	1438
335337	2101	2115	AACTGCTAGCCTCTG	1-10-4 MOE	1437
335336	2100	2114	ACTGCTAGCCTCTGG	1-10-4 MOE	1436
390430	2099	2111	GCTAGCCTCTGGA	1-10-2 MOE Unmodified cytosines	1163
390431	2099	2111	GCTAGCCTCTGGA	1-10-2 MOE Unmodified cytosines C in wing 9-(aminoethoxy)phenoxazine	1163
390432	2099	2111	GCTAGCCTCTGGA	1-10-2 MOE	1163
390433	2099	2111	GCTAGCCTCTGGA	1-10-2 MOE Unmodified cytosines Nt 6 is 9-(aminoethoxy)phenoxazine	1163
390434	2099	2111	GCTAGCCTCTGGA	1-10-2 MOE Unmodified cytosines Nt 7 is 9-(aminoethoxy)phenoxazine	1163
390435	2099	2111	GCTAGCCTCTGGA	1-10-2 MOE Unmodified cytosines Nt 9 is 9-(aminoethoxy)phenoxazine	1163
335335	2099	2113	CTGCTAGCCTCTGGA	1-10-4 MOE	1435
389777	2098	2109	TAGCCTCTGGAT	1-9-2 MOE	1434
389954	2098	2109	TAGCCTCTGGAT	1-10-1 MOE	1434
335334	2098	2112	TGCTAGCCTCTGGAT	1-10-4 MOE	1433
331429	2097	2110	CTAGCCTCTGGATT	2-10-2 MOE	1431
335349	2097	2110	CTAGCCTCTGGATT	2-10-2 MOE	1431
335367	2097	2110	CTAGCCTCTGGATT	2-10-2 Methyleneoxy BNA	1431
335378	2097	2110	CTAGCCTCTGGATT	2-10-2 Methyleneoxy BNA	1431
392061	2097	2110	CTAGCCTCTGGATT	2-10-2 Methyleneoxy BNA Unmodified cytosines in gap	1431
383991	2097	2109	TAGCCTCTGGATT	1-10-2 2'-(acetylamino-butyl-acetamido)-cholesterol/MOE	1432
383992	2097	2109	TAGCCTCTGGATT	1-10-2 2'-(acetylamino-butyl-acetamido)-cholic acid/MOE	1432
386970	2097	2109	TAGCCTCTGGATT	1-10-2 MOE	1432
390578	2097	2109	TAGCCTCTGGATT	1-10-2 MOE Unmodified cytosines Ts in wings are 2-thiothymines	1432
390614	2097	2109	TAGCCTCTGGATT	1-10-2 PentaF	1432
335333	2097	2111	GCTAGCCTCTGGATT	1-10-4 MOE	1430
386683	2097	2109	TAGCCTCTGGATT	1-10-2 2'-(butylacetamido)-palmitamide/MOE	1432
371975	2096	2110	CTAGCCTCTGGATTT	3-10-2 MOE	1429
335341	2096	2111	GCTAGCCTCTGGATTT	3-10-3 MOE	1428
335350	2096	2111	GCTAGCCTCTGGATTT	3-10-3 MOE	1428
335368	2096	2111	GCTAGCCTCTGGATTT	3-10-3 Methyleneoxy BNA	1428

				Phosphodiester linkages in wings	
335379	2096	2111	GCTAGCCTCTGGATTT	3-10-3 Methyleneoxy BNA	1428
383739	2096	2111	GCTAGCCTCTGGATTT	3-10-3 MOE 5-methylcytosine in gap	1428
384071	2096	2111	GCTAGCCTCTGGATTT	3-10-3 OMe 5-methylcytosine in gap	1428
384073	2096	2111	GCTAGCCTCTGGATTT	3-10-3 Methyleneoxy BNA 5-methylcytosine in gap	1428
390576	2096	2111	GCTAGCCTCTGGATTT	3-10-3 MOE 5-methylcytosine in gap T's in wings are 2-thiothymines	1428
390580	2096	2111	GCTAGCCTCTGGATTT	3-10-3 MOE Pyrimidines in wings are 5-thiazole Unmodified cytosines in gap	1428
390581	2096	2111	GCTAGCCTCTGGATTT	3-10-3 MOE Unmodified cytosines in gap	1428
391863	2096	2111	GCTAGCCTCTGGATTT	3-10-3 MOE Unmodified cytosines	1428
391864	2096	2111	GCTAGCCTCTGGATTT	3-10-3 Methyleneoxy BNA Unmodified cytosines in gap	1428
391865	2096	2111	GCTAGCCTCTGGATTT	3-10-3 Methyleneoxy BNA Unmodified cytosines	1428
375560	2096	2110	CTAGCCTCTGGATTT	2-10-3 MOE	1429
391172	2096	2110	CTAGCCTCTGGATTT	2-10-2 Methyleneoxy BNA Unmodified cytosines	1429
391175	2096	2110	CTAGCCTCTGGATTT	2-10-3 Methyleneoxy BNA	1429
391449	2096	2110	CTAGCCTCTGGATTT	2-10-3 MOE Unmodified cytosines	1429
392054	2096	2110	CTAGCCTCTGGATTT	2-10-3 Methyleneoxy BNA Unmodified cytosines in gap	1429
392055	2096	2110	CTAGCCTCTGGATTT	2-10-3 MOE Unmodified cytosines in gap	1429
362977	2096	2111	GCTAGCCTCTGGATTT	2-12-2 MOE	1428
386770	2096	2109	TAGCCTCTGGATTT	1-11-2 MOE	1427
390577	2096	2109	TAGCCTCTGGATTT	1-10-3 MOE Unmodified cytosines T's in wings are 2-thiothymines	1427
335332	2096	2110	CTAGCCTCTGGATTT	1-10-4 MOE	1429
390579	2096	2111	GCTAGCCTCTGGATTT	1-1-1-10-3 MOE/4'-thio/2'-O-[(2-methoxy)ethyl]-4'-thio/2'-O-[(2-methoxy)ethyl]-4'-thio Unmodified cytosines in wings Phosphorodiester linkage in wings	1428
391173	2096	2110	CTAGCCTCTGGATTT	2-10-3 (5'R)-5'-methyl-Methyleneoxy BNA Unmodified cytosines	1429
391174	2096	2110	CTAGCCTCTGGATTT	2-10-3 (5'S)-5'-methyl-Methyleneoxy BNA Unmodified cytosines	1429
390607	2096	2111	GCTAGCCTCTGGATTT	3-10-3 MOE/pentaF Unmodified cytosines in wing	1428

390609	2096	2111	GCTAGCCTCTGGATTT	3-10-2-1 MOE/MOE/pentaF Unmodified cytosines in wing	1428
384072	2096	2111	GCTAGCCTCTGGATTT	1-2-10-3 MOE/pentaF/pentaF Unmodified cytosines in wings	1428
390606	2096	2111	GCTAGCCTCTGGATTT	1-2-10-3 MOE/pentaF/pentaF Unmodified cytosines in wing	1428
390608	2096	2111	GCTAGCCTCTGGATTT	1-2-10-3 MOE/pentaF/pentaF Unmodified cytosines in wing	1428
391869	2096	2111	GCTAGCCTCTGGATTT	1-2-10-3 Methyleneoxy BNA /(5'S)-5'-methyl- Methyleneoxy BNA /(5'S)-5'-methyl- Methyleneoxy BNA Unmodified cytosines	1428
385036	2096	2111	GCTAGCCTCTGGATTT	1-2-10-3 OMe/2'-O-methyl-4'-thio/2'-O-methyl-4'-thio Unmodified cytosines in wing	1428
385871	2096	2111	GCTAGCCTCTGGATTT	1-2-10-3 OMe/ 2'-O-[(2-methoxy)ethyl]-4'-thio/ 2'-O-[(2-methoxy)ethyl]-4'-thio Unmodified cytosines in wing	1428
386682	2096	2111	GCTAGCCTCTGGATTT	1-2-10-3 2'-(butylacetamido)-palmitamide /MOE /MOE	1428
390582	2096	2111	GCTAGCCTCTGGATTT	1-2-10-3 MOE/2'-O-[(2-methoxy)ethyl]-4'-thio / 2'-O-[(2-methoxy)ethyl]-4'-thio Unmodified cytosines in wings Phosphodiester linkage in wings	1428
391868	2096	2111	GCTAGCCTCTGGATTT	1-2-10-3 (5'R)-5'-methyl-Methyleneoxy BNA / Methyleneoxy BNA /(5'R)-5'-methyl-Methyleneoxy BNA Unmodified cytosines	1428
336209	2095	2108	AGCCTCTGGATTTG	3-8-3 MOE	1425
335331	2095	2109	TAGCCTCTGGATTTG	1-10-4 MOE	1426
335376	2095	2109	TAGCCTCTGGATTTG	1-10-4 Methyleneoxy BNA	1426
335377	2095	2109	TAGCCTCTGGATTTG	1-10-4 Methyleneoxy BNA Phosphodiester in 3' wing	1426
335330	2094	2108	AGCCTCTGGATTTGA	1-10-4 MOE	1424
336208	2079	2092	GGCTCCTCTACTGT	3-8-3 MOE	1423
336207	2073	2086	TCTACTGTTTTTGT	3-8-3 MOE	1422
336206	2047	2060	CACCTTAAAATTTG	3-8-3 MOE	1518
389776	2046	2057	CTTAAAATTTGG	1-9-2 MOE	1421
389977	2046	2057	CTTAAAATTTGG	1-10-1 MOE	1421
397990	2045	2058	CCTTAAAATTTGGA	2-10-2 MOE	1420
336205	2043	2056	TTAAAATTTGGAGA	3-8-3 MOE	1419
398058	2029	2040	AGTATCGGTTGG	1-10-1 MOE	1418
336204	2028	2041	AAGTATCGGTTGGC	3-8-3 MOE	1417
397989	2028	2041	AAGTATCGGTTGGC	2-10-2 MOE	1417
336203	2002	2015	TGCTTTGTCAAGAT	3-8-3 MOE	1416
389775	2002	2013	CTTTGTCAAGAT	1-9-2 MOE	1177
389976	2002	2013	CTTTGTCAAGAT	1-10-1 MOE	1177

397988	2001	2014	GCTTTGTCAAGATC	2-10-2 MOE	1415
336202	1959	1972	TCCTTGTCATTATC	3-8-3 MOE	1414
389774	1945	1956	CACGCTCTATAC	1-9-2 MOE	1413
389975	1945	1956	CACGCTCTATAC	1-10-1 MOE	1413
336201	1944	1957	GCACGCTCTATACT	3-8-3 MOE	1412
336200	1929	1942	CAAATGCTATCGAT	3-8-3 MOE	1411
389773	1904	1915	AGACTTCCATTT	1-9-2 MOE	1410
389974	1904	1915	AGACTTCCATTT	1-10-1 MOE	1410
336199	1902	1915	AGACTTCCATTTTC	3-8-3 MOE	1409
336198	1884	1897	TTTTCTGAGGTTTC	3-8-3 MOE	1408
398057	1878	1889	GGTTTCCTCTGG	1-10-1 MOE	1407
397987	1877	1890	AGGTTTCCTCTGGT	2-10-2 MOE	1406
336197	1873	1886	TTCCTCTGGTCCTG	3-8-3 MOE	1405
390015	1868	1879	GGTCCTGGTATG	1-10-1 MOE	1404
398056	1865	1876	CCTGGTATGAAG	1-10-1 MOE	1403
336196	1864	1877	TCCTGGTATGAAGA	3-8-3 MOE	1402
397986	1864	1877	TCCTGGTATGAAGA	2-10-2 MOE	1402
398055	1849	1860	TATTTACCCAAA	1-10-1 MOE	1401
397985	1848	1861	GTATTTACCCAAAA	2-10-2 MOE	1400
336195	1847	1860	TATTTACCCAAAAG	3-8-3 MOE	1399
389772	1846	1857	TTACCCAAAAGT	1-9-2 MOE	1398
389973	1846	1857	TTACCCAAAAGT	1-10-1 MOE	1398
336194	1838	1851	AAAAGTGAAACATT	3-8-3 MOE	1145
398054	1836	1847	GTGAAACATTTT	1-10-1 MOE	1144
397984	1835	1848	AGTGAAACATTTTG	2-10-2 MOE	1397
336193	1828	1841	CATTTTGTCCTTTT	3-8-3 MOE	1182
336192	1810	1823	CATCTTGTTCTGTT	3-8-3 MOE	1396
336191	1800	1813	TGTTTGTGGAAGAA	3-8-3 MOE	1395
398053	1796	1807	TGGAAGAACTCT	1-10-1 MOE	1394
397983	1795	1808	GTGGAAGAACTCTA	2-10-2 MOE	1393
389771	1794	1805	GAAGAACTCTAC	1-9-2 MOE	1392
389972	1794	1805	GAAGAACTCTAC	1-10-1 MOE	1392
336190	1789	1802	GAACTCTACTTTGA	3-8-3 MOE	1391
336189	1773	1786	TCACCACACACAGG	3-8-3 MOE	1390
336188	1754	1767	GCTGAGGGAACTCA	3-8-3 MOE	1389
398052	1751	1762	GGGAACTCAAAG	1-10-1 MOE	1388
389770	1750	1761	GGAACTCAAAGT	1-9-2 MOE	1386
389971	1750	1761	GGAACTCAAAGT	1-10-1 MOE	1386
397982	1750	1763	AGGGAACTCAAAGT	2-10-2 MOE	1387
336187	1747	1760	GAACTCAAAGTACA	3-8-3 MOE	1385
390012	1745	1756	TCAAAGTACATG	1-10-1 MOE	1384
336186	1688	1701	TCTTCACCTTTAGC	3-8-3 MOE	1383
398051	1684	1695	CCTTTAGCTGGC	1-10-1 MOE	1220
397981	1683	1696	ACCTTTAGCTGGCA	2-10-2 MOE	1382
336185	1677	1690	AGCTGGCAGACCAC	3-8-3 MOE	1381
389769	1676	1687	TGGCAGACCACA	1-9-2 MOE	1249
389970	1676	1687	TGGCAGACCACA	1-10-1 MOE	1249
392060	1675	1688	CTGGCAGACCACAA	2-10-2 Methyleneoxy BNA Unmodified cytosines in gap	1380
398050	1672	1683	AGACCACAAACT	1-10-1 MOE	1379

397980	1671	1684	CAGACCACAAACTG	2-10-2 MOE	1378
390011	1658	1669	GGATTGCAAGTT	1-10-1 MOE	1238
336184	1655	1668	GATTGCAAGTTCCG	3-8-3 MOE	1508
336183	1644	1657	CCGCCACTGAACAT	3-8-3 MOE	1377
390010	1643	1654	CCACTGAACATT	1-10-1 MOE	1240
398049	1641	1652	ACTGAACATTGG	1-10-1 MOE	1376
397979	1640	1653	CACTGAACATTGGA	2-10-2 MOE	1375
336182	1633	1646	CATTGGAATAGTTT	3-8-3 MOE	1374
389768	1630	1641	GAATAGTTTCAA	1-9-2 MOE	1373
389969	1630	1641	GAATAGTTTCAA	1-10-1 MOE	1373
398048	1626	1637	AGTTTCAAACAT	1-10-1 MOE	1372
397978	1625	1638	TAGTTTCAAACATC	2-10-2 MOE	1371
336181	1623	1636	GTTTCAAACATCAT	3-8-3 MOE	1370
398047	1614	1625	CATCTTGTGAAA	1-10-1 MOE	1369
336180	1613	1626	TCATCTTGTGAAAC	3-8-3 MOE	1368
390009	1613	1624	ATCTTGTGAAAC	1-10-1 MOE	1175
397977	1613	1626	TCATCTTGTGAAAC	2-10-2 MOE	1368
390007	1563	1574	CAGGTAGCTATA	1-10-1 MOE	1367
336179	1561	1574	CAGGTAGCTATAAT	3-8-3 MOE	1366
336178	1541	1554	CATAGCGCCTCTGA	3-8-3 MOE	1365
336177	1534	1547	CCTCTGACTGGGAA	3-8-3 MOE	1364
389767	1534	1545	TCTGACTGGGAA	1-9-2 MOE	1151
389968	1534	1545	TCTGACTGGGAA	1-10-1 MOE	1151
335344	1503	1516	TCTCTGGTCCTTAC	2-10-2 MOE	1363
335355	1503	1516	TCTCTGGTCCTTAC	2-10-2 MOE Phosphodiester linkage in wings	1363
335370	1503	1516	TCTCTGGTCCTTAC	2-10-2 Methyleneoxy BNA Phosphodiester linkage in wings	1363
335381	1503	1516	TCTCTGGTCCTTAC	2-10-2 Methyleneoxy BNA	1363
335411	1503	1516	TCTCTGGTCCTTAC	2-10-2 MOE 3’ C is 9-(aminoethoxy)phenoxazine	1363
335412	1503	1516	TCTCTGGTCCTTAC	2-10-2 MOE C in 5’ wing is 9-(aminoethoxy)phenoxazine	1363
335413	1503	1516	TCTCTGGTCCTTAC	2-10-2 MOE C in wings are 9-(aminoethoxy)phenoxazine	1363
336176	1502	1515	CTCTGGTCCTTACT	3-8-3 MOE	1361
335345	1502	1517	GTCTCTGGTCCTTACT	3-10-3 MOE	1362
335356	1502	1517	GTCTCTGGTCCTTACT	3-10-3 MOE Phosphodiester linkage in wings	1362
335371	1502	1517	GTCTCTGGTCCTTACT	3-10-3 Methyleneoxy BNA Phosphodiester linkage in wings	1362
335382	1502	1517	GTCTCTGGTCCTTACT	3-10-3 Methyleneoxy BNA	1362
335414	1502	1517	GTCTCTGGTCCTTACT	3-10-3 MOE C in 3’ wing is 9-(aminoethoxy)phenoxazine	1362
335415	1502	1517	GTCTCTGGTCCTTACT	3-10-3 MOE C in 5’ wing is 9-(aminoethoxy)phenoxazine	1362

335416	1502	1517	GTCTCTGGTCCTTACT	3-10-3 MOE C's in wings are 9-(aminoethoxy)phenoxazine	1362
336175	1495	1508	CCTTACTTCCCCAT	3-8-3 MOE	1360
336174	1472	1485	GGGCCTCTTGTGCC	3-8-3 MOE	1359
336173	1465	1478	TTGTGCCTTTAAAA	3-8-3 MOE	1358
398046	1465	1476	GTGCCTTTAAAA	1-10-1 MOE	1199
389766	1464	1475	TGCCTTTAAAAA	1-9-2 MOE	1217
389967	1464	1475	TGCCTTTAAAAA	1-10-1 MOE	1217
397976	1464	1477	TGTGCCTTTAAAAA	2-10-2 MOE	1357
336172	1437	1450	AATAAATATGCACA	3-8-3 MOE	1356
398045	1423	1434	TCATTACACCAG	1-10-1 MOE	1355
336171	1422	1435	ATCATTACACCAGT	3-8-3 MOE	1354
389765	1422	1433	CATTACACCAGT	1-9-2 MOE	1353
389966	1422	1433	CATTACACCAGT	1-10-1 MOE	1353
397975	1422	1435	ATCATTACACCAGT	2-10-2 MOE	1354
390005	1400	1411	CCAGCTTTACAG	1-10-1 MOE	1352
336170	1392	1405	TTACAGTGAATTGC	3-8-3 MOE	1351
398044	1382	1393	GCTGCAACATGA	1-10-1 MOE	1350
336169	1381	1394	TGCTGCAACATGAT	3-8-3 MOE	1349
389764	1381	1392	CTGCAACATGAT	1-9-2 MOE	1018
389965	1381	1392	CTGCAACATGAT	1-10-1 MOE	1018
397974	1381	1394	TGCTGCAACATGAT	2-10-2 MOE	1349
336168	1362	1375	TCTTCACTTAGCCA	3-8-3 MOE	1348
390004	1362	1373	TTCACTTAGCCA	1-10-1 MOE	1208
336167	1353	1366	AGCCATTGGTCAAG	3-8-3 MOE	1347
398043	1345	1356	CAAGATCTTCAC	1-10-1 MOE	1244
336166	1344	1357	TCAAGATCTTCACA	3-8-3 MOE	1346
390003	1344	1355	AAGATCTTCACA	1-10-1 MOE	1243
397973	1344	1357	TCAAGATCTTCACA	2-10-2 MOE	1346
336165	1329	1342	AAGGGTTTGATAAG	3-8-3 MOE	1345
390002	1322	1333	ATAAGTTCTAGC	1-10-1 MOE	1344
336164	1318	1331	AAGTTCTAGCTGTG	3-8-3 MOE	1343
398042	1305	1316	TGGGTTATGGTC	1-10-1 MOE	1214
336163	1304	1317	GTGGGTTATGGTCT	3-8-3 MOE	1342
397972	1304	1317	GTGGGTTATGGTCT	2-10-2 MOE	1342
398089	1298	1309	TGGTCTTCAAAA	1-10-1 MOE	1341
389763	1296	1307	GTCTTCAAAAGG	1-9-2 MOE	1197
389964	1296	1307	GTCTTCAAAAGG	1-10-1 MOE	1197
398041	1294	1305	CTTCAAAAGGAT	1-10-1 MOE	1196
336162	1293	1306	TCTTCAAAAGGATA	3-8-3 MOE	1340
397971	1293	1306	TCTTCAAAAGGATA	2-10-2 MOE	1340
398040	1279	1290	GTGCAACTCTGC	1-10-1 MOE	1236
336161	1278	1291	TGTGCAACTCTGCA	3-8-3 MOE	1235
397970	1278	1291	TGTGCAACTCTGCA	2-10-2 MOE	1235
398039	1264	1275	TAAATTTGGCGG	1-10-1 MOE	1339
397969	1263	1276	TTAAATTTGGCGGT	2-10-2 MOE	1338
336160	1261	1274	AAATTTGGCGGTGT	3-8-3 MOE	1337
336159	1253	1266	CGGTGTCATAATGT	3-8-3 MOE	1336
398038	1252	1263	TGTCATAATGTC	1-10-1 MOE	1200

390000	1251	1262	GTCATAATGTCT	1-10-1 MOE	1194
397968	1251	1264	GTGTCATAATGTCT	2-10-2 MOE	1195
336158	1227	1240	AGATTGTATATCTT	3-8-3 MOE	1335
389762	1220	1231	ATCTTGTAATGG	1-9-2 MOE	1334
389963	1220	1231	ATCTTGTAATGG	1-10-1 MOE	1334
336157	1215	1228	TTGTAATGGTTTTT	3-8-3 MOE	1333
336156	1202	1215	TATGCTTTGAATCC	3-8-3 MOE	1332
389998	1199	1210	TTTGAATCCAAA	1-10-1 MOE	1331
397967	1198	1211	CTTTGAATCCAAAA	2-10-2 MOE	1330
336155	1190	1203	CCAAAAACCTTACT	3-8-3 MOE	1500
336154	1176	1189	ACATCATCAATATT	3-8-3 MOE	1329
389761	1171	1182	CAATATTGTTCC	1-9-2 MOE	1328
389962	1171	1182	CAATATTGTTCC	1-10-1 MOE	1328
398037	1170	1181	AATATTGTTCCT	1-10-1 MOE	1202
397966	1169	1182	CAATATTGTTCCTG	2-10-2 MOE	1327
336153	1164	1177	TTGTTCCTGTATAC	3-8-3 MOE	1326
336152	1149	1162	CCTTCAAGTCTTTC	3-8-3 MOE	1325
389996	1141	1152	TTTCTGCAGGAA	1-10-1 MOE	1165
336151	1138	1151	TTCTGCAGGAAATC	3-8-3 MOE	1324
398036	1138	1149	CTGCAGGAAATC	1-10-1 MOE	1323
397965	1137	1150	TCTGCAGGAAATCC	2-10-2 MOE	1322
389760	1129	1140	ATCCCATAGCAA	1-9-2 MOE	1321
389961	1129	1140	ATCCCATAGCAA	1-10-1 MOE	1321
398035	1126	1137	CCATAGCAATAA	1-10-1 MOE	1320
336150	1125	1138	CCCATAGCAATAAT	3-8-3 MOE	1319
397964	1125	1138	CCCATAGCAATAAT	2-10-2 MOE	1319
336149	1110	1123	TTTGGATAAATATA	3-8-3 MOE	1496
389995	1106	1117	TAAATATAGGTC	1-10-1 MOE	1516
336148	1100	1113	TATAGGTCAAGTCT	3-8-3 MOE	1495
398034	1099	1110	AGGTCAAGTCTA	1-10-1 MOE	1300
397963	1098	1111	TAGGTCAAGTCTAA	2-10-2 MOE	1494
389994	1095	1106	CAAGTCTAAGTC	1-10-1 MOE	1299
336147	1090	1103	GTCTAAGTCGAATC	3-8-3 MOE	1298
389993	1083	1094	GAATCCATCCTC	1-10-1 MOE	1297
336146	1080	1093	AATCCATCCTCTTG	3-8-3 MOE	1296
398033	1077	1088	ATCCTCTTGATA	1-10-1 MOE	1198
397962	1076	1089	CATCCTCTTGATAT	2-10-2 MOE	1295
336145	1070	1083	CTTGATATCTCCTT	3-8-3 MOE	1294
336144	1057	1070	TTTGTTTCTGCTAA	3-8-3 MOE	1293
389759	1056	1067	GTTTCTGCTAAC	1-9-2 MOE	1292
389960	1056	1067	GTTTCTGCTAAC	1-10-1 MOE	1292
392059	1055	1068	TGTTTCTGCTAACG	2-10-2 Methyleneoxy BNA Unmodified cytosines in gap	1291
336143	1044	1057	ACGATCTCTTTGAT	3-8-3 MOE	1290
398032	1038	1049	TTTGATGATGGC	1-10-1 MOE	1222
397961	1037	1050	CTTTGATGATGGCT	2-10-2 MOE	1289
389992	1036	1047	TGATGATGGCTG	1-10-1 MOE	1288
336142	1032	1045	ATGATGGCTGTCAT	3-8-3 MOE	1287
389991	1021	1032	TGTCTGGGAGCC	1-10-1 MOE	1286
392058	1020	1033	ATGTCTGGGAGCCT	2-10-2 Methyleneoxy BNA	1285

				Unmodified cytosines in gap	
397960	1020	1033	ATGTCTGGGAGCCT	2-10-2 MOE	1285
389990	1007	1018	TGGCTGAAGAAA	1-10-1 MOE	1284
397959	1006	1019	GTGGCTGAAGAAAA	2-10-2 MOE	1283
398031	987	998	GAGAGATGGCAG	1-10-1 MOE	1282
397958	986	999	AGAGAGATGGCAGA	2-10-2 MOE	1281
389758	983	994	GATGGCAGAAGC	1-9-2 MOE	1280
389959	983	994	GATGGCAGAAGC	1-10-1 MOE	1280
398030	976	987	GAAGCTGCTGGT	1-10-1 MOE	1143
397957	975	988	AGAAGCTGCTGGTG	2-10-2 MOE	1279
389989	953	964	TTCTGCAGGATG	1-10-1 MOE	1170
389757	941	952	GAAATGGCTCTG	1-9-2 MOE	1278
389958	941	952	GAAATGGCTCTG	1-10-1 MOE	1278
397956	940	953	GGAAATGGCTCTGG	2-10-2 MOE	1277
398029	931	942	TGGACTTGGCGG	1-10-1 MOE	1186
397955	930	943	CTGGACTTGGCGGT	2-10-2 MOE	1276
398028	914	925	GATGCCCCTCGC	1-10-1 MOE	1275
397954	913	926	TGATGCCCCTCGCT	2-10-2 MOE	1274
398027	883	894	GGACCGCAGCCG	1-10-1 MOE	1155
397953	882	895	TGGACCGCAGCCGG	2-10-2 MOE	1273
389756	874	885	CCGGGTAATGGC	1-9-2 MOE	1272
389957	874	885	CCGGGTAATGGC	1-10-1 MOE	1272
398026	867	878	ATGGCTGCTGCG	1-10-1 MOE	1160
397952	866	879	AATGGCTGCTGCGG	2-10-2 MOE	1271
389987	848	859	CTGGATGGTTGC	1-10-1 MOE	1270
389755	806	817	AGAGGCCTGGCA	1-9-2 MOE	1269
389956	806	817	AGAGGCCTGGCA	1-10-1 MOE	1269
389985	584	595	ATGGTGACAGGC	1-10-1 MOE	1268
398025	581	592	GTGACAGGCGAC	1-10-1 MOE	1267
397951	580	593	GGTGACAGGCGACT	2-10-2 MOE	1266
389754	312	323	TGCTCACAGGCG	1-9-2 MOE	1158
389955	312	323	TGCTCACAGGCG	1-10-1 MOE	1158
398024	231	242	CAGCGGCTCAAC	1-10-1 MOE	1265
397950	230	243	ACAGCGGCTCAACT	2-10-2 MOE	1264
389982	205	216	CATGGCTGCAGC	1-10-1 MOE	1161
392056	204	217	TCATGGCTGCAGCT	2-10-2 Methyleneoxy BNA	1263
394424	204	217	TCATGGCTGCAGCT	2-10-2 MOE	1263
396007	204	217	TCATGGCTGCAGCT	2-10-2 (R)-CMOE BNA Unmodified cytosines	1263
396008	204	217	TCATGGCTGCAGCT	2-10-2 (S)-CMOE BNA Unmodified cytosines	1263
396009	204	217	TCATGGCTGCAGCT	2-10-2 α-L-methyleneoxy BNA Unmodified cytosines	1263
396566	204	217	TCATGGCTGCAGCT	2-10-2 Oxyamino BNA Unmodified cytosines	1263
396567	204	217	TCATGGCTGCAGCT	2-10-2 N-Methyl-Oxyamino BNA Unmodified cytosines	1263
396568	204	217	TCATGGCTGCAGCT	2-10-2 (6R)-6-Methyl Methyleneoxy BNA Unmodified cytosines	1263

397913	204	217	TCATGGCTGCAGCT	2-10-2 OMe Unmodified cytosines in gap	1263
401974	204	217	TCATGGCTGCAGCT	2-10-2 OMe Unmodified cytosines	1263
403737	204	217	TCATGGCTGCAGCT	2-10-2 Methyleneoxy BNA 5-thiazole nucleobases in wings	1263
404121	204	217	TCATGGCTGCAGCT	2-10-2 Methyleneoxy BNA 5-methylcytosine in gaps 3' Terminal THF phosphorothioate	1263
404228	204	217	TCATGGCTGCAGCT	2-10-2 Methyleneoxy BNA 5-methylcytosinse in gaps 5'-terminal reverse abasic	1263
396024	204	217	TCATGGCTGCAGCT	2-10-2 (6'S)-6'-methyl- Methyleneoxy BNA Unmodified cytosines	1263
396569	204	217	TCATGGCTGCAGCT	2-10-2 (5'S)-5'-methyl- Methyleneoxy BNA Unmodified cytosines	1263
396577	204	217	TCATGGCTGCAGCT	2-10-1-1 Methyleneoxy BNA / Methyleneoxy BNA /2'- (butylacetamido)-palmitamide/ Unmodified cytosines in gap	1263
396576	204	217	TCATGGCTGCAGCT	1-1-10-2 2'-(butylacetamido)- palmitamide/ Methyleneoxy BNA / Methyleneoxy BNA Unmodified cytosines in gap	1263
398023	191	202	CCGAGAGGAGAG	1-10-1 MOE	1262
397949	190	203	TCCGAGAGGAGAGA	2-10-2 MOE	1261
398022	126	137	AAGAGTCCCGCC	1-10-1 MOE	1260
397948	125	138	AAAGAGTCCCGCCA	2-10-2 MOE	1259

Table 22: Short Antisense Compounds targeted to SEQ ID NO: 15

ISIS No.	5' Target Site	3' Target Site	Sequence (5'-3')	Gapmer Motif	SEQ ID NO
397948	525	538	AAAGAGTCCCGCCA	2-10-2 MOE	1259
398022	526	537	AAGAGTCCCGCC	1-10-1 MOE	1260
397949	590	603	TCCGAGAGGAGAGA	2-10-2 MOE	1261
398023	591	602	CCGAGAGGAGAG	1-10-1 MOE	1262
394424	604	617	TCATGGCTGCAGCT	2-10-2 MOE	1263
397913	604	617	TCATGGCTGCAGCT	2-10-2 OMe Unmodified cytosines in gap	1263
401974	604	617	TCATGGCTGCAGCT	2-10-2 Ome Unmodified cytosines	1263
403737	604	617	TCATGGCTGCAGCT	2-10-2 Methyleneoxy BNA 5-thiazole nucleobases in wings	1263
392056	604	617	TCATGGCTGCAGCT	2-10-2 Methyleneoxy BNA Unmodified cytosines in gap	1263

396576	604	617	TCATGGCTGCAGCT	1-1-10-2 2'-(butylacetamido)-palmitamide / Methyleneoxy BNA / Methyleneoxy BNA Unmodified cytosines in gap	1263
396577	604	617	TCATGGCTGCAGCT	2-10-1-2 Methyleneoxy BNA / Methyleneoxy BNA /2'-(butylacetamido)-palmitamide/ Unmodified cytosines in gap	1263
404121	604	617	TCATGGCTGCAGCT	2-10-2 Methyleneoxy BNA 5-methylcytosine in gaps 3' Terminal THF phosphorothioate	1263
404228	604	617	TCATGGCTGCAGCT	2-10-2 Methyleneoxy BNA 5-methylcytosinse in gaps 5'-terminal reverse abasic	1263
396007	604	617	TCATGGCTGCAGCT	2-10-2 (R)-CMOE BNA Unmodified cytosines	1263
396008	604	617	TCATGGCTGCAGCT	2-10-2 (S)-CMOE BNA Unmodified cytosines	1263
396009	604	617	TCATGGCTGCAGCT	2-10-2 α-L-methyleneoxy BNA Unmodified cytosines	1263
396024	604	617	TCATGGCTGCAGCT	2-10-2 (6'S)-6'-methyl-Methyleneoxy BNA Unmodified cytosines	1263
396566	604	617	TCATGGCTGCAGCT	2-10-2 Oxyamino BNA Unmodified cytosines	1263
396567	604	617	TCATGGCTGCAGCT	2-10-2 N-Methyl-Oxyamino BNA Unmodified cytosines	1263
396568	604	617	TCATGGCTGCAGCT	2-10-2 (6R)-6-Methyl Methyleneoxy BNA Unmodified cytosines	1263
396569	604	617	TCATGGCTGCAGCT	2-10-2 (5'S)-5'-methyl-Methyleneoxy BNA Unmodified cytosines	1263
389982	605	616	CATGGCTGCAGC	1-10-1 MOE	1161
397950	630	643	ACAGCGGCTCAACT	2-10-2 MOE	1264
398024	631	642	CAGCGGCTCAAC	1-10-1 MOE	1265
389955	712	723	TGCTCACAGGCG	1-10-1 MOE	1158
389754	712	723	TGCTCACAGGCG	1-9-2 MOE	1158
397951	980	993	GGTGACAGGCGACT	2-10-2 MOE	1266
398025	981	992	GTGACAGGCGAC	1-10-1 MOE	1267
389985	984	995	ATGGTGACAGGC	1-10-1 MOE	1268
389956	1206	1217	AGAGGCCTGGCA	1-10-1 MOE	1269
389755	1206	1217	AGAGGCCTGGCA	1-9-2 MOE	1269
389987	1248	1259	CTGGATGGTTGC	1-10-1 MOE	1270
397952	1266	1279	AATGGCTGCTGCGG	2-10-2 MOE	1271
398026	1267	1278	ATGGCTGCTGCG	1-10-1 MOE	1160

389957	1274	1285	CCGGGTAATGGC	1-10-1 MOE	1272
389756	1274	1285	CCGGGTAATGGC	1-9-2 MOE	1272
397953	1282	1295	TGGACCGCAGCCGG	2-10-2 MOE	1273
398027	1283	1294	GGACCGCAGCCG	1-10-1 MOE	1155
397954	1313	1326	TGATGCCCCTCGCT	2-10-2 MOE	1274
398028	1314	1325	GATGCCCCTCGC	1-10-1 MOE	1275
397955	1330	1343	CTGGACTTGGCGGT	2-10-2 MOE	1276
398029	1331	1342	TGGACTTGGCGG	1-10-1 MOE	1186
397956	1340	1353	GGAAATGGCTCTGG	2-10-2 MOE	1277
389958	1341	1352	GAAATGGCTCTG	1-10-1 MOE	1278
389757	1341	1352	GAAATGGCTCTG	1-9-2 MOE	1278
389989	1353	1364	TTCTGCAGGATG	1-10-1 MOE	1170
397957	1375	1388	AGAAGCTGCTGGTG	2-10-2 MOE	1279
398030	1376	1387	GAAGCTGCTGGT	1-10-1 MOE	1143
389959	1383	1394	GATGGCAGAAGC	1-10-1 MOE	1280
389758	1383	1394	GATGGCAGAAGC	1-9-2 MOE	1280
397958	1386	1399	AGAGAGATGGCAGA	2-10-2 MOE	1281
398031	1387	1398	GAGAGATGGCAG	1-10-1 MOE	1282
397959	1406	1419	GTGGCTGAAGAAAA	2-10-2 MOE	1283
389990	1407	1418	TGGCTGAAGAAA	1-10-1 MOE	1284
397960	1420	1433	ATGTCTGGGAGCCT	2-10-2 MOE	1285
392058	1420	1433	ATGTCTGGGAGCCT	2-10-2 Methyleneoxy BNA 5-methylcytosine in wing	1285
389991	1421	1432	TGTCTGGGAGCC	1-10-1 MOE	1286
336142	1432	1445	ATGATGGCTGTCAT	3-8-3 MOE	1287
389992	1436	1447	TGATGATGGCTG	1-10-1 MOE	1288
397961	1437	1450	CTTTGATGATGGCT	2-10-2 MOE	1289
398032	1438	1449	TTTGATGATGGC	1-10-1 MOE	1222
336143	1444	1457	ACGATCTCTTTGAT	3-8-3 MOE	1290
392059	1455	1468	TGTTTCTGCTAACG	2-10-2 Methyleneoxy BNA 5-methylcytosine in wing	1291
389960	1456	1467	GTTTCTGCTAAC	1-10-1 MOE	1292
389759	1456	1467	GTTTCTGCTAAC	1-9-2 MOE	1292
336144	1457	1470	TTTGTTTCTGCTAA	3-8-3 MOE	1293
336145	1470	1483	CTTGATATCTCCTT	3-8-3 MOE	1294
397962	1476	1489	CATCCTCTTGATAT	2-10-2 MOE	1295
398033	1477	1488	ATCCTCTTGATA	1-10-1 MOE	1198
336146	1480	1493	AATCCATCCTCTTG	3-8-3 MOE	1296
389993	1483	1494	GAATCCATCCTC	1-10-1 MOE	1297
336147	1490	1503	GTCTAAGTCGAATC	3-8-3 MOE	1298
389994	1495	1506	CAAGTCTAAGTC	1-10-1 MOE	1299
398034	1499	1510	AGGTCAAGTCTA	1-10-1 MOE	1300
398010	1500	1513	TACAGGTCAAGTCT	2-10-2 MOE	1166
398077	1501	1512	ACAGGTCAAGTC	1-10-1 MOE	1167
398011	1512	1525	CGCAGAAATGGATA	2-10-2 MOE	1301
398078	1513	1524	GCAGAAATGGAT	1-10-1 MOE	1302
398012	1570	1583	TTCGCATCCGTCTA	2-10-2 MOE	1303
398079	1571	1582	TCGCATCCGTCT	1-10-1 MOE	1304
398013	1663	1676	CCCTAGGTTGAATA	2-10-2 MOE	1305
398080	1664	1675	CCTAGGTTGAAT	1-10-1 MOE	1306

398014	2025	2038	GTTATGCAAATCAG	2-10-2 MOE	1307
398081	2026	2037	TTATGCAAATCA	1-10-1 MOE	1308
398015	2620	2633	TGACTCAGTAAATT	2-10-2 MOE	1309
398082	2621	2632	GACTCAGTAAAT	1-10-1 MOE	1310
398016	2655	2668	TTAAAATTCTTGGG	2-10-2 MOE	1311
398083	2656	2667	TAAAATTCTTGG	1-10-1 MOE	1312
398017	2687	2700	CCTAACTTTTAGAC	2-10-2 MOE	1313
398084	2688	2699	CTAACTTTTAGA	1-10-1 MOE	1314
398018	2745	2758	ACCTGAAACTGCAA	2-10-2 MOE	1315
398085	2746	2757	CCTGAAACTGCA	1-10-1 MOE	1157
398019	13166	13179	GTGTCAAAACCACT	2-10-2 MOE	1316
398086	13167	13178	TGTCAAAACCAC	1-10-1 MOE	1204
398020	14675	14688	CCTATTCCCACTGA	2-10-2 MOE	1317
398087	14676	14687	CTATTCCCACTG	1-10-1 MOE	1318
390033	15351	15362	AGCCAACTGCAA	1-10-1 MOE	1483
398021	30985	30998	TTGGATAAATATCT	2-10-2 MOE	1168
398088	30986	30997	TGGATAAATATC	1-10-1 MOE	1169
397964	31001	31014	CCCATAGCAATAAT	2-10-2 MOE	1319
336150	31001	31014	CCCATAGCAATAAT	3-8-3 MOE	1319
398035	31002	31013	CCATAGCAATAA	1-10-1 MOE	1320
389961	31005	31016	ATCCCATAGCAA	1-10-1 MOE	1321
389760	31005	31016	ATCCCATAGCAA	1-9-2 MOE	1321
397965	31013	31026	TCTGCAGGAAATCC	2-10-2 MOE	1322
398036	31014	31025	CTGCAGGAAATC	1-10-1 MOE	1323
336151	31014	31027	TTCTGCAGGAAATC	3-8-3 MOE	1324
389996	31017	31028	TTTCTGCAGGAA	1-10-1 MOE	1165
336152	31025	31038	CCTTCAAGTCTTTC	3-8-3 MOE	1325
336153	31040	31053	TTGTTCCTGTATAC	3-8-3 MOE	1326
397966	31045	31058	CAATATTGTTCCTG	2-10-2 MOE	1327
398037	31046	31057	AATATTGTTCCT	1-10-1 MOE	1202
389962	31047	31058	CAATATTGTTCC	1-10-1 MOE	1328
389761	31047	31058	CAATATTGTTCC	1-9-2 MOE	1328
336154	31052	31065	ACATCATCAATATT	3-8-3 MOE	1329
389977	31480	31491	CTTAAAATTTGG	1-10-1 MOE	1421
389776	31480	31491	CTTAAAATTTGG	1-9-2 MOE	1421
397967	62446	62459	CTTTGAATCCAAAA	2-10-2 MOE	1330
389998	62447	62458	TTTGAATCCAAA	1-10-1 MOE	1331
336156	62450	62463	TATGCTTTGAATCC	3-8-3 MOE	1332
336157	62463	62476	TTGTAATGGTTTTT	3-8-3 MOE	1333
389963	62468	62479	ATCTTGTAATGG	1-10-1 MOE	1334
389762	62468	62479	ATCTTGTAATGG	1-9-2 MOE	1334
336158	62475	62488	AGATTGTATATCTT	3-8-3 MOE	1335
390000	67987	67998	GTCATAATGTCT	1-10-1 MOE	1194
397968	67987	68000	GTGTCATAATGTCT	2-10-2 MOE	1195
398038	67988	67999	TGTCATAATGTC	1-10-1 MOE	1200
336159	67989	68002	CGGTGTCATAATGT	3-8-3 MOE	1336
336160	67997	68010	AAATTTGGCGGTGT	3-8-3 MOE	1337
397969	67999	68012	TTAAATTTGGCGGT	2-10-2 MOE	1338
398039	68000	68011	TAAATTTGGCGG	1-10-1 MOE	1339
397971	69952	69965	TCTTCAAAAGGATA	2-10-2 MOE	1340

336162	69952	69965	TCTTCAAAAGGATA	3-8-3 MOE	1340
398041	69953	69964	CTTCAAAAGGAT	1-10-1 MOE	1196
389964	69955	69966	GTCTTCAAAAGG	1-10-1 MOE	1197
389763	69955	69966	GTCTTCAAAAGG	1-9-2 MOE	1197
398089	69957	69968	TGGTCTTCAAAA	1-10-1 MOE	1341
397972	69963	69976	GTGGGTTATGGTCT	2-10-2 MOE	1342
336163	69963	69976	GTGGGTTATGGTCT	3-8-3 MOE	1342
398042	69964	69975	TGGGTTATGGTC	1-10-1 MOE	1214
336164	69977	69990	AAGTTCTAGCTGTG	3-8-3 MOE	1343
390002	69981	69992	ATAAGTTCTAGC	1-10-1 MOE	1344
336165	69988	70001	AAGGGTTTGATAAG	3-8-3 MOE	1345
390003	70003	70014	AAGATCTTCACA	1-10-1 MOE	1243
397973	70003	70016	TCAAGATCTTCACA	2-10-2 MOE	1346
336166	70003	70016	TCAAGATCTTCACA	3-8-3 MOE	1346
398043	70004	70015	CAAGATCTTCAC	1-10-1 MOE	1244
336167	70012	70025	AGCCATTGGTCAAG	3-8-3 MOE	1347
390004	70021	70032	TTCACTTAGCCA	1-10-1 MOE	1208
336168	70021	70034	TCTTCACTTAGCCA	3-8-3 MOE	1348
389965	70040	70051	CTGCAACATGAT	1-10-1 MOE	1018
389764	70040	70051	CTGCAACATGAT	1-9-2 MOE	1018
397974	70040	70053	TGCTGCAACATGAT	2-10-2 MOE	1349
336169	70040	70053	TGCTGCAACATGAT	3-8-3 MOE	1349
398044	70041	70052	GCTGCAACATGA	1-10-1 MOE	1350
336170	70051	70064	TTACAGTGAATTGC	3-8-3 MOE	1351
390005	70059	70070	CCAGCTTTACAG	1-10-1 MOE	1352
389966	70081	70092	CATTACACCAGT	1-10-1 MOE	1353
389765	70081	70092	CATTACACCAGT	1-9-2 MOE	1353
397975	70081	70094	ATCATTACACCAGT	2-10-2 MOE	1354
336171	70081	70094	ATCATTACACCAGT	3-8-3 MOE	1354
398045	70082	70093	TCATTACACCAG	1-10-1 MOE	1355
336172	70096	70109	AATAAATATGCACA	3-8-3 MOE	1356
389967	70123	70134	TGCCTTTAAAAA	1-10-1 MOE	1217
389766	70123	70134	TGCCTTTAAAAA	1-9-2 MOE	1217
397976	70123	70136	TGTGCCTTTAAAAA	2-10-2 MOE	1357
398046	70124	70135	GTGCCTTTAAAA	1-10-1 MOE	1199
336173	70124	70137	TTGTGCCTTTAAAA	3-8-3 MOE	1358
336174	70131	70144	GGGCCTCTTGTGCC	3-8-3 MOE	1359
336175	70154	70167	CCTTACTTCCCCAT	3-8-3 MOE	1360
335345	70161	70176	GTCTCTGGTCCTTACT	3-10-3 MOE	1362
335356	70161	70176	GTCTCTGGTCCTTACT	3-10-3 MOE Phosphodiester linkage in wings	1362
335414	70161	70176	GTCTCTGGTCCTTACT	3-10-3 MOE C in 3' wing is 9-(aminoethoxy)phenoxazine	1362
335415	70161	70176	GTCTCTGGTCCTTACT	3-10-3 MOE C in 5' wing is 9-(aminoethoxy)phenoxazine	1362
335416	70161	70176	GTCTCTGGTCCTTACT	3-10-3 MOE C's in wings are	1362

				9- (aminoethoxy)phenoxazine	
336176	70161	70174	CTCTGGTCCTTACT	3-8-3 MOE	1361
335371	70161	70176	GTCTCTGGTCCTTACT	3-10-3 Methyleneoxy BNA Phosphodiester linkage in wings	1362
335382	70161	70176	GTCTCTGGTCCTTACT	3-10-3 Methyleneoxy BNA	1362
335344	70162	70175	TCTCTGGTCCTTAC	2-10-2 MOE	1363
335355	70162	70175	TCTCTGGTCCTTAC	2-10-2 MOE Phosphodiester linkage in wings	1363
335411	70162	70175	TCTCTGGTCCTTAC	2-10-2 MOE 3' C is 9-(aminoethoxy)phenoxazine	1363
335412	70162	70175	TCTCTGGTCCTTAC	2-10-2 MOE 2nd C is 9-(aminoethoxy)phenoxazine	1363
335413	70162	70175	TCTCTGGTCCTTAC	2-10-2 MOE 2nd and 3' terminal C's are 9-(aminoethoxy)phenoxazine	1363
335370	70162	70175	TCTCTGGTCCTTAC	2-10-2 Methyleneoxy BNA Phosphodiester linkage in wings	1363
335381	70162	70175	TCTCTGGTCCTTAC	2-10-2 Methyleneoxy BNA	1363
398068	79799	79810	ACAGCTACACAA	1-10-1 MOE	1472
389968	89056	89067	TCTGACTGGGAA	1-10-1 MOE	1151
389767	89056	89067	TCTGACTGGGAA	1-9-2 MOE	1151
336177	89056	89069	CCTCTGACTGGGAA	3-8-3 MOE	1364
336178	89063	89076	CATAGCGCCTCTGA	3-8-3 MOE	1365
336179	89083	89096	CAGGTAGCTATAAT	3-8-3 MOE	1366
390007	89085	89096	CAGGTAGCTATA	1-10-1 MOE	1367
390009	89135	89146	ATCTTGTGAAAC	1-10-1 MOE	1175
397977	89135	89148	TCATCTTGTGAAAC	2-10-2 MOE	1368
336180	89135	89148	TCATCTTGTGAAAC	3-8-3 MOE	1368
398047	89136	89147	CATCTTGTGAAA	1-10-1 MOE	1369
336181	89145	89158	GTTTCAAACATCAT	3-8-3 MOE	1370
397978	89147	89160	TAGTTTCAAACATC	2-10-2 MOE	1371
398048	89148	89159	AGTTTCAAACAT	1-10-1 MOE	1372
389969	89152	89163	GAATAGTTTCAA	1-10-1 MOE	1373
389768	89152	89163	GAATAGTTTCAA	1-9-2 MOE	1373
336182	89155	89168	CATTGGAATAGTTT	3-8-3 MOE	1374
397979	89162	89175	CACTGAACATTGGA	2-10-2 MOE	1375
398049	89163	89174	ACTGAACATTGG	1-10-1 MOE	1376
390010	89165	89176	CCACTGAACATT	1-10-1 MOE	1240
336183	89166	89179	CCGCCACTGAACAT	3-8-3 MOE	1377
397980	94786	94799	CAGACCACAAACTG	2-10-2 MOE	1378
398050	94787	94798	AGACCACAAACT	1-10-1 MOE	1379
392060	94790	94803	CTGGCAGACCACAA	2-10-2 Methyleneoxy BNA Unmodified cytosines in gap	1380

389970	94791	94802	TGGCAGACCACA	1-10-1 MOE	1249
389769	94791	94802	TGGCAGACCACA	1-9-2 MOE	1249
336185	94792	94805	AGCTGGCAGACCAC	3-8-3 MOE	1381
397981	94798	94811	ACCTTTAGCTGGCA	2-10-2 MOE	1382
398051	94799	94810	CCTTTAGCTGGC	1-10-1 MOE	1220
336186	94803	94816	TCTTCACCTTTAGC	3-8-3 MOE	1383
390012	94860	94871	TCAAAGTACATG	1-10-1 MOE	1384
336187	94862	94875	GAACTCAAAGTACA	3-8-3 MOE	1385
389971	94865	94876	GGAACTCAAAGT	1-10-1 MOE	1386
389770	94865	94876	GGAACTCAAAGT	1-9-2 MOE	1386
397982	94865	94878	AGGGAACTCAAAGT	2-10-2 MOE	1387
398052	94866	94877	GGGAACTCAAAG	1-10-1 MOE	1388
336188	94869	94882	GCTGAGGGAACTCA	3-8-3 MOE	1389
336189	94888	94901	TCACCACACACAGG	3-8-3 MOE	1390
336190	94904	94917	GAACTCTACTTTGA	3-8-3 MOE	1391
389972	94909	94920	GAAGAACTCTAC	1-10-1 MOE	1392
389771	94909	94920	GAAGAACTCTAC	1-9-2 MOE	1392
397983	94910	94923	GTGGAAGAACTCTA	2-10-2 MOE	1393
398053	94911	94922	TGGAAGAACTCT	1-10-1 MOE	1394
336191	94915	94928	TGTTTGTGGAAGAA	3-8-3 MOE	1395
336192	94925	94938	CATCTTGTTCTGTT	3-8-3 MOE	1396
397984	97824	97837	AGTGAAACATTTTG	2-10-2 MOE	1397
398054	97825	97836	GTGAAACATTTT	1-10-1 MOE	1144
336194	97827	97840	AAAAGTGAAACATT	3-8-3 MOE	1145
389973	97835	97846	TTACCCAAAAGT	1-10-1 MOE	1398
389772	97835	97846	TTACCCAAAAGT	1-9-2 MOE	1398
336195	97836	97849	TATTTACCCAAAAG	3-8-3 MOE	1399
397985	97837	97850	GTATTTACCCAAAA	2-10-2 MOE	1400
398055	97838	97849	TATTTACCCAAA	1-10-1 MOE	1401
397986	97853	97866	TCCTGGTATGAAGA	2-10-2 MOE	1402
336196	97853	97866	TCCTGGTATGAAGA	3-8-3 MOE	1402
398056	97854	97865	CCTGGTATGAAG	1-10-1 MOE	1403
390015	97857	97868	GGTCCTGGTATG	1-10-1 MOE	1404
336197	97862	97875	TTCCTCTGGTCCTG	3-8-3 MOE	1405
397987	97866	97879	AGGTTTCCTCTGGT	2-10-2 MOE	1406
398057	97867	97878	GGTTTCCTCTGG	1-10-1 MOE	1407
336198	97873	97886	TTTTCTGAGGTTTC	3-8-3 MOE	1408
336199	97891	97904	AGACTTCCATTTTC	3-8-3 MOE	1409
389974	97893	97904	AGACTTCCATTT	1-10-1 MOE	1410
389773	97893	97904	AGACTTCCATTT	1-9-2 MOE	1410
336200	97918	97931	CAAATGCTATCGAT	3-8-3 MOE	1411
336201	97933	97946	GCACGCTCTATACT	3-8-3 MOE	1412
389975	97934	97945	CACGCTCTATAC	1-10-1 MOE	1413
389774	97934	97945	CACGCTCTATAC	1-9-2 MOE	1413
336202	97948	97961	TCCTTGTCATTATC	3-8-3 MOE	1414
397988	97990	98003	GCTTTGTCAAGATC	2-10-2 MOE	1415
389976	97991	98002	CTTTGTCAAGAT	1-10-1 MOE	1177
389775	97991	98002	CTTTGTCAAGAT	1-9-2 MOE	1177
336203	97991	98004	TGCTTTGTCAAGAT	3-8-3 MOE	1416
397989	98017	98030	AAGTATCGGTTGGC	2-10-2 MOE	1417

336204	98017	98030	AAGTATCGGTTGGC	3-8-3 MOE	1417
398058	98018	98029	AGTATCGGTTGG	1-10-1 MOE	1418
336205	98032	98045	TTAAAATTTGGAGA	3-8-3 MOE	1419
397990	98034	98047	CCTTAAAATTTGGA	2-10-2 MOE	1420
389977	98035	98046	CTTAAAATTTGG	1-10-1 MOE	1421
389776	98035	98046	CTTAAAATTTGG	1-9-2 MOE	1421
336207	102230	102243	TCTACTGTTTTTGT	3-8-3 MOE	1422
336208	102236	102249	GGCTCCTCTACTGT	3-8-3 MOE	1423
335330	102251	102265	AGCCTCTGGATTTGA	1-10-4 MOE	1424
335331	102252	102266	TAGCCTCTGGATTTG	1-10-4 MOE	1426
336209	102252	102265	AGCCTCTGGATTTG	3-8-3 MOE	1425
335377	102252	102266	TAGCCTCTGGATTTG	1-10-4 Methyleneoxy BNA Phosphodiester in 3' wing	1426
335376	102252	102266	TAGCCTCTGGATTTG	1-10-4 Methyleneoxy BNA	1426
390577	102253	102266	TAGCCTCTGGATTT	1-10-3 MOE Unmodified cytosines T's in wings are 2-thiothymines	1427
335332	102253	102267	CTAGCCTCTGGATTT	1-10-4 MOE	1429
386770	102253	102266	TAGCCTCTGGATTT	1-11-2 MOE	1427
375560	102253	102267	CTAGCCTCTGGATTT	2-10-3 MOE	1429
391449	102253	102267	CTAGCCTCTGGATTT	2-10-3 MOE Unmodified cytosines	1429
392055	102253	102267	CTAGCCTCTGGATTT	2-10-3 MOE Unmodified cytosines in gap	1429
362977	102253	102268	GCTAGCCTCTGGATTT	2-12-2 MOE	1428
371975	102253	102267	CTAGCCTCTGGATTT	3-10-2 MOE	1429
386556	102253	102268	GCTAGCCTCTGGATTT	3-10-3 MOE	1428
335341	102253	102268	GCTAGCCTCTGGATTT	3-10-3 MOE	1428
335350	102253	102268	GCTAGCCTCTGGATTT	3-10-3 MOE	1428
383739	102253	102268	GCTAGCCTCTGGATTT	3-10-3 MOE 5-methylcytosine in gap	1428
390576	102253	102268	GCTAGCCTCTGGATTT	3-10-3 MOE 5-methylcytosine in gap T's in wings are 2-thiothymines	1428
390580	102253	102268	GCTAGCCTCTGGATTT	3-10-3 MOE Pyrimidines in wings are 5-thiazole Unmodified cytosines in gap	1428
390581	102253	102268	GCTAGCCTCTGGATTT	3-10-3 MOE Unmodified cytosines in gap	1428
391096	102253	102268	GCTAGCCTCTGGATTT	3-10-3 MOE	1428
391098	102253	102268	GCTAGCCTCTGGATTT	3-10-3 MOE	1428
391863	102253	102268	GCTAGCCTCTGGATTT	3-10-3 MOE Unmodified cytosines	1428
384071	102253	102268	GCTAGCCTCTGGATTT	3-10-3 OMe 5-methylcytosine in gap	1428
385036	102253	102268	GCTAGCCTCTGGATTT	1-2-10-3 OMe/2'-O-methyl-4'-thio/2'-O-methyl-4'-thio Unmodified cytosines in	1428

				wing	
335368	102253	102268	GCTAGCCTCTGGATTT	3-10-3 Methyleneoxy BNA Phosphodiester linkages in wings	1428
391864	102253	102268	GCTAGCCTCTGGATTT	3-10-3 Methyleneoxy BNA Unmodified cytosines in gap	1428
392054	102253	102267	CTAGCCTCTGGATTT	2-10-3 Methyleneoxy BNA Unmodified cytosines in gap	1429
391172	102253	102267	CTAGCCTCTGGATTT	2-10-3 Methyleneoxy BNA Unmodified cytosines	1429
391865	102253	102268	GCTAGCCTCTGGATTT	3-10-3 Methyleneoxy BNA Unmodified cytosines	1428
391868	102253	102268	GCTAGCCTCTGGATTT	1-2-10-3 (5'R)-5'-methyl- Methyleneoxy BNA / Methyleneoxy BNA /(5'R)-5'-methyl- Methyleneoxy BNA Unmodified cytosines	1428
391869	102253	102268	GCTAGCCTCTGGATTT	1-2-10-3 Methyleneoxy BNA /(5'S)-5'-methyl- Methyleneoxy BNA /(5'S)-5'-methyl- Methyleneoxy BNA Unmodified cytosines	1428
384073	102253	102268	GCTAGCCTCTGGATTT	3-10-3 Methyleneoxy BNA 5-methylcytosine in gap	1428
335379	102253	102268	GCTAGCCTCTGGATTT	3-10-3 Methyleneoxy BNA	1428
390579	102253	102268	GCTAGCCTCTGGATTT	1-1-1-10-3 MOE/4'thio/2'-O-[(2-methoxy)ethyl]-4'-thio/2'-O-[(2-methoxy)ethyl]-4'-thio Unmodified cytosines in wings Phosphorodiester linkage in wings	1428
390582	102253	102268	GCTAGCCTCTGGATTT	1-2-10-3 MOE/4'thio/2'-O-[(2-methoxy)ethyl]-4'-thio Unmodified cytosines in wings Phosphorodiester linkage in wings	1428
390606	102253	102268	GCTAGCCTCTGGATTT	1-2-10-3 MOE/pentaF/pentaF Unmodified cytosines in wings Phosphodiester linkage in wings	1428
384072	102253	102268	GCTAGCCTCTGGATTT	1-2-10-3 MOE/pentaF/pentaF Unmodified cytosines in wings	1428

385871	102253	102268	GCTAGCCTCTGGATTT	1-2-10-3 OMe/ 2'-O-[(2-methoxy)ethyl]-4'-thio/ 2'-O-[(2-methoxy)ethyl]-4'-thio Unmodified cytosines in wing	1428
390607	102253	102268	GCTAGCCTCTGGATTT	3-10-3 MOE/pentaF Unmodified cytosines in wing	1428
390608	102253	102268	GCTAGCCTCTGGATTT	1-2-10-3 MOE/pentaF/pentaF Unmodified cytosines in wing	1428
390609	102253	102268	GCTAGCCTCTGGATTT	3-10-2-1 MOE/MOE/pentaF Unmodified cytosines in wing	1428
386682	102253	102268	GCTAGCCTCTGGATTT	1-2-10-3 2'-(butylacetamido)-palmitamide /MOE /MOE	1428
391173	102253	102267	CTAGCCTCTGGATTT	2-10-3 (5'R)-5'-methyl-Methyleneoxy BNA Unmodified cytosines	1429
391174	102253	102267	CTAGCCTCTGGATTT	2-10-3 (5'S)-5'-methyl-Methyleneoxy BNA Unmodified cytosines	1429
386970	102254	102266	TAGCCTCTGGATT	1-10-2 MOE	1432
390578	102254	102266	TAGCCTCTGGATT	1-10-2 MOE Unmodified cytosines Ts in wings are 2-thiothymines	1432
335333	102254	102268	GCTAGCCTCTGGATT	1-10-4 MOE	1430
331429	102254	102267	CTAGCCTCTGGATT	2-10-2 MOE	1431
335349	102254	102267	CTAGCCTCTGGATT	2-10-2 MOE	1431
335367	102254	102267	CTAGCCTCTGGATT	2-10-2 Methyleneoxy BNA Phosphodiester linkages in wings	1431
392061	102254	102267	CTAGCCTCTGGATT	2-10-2 Methyleneoxy BNA Unmodified cytosines in gap	1431
335378	102254	102267	CTAGCCTCTGGATT	2-10-2 Methyleneoxy BNA	1431
383991	102254	102266	TAGCCTCTGGATT	1-10-2 2'-(acetylamino-butyl-acetamido)-cholesterol /MOE	1432
383992	102254	102266	TAGCCTCTGGATT	1-10-2 2'-(acetylamino-butyl-acetamido)-cholic acid/MOE	1432
386683	102254	102266	TAGCCTCTGGATT	1-10-2 5' terminal 2'-(butylacetamido)-palmitamide/MOE	1432
390614	102254	102266	TAGCCTCTGGATT	1-10-2 PentaF	1432
389954	102255	102266	TAGCCTCTGGAT	1-10-1 MOE	1434

335334	102255	102269	TGCTAGCCTCTGGAT	1-10-4 MOE	1433
389777	102255	102266	TAGCCTCTGGAT	1-9-2 MOE	1434
390430	102256	102268	GCTAGCCTCTGGA	1-10-2 MOE Unmodified cytosines	1163
390431	102256	102268	GCTAGCCTCTGGA	1-10-2 MOE Unmodified cytosines C in wing 9-(aminoethoxy)phenoxazine	1163
390432	102256	102268	GCTAGCCTCTGGA	1-10-2 MOE	1163
390433	102256	102268	GCTAGCCTCTGGA	1-10-2 MOE Unmodified cytosines Nt 6 is 9-(aminoethoxy)phenoxazine	1163
390434	102256	102268	GCTAGCCTCTGGA	1-10-2 MOE Unmodified cytosines Nt 7 is 9-(aminoethoxy)phenoxazine	1163
390435	102256	102268	GCTAGCCTCTGGA	1-10-2 MOE Unmodified cytosines Nt 9 is 9-(aminoethoxy)phenoxazine	1163
335335	102256	102270	CTGCTAGCCTCTGGA	1-10-4 MOE	1435
335336	102257	102271	ACTGCTAGCCTCTGG	1-10-4 MOE	1436
335337	102258	102272	AACTGCTAGCCTCTG	1-10-4 MOE	1437
335338	102259	102273	GAACTGCTAGCCTCT	1-10-4 MOE	1438
335339	102260	102274	TGAACTGCTAGCCTC	1-10-4 MOE	1439
335340	102261	102275	TTGAACTGCTAGCCT	1-10-4 MOE	1440
336210	102261	102274	TGAACTGCTAGCCT	3-8-3 MOE	1441
397991	102264	102277	AGTTGAACTGCTAG	2-10-2 MOE	1442
398059	102265	102276	GTTGAACTGCTA	1-10-1 MOE	1443
390017	102268	102279	GAAGTTGAACTG	1-10-1 MOE	1444
336211	102269	102282	ACAGAAGTTGAACT	3-8-3 MOE	1445
397992	102293	102306	TCATTGTCACTAAC	2-10-2 MOE	1446
336212	102293	102306	TCATTGTCACTAAC	3-8-3 MOE	1446
398060	102294	102305	CATTGTCACTAA	1-10-1 MOE	1447
389978	102301	102312	TCAGGTTCATTG	1-10-1 MOE	1448
389778	102301	102312	TCAGGTTCATTG	1-9-2 MOE	1448
336213	102303	102316	ATGATCAGGTTCAT	3-8-3 MOE	1449
397993	102307	102320	TATAATGATCAGGT	2-10-2 MOE	1450
398061	102308	102319	ATAATGATCAGG	1-10-1 MOE	1451
336214	102314	102327	GAATATCTATAATG	3-8-3 MOE	1139
390019	102320	102331	GTCAGAATATCT	1-10-1 MOE	1173
397994	102322	102335	TGGTGTCAGAATAT	2-10-2 MOE	1452
398062	102323	102334	GGTGTCAGAATA	1-10-1 MOE	1255
336215	102326	102339	TCAGTGGTGTCAGA	3-8-3 MOE	1453
336216	102339	102352	CTCTGGATCAGAGT	3-8-3 MOE	1454
390020	102340	102351	TCTGGATCAGAG	1-10-1 MOE	1149
336217	102349	102362	AAGGTTCATTCTCT	3-8-3 MOE	1455
397995	102357	102370	TTCATCAAAAGGTT	2-10-2 MOE	1456
389979	102358	102369	TCATCAAAAGGT	1-10-1 MOE	1176

389779	102358	102369	TCATCAAAAGGT	1-9-2 MOE	1176
336218	102358	102371	CTTCATCAAAAGGT	3-8-3 MOE	1457
390021	102360	102371	CTTCATCAAAAG	1-10-1 MOE	1458
336219	102366	102379	ATGCTGATCTTCAT	3-8-3 MOE	1459
336220	102381	102394	TTTTGTAATTTGTG	3-8-3 MOE	1460
336221	102387	102400	TCAGACTTTTGTAA	3-8-3 MOE	1461
390022	102443	102454	CAGTTTATTCAA	1-10-1 MOE	1142
397996	102477	102490	TGTCCTATTGCCAT	2-10-2 MOE	1462
398063	102478	102489	GTCCTATTGCCA	1-10-1 MOE	1205
397997	102487	102500	TCTGACACAATGTC	2-10-2 MOE	1463
398064	102488	102499	CTGACACAATGT	1-10-1 MOE	1464
397998	102505	102518	TGTTCCTATAACTG	2-10-2 MOE	1465
398065	102506	102517	GTTCCTATAACT	1-10-1 MOE	1466
397999	102528	102541	AAGATTGGTCAGGA	2-10-2 MOE	1467
398066	102529	102540	AGATTGGTCAGG	1-10-1 MOE	1468
398000	102561	102574	GTGTCAAAACCCTG	2-10-2 MOE	1469
398067	102562	102573	TGTCAAAACCCT	1-10-1 MOE	1210
390025	102563	102574	GTGTCAAAACCC	1-10-1 MOE	1211
390026	102595	102606	AGCTACACAACC	1-10-1 MOE	1470
398001	102596	102609	CACAGCTACACAAC	2-10-2 MOE	1471
398068	102597	102608	ACAGCTACACAA	1-10-1 MOE	1472
398002	102607	102620	TATATACATGACAC	2-10-2 MOE	1473
398069	102608	102619	ATATACATGACA	1-10-1 MOE	1474
390027	102612	102623	AGGTATATACAT	1-10-1 MOE	1206
398003	102637	102650	AATTTTAAATGTCC	2-10-2 MOE	1475
398070	102638	102649	ATTTTAAATGTC	1-10-1 MOE	1476
390028	102648	102659	TCCTAATTGAAT	1-10-1 MOE	1477
390029	102667	102678	AAAGTGCCATCT	1-10-1 MOE	1478
398004	102689	102702	TTTATAAAACTGGA	2-10-2 MOE	1479
398071	102690	102701	TTATAAAACTGG	1-10-1 MOE	1480
390030	102691	102702	TTTATAAAACTG	1-10-1 MOE	1074
398005	102827	102840	TGCAAACTTATCTG	2-10-2 MOE	1481
398072	102828	102839	GCAAACTTATCT	1-10-1 MOE	1482
390033	102836	102847	AGCCAACTGCAA	1-10-1 MOE	1483
398006	102837	102850	CTTAGCCAACTGCA	2-10-2 MOE	1484
398073	102838	102849	TTAGCCAACTGC	1-10-1 MOE	1485
398007	103069	103082	AGCACCAATATGCT	2-10-2 MOE	1247
398074	103070	103081	GCACCAATATGC	1-10-1 MOE	1248
398008	103267	103280	TAAATCATTGTCAA	2-10-2 MOE	1486
398075	103268	103279	AAATCATTGTCA	1-10-1 MOE	1233
398009	103327	103340	GCACTGGCCTTGAT	2-10-2 MOE	1487
398076	103328	103339	CACTGGCCTTGA	1-10-1 MOE	1488
390041	103332	103343	TTAGCACTGGCC	1-10-1 MOE	1489
390047	103585	103596	TGTGTAAGGTCA	1-10-1 MOE	1490
390049	103636	103647	GTTAATGACATT	1-10-1 MOE	1491
390050	103660	103671	GTATTCAAGTAA	1-10-1 MOE	1140
390052	103780	103791	GACAATTTCTAC	1-10-1 MOE	1492
390054	103862	103873	AACACTGCACAT	1-10-1 MOE	1493

Salts, prodrugs and bioequivalents

The antisense compounds provided herein comprise any pharmaceutically acceptable salts, esters, or salts of such esters, or any other functional chemical equivalent which, upon administration to an animal including a human, is capable of providing (directly or indirectly) the biologically active metabolite or residue thereof. Accordingly, for example, the disclosure is also drawn to prodrugs and pharmaceutically acceptable salts of the antisense compounds, pharmaceutically acceptable salts of such prodrugs, and other bioequivalents.

The term "prodrug" indicates a therapeutic agent that is prepared in an inactive or less active form that is converted to an active form (i.e., drug) within the body or cells thereof by the action of endogenous enzymes, chemicals, and/or conditions. In particular, prodrug versions of the oligonucleotides are prepared as SATE ((S-acetyl-2-thioethyl) phosphate) derivatives according to the methods disclosed in WO 93/24510 or WO 94/26764. Prodrugs can also include antisense compounds wherein one or both ends comprise nucleobases that are cleaved (e.g., by incorporating phosphodiester backbone linkages at the ends) to produce the active compound. In certain embodiments, one or more non-drug moieties is cleaved from a prodrug to yield the active form. In certain such embodiments, such non-drug moieties is not a nucleotide or oligonucleotide.

The term "pharmaceutically acceptable salts" refers to physiologically and pharmaceutically acceptable salts of the compounds described herein: i.e., salts that retain the desired biological activity of the parent compound and do not impart undesired toxicological effects thereto. Sodium salts of antisense oligonucleotides are useful and are well accepted for therapeutic administration to humans.

In certain embodiments, salts, including, but not limited to sodium salts, of double stranded nucleic acids (including but not limited to dsRNA compounds) are also provided.

G. Certain Pharmaceutical Compositions

In certain embodiments, pharmaceutical compositions of the present invention comprise one or more short antisense compound and one or more excipients. In certain such 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, a pharmaceutical composition of the present invention is prepared using known techniques, including, but not limited to mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or tabletting processes.

In certain embodiments, a pharmaceutical composition of the present invention is a liquid (e.g., a suspension, elixir and/or solution). In certain of such embodiments, a liquid pharmaceutical composition is prepared using ingredients known in the art, including, but not limited to, water, glycols, oils, alcohols, flavoring agents, preservatives, and coloring agents.

In certain embodiments, a pharmaceutical composition of the present invention is a solid (e.g., a powder, tablet, and/or capsule). In certain of such embodiments, a solid pharmaceutical composition comprising one or more oligonucleotides is prepared using ingredients known in the art, including, but not limited to, starches, sugars, diluents, granulating agents, lubricants, binders, and disintegrating agents.

In certain embodiments, a pharmaceutical composition of the present invention is formulated as a depot preparation. Certain such depot preparations are typically longer acting than non-depot preparations. In certain embodiments, such preparations are administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. In certain embodiments, depot preparations are prepared using suitable polymeric or hydrophobic materials (for example an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

In certain embodiments, a pharmaceutical composition of the present invention comprises 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, a pharmaceutical composition of the present invention comprises 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, a pharmaceutical composition of the present invention comprises 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.TM., 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.TM.; 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, a pharmaceutical composition of the present invention comprises a sustained-release system. A non-limiting example of such a sustained-release system is a semi-permeable matrix of solid hydrophobic polymers. In certain embodiments, sustained-release systems may, depending on their chemical nature, release pharmaceutical agents over a period of hours, days, weeks or months.

In certain embodiments, a pharmaceutical composition of the present invention is prepared for oral administration. In certain of such embodiments, a pharmaceutical composition is formulated by combining one or more oligonucleotides with one or more pharmaceutically acceptable carriers. Certain of such carriers enable pharmaceutical compositions to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a subject. In certain embodiments, pharmaceutical compositions for oral use are obtained by mixing oligonucleotide and one or more solid excipient. Suitable excipients include, but are not limited to, fillers, such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). In certain embodiments, such a mixture is optionally ground and auxiliaries are optionally added. In certain embodiments, pharmaceutical compositions are formed to obtain tablets or dragee cores. In certain embodiments, disintegrating agents (e.g., cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as sodium alginate) are added.

In certain embodiments, dragee cores are provided with coatings. In certain such embodiments, concentrated sugar solutions may be used, which may optionally comprise gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to tablets or dragee coatings.

In certain embodiments, pharmaceutical compositions for oral administration are push-fit capsules made of gelatin. Certain of such push-fit capsules comprise one or more pharmaceutical agents of the present invention in admixture with one or more filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In certain embodiments, pharmaceutical compositions for oral administration are soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. In certain soft capsules, one or more pharmaceutical agents of the present invention are be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added.

In certain embodiments, pharmaceutical compositions are prepared for buccal administration. Certain of such pharmaceutical compositions are tablets or lozenges formulated in conventional manner.

In certain embodiments, a pharmaceutical composition is prepared for administration by injection (e.g., intravenous, subcutaneous, intramuscular, 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 comprise 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. Aqueous injection suspensions may comprise substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, such suspensions may also comprise suitable stabilizers or agents that increase the solubility of the pharmaceutical agents to allow for the preparation of highly concentrated solutions.

In certain embodiments, a pharmaceutical composition is prepared for transmucosal administration. In certain of such embodiments penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

In certain embodiments, a pharmaceutical composition is prepared for administration by inhalation. Certain of such pharmaceutical compositions for inhalation are prepared in the form of an aerosol spray in a pressurized pack or a nebulizer. Certain of such pharmaceutical compositions comprise a propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In certain embodiments using a pressurized aerosol, the dosage unit may be determined with a valve that delivers a metered amount. In certain embodiments, capsules and cartridges for use in an inhaler or insufflator may be formulated. Certain of such formulations comprise a powder mixture of a pharmaceutical agent of the invention and a suitable powder base such as lactose or starch.

In certain embodiments, a pharmaceutical composition is prepared for rectal administration, such as a suppositories or retention enema. Certain of such pharmaceutical compositions comprise known ingredients, such as cocoa butter and/or other glycerides.

In certain embodiments, a pharmaceutical composition is prepared for topical administration. Certain of such pharmaceutical compositions comprise bland moisturizing bases, such as ointments or creams. Exemplary suitable ointment bases include, but are not limited to, petrolatum, petrolatum plus volatile silicones, lanolin and water in oil emulsions such as Eucerin.TM., available from Beiersdorf (Cincinnati, Ohio). Exemplary suitable cream bases include, but are not limited to, Nivea.TM. Cream, available from Beiersdorf (Cincinnati, Ohio), cold cream (USP), Purpose Cream.TM., available from Johnson & Johnson (New Brunswick, N.J.), hydrophilic ointment (USP) and Lubriderm.TM., available from Pfizer (Morris Plains, N.J.).

In certain embodiments, a pharmaceutical composition of the present invention comprises an oligonucleotide in a therapeutically effective amount. In certain embodiments, the therapeutically effective amount is sufficient to prevent, alleviate or ameliorate symptoms of a disease or to prolong the survival of the subject being treated. Determination of a therapeutically effective amount is well within the capability of those skilled in the art.

In certain embodiments, one or more short antisense compound of the present invention is formulated as a prodrug. In certain embodiments, upon in vivo administration, a prodrug is chemically converted to the biologically, pharmaceutically or therapeutically more active form of the short antisense compound. In certain embodiments, prodrugs are useful because they are easier to administer than the corresponding active form. For example, in certain instances, a prodrug may be more bioavailable (e.g., through oral administration) than is the corresponding active form. In certain instances, a prodrug may have improved solubility compared to the corresponding active form. In certain embodiments, prodrugs are less water soluble than the corresponding active form. In certain instances, such prodrugs possess superior transmittal across cell membranes, where water solubility is detrimental to mobility. In certain embodiments, a prodrug is an ester. In certain such embodiments, the ester is metabolically hydrolyzed to carboxylic acid upon administration. In certain instances the carboxylic acid containing compound is the corresponding active form. In certain embodiments, a prodrug comprises a short peptide (polyaminoacid) bound to an acid group. In certain of such embodiments, the peptide is cleaved upon administration to form the corresponding active form.

In certain embodiments, a prodrug is produced by modifying a pharmaceutically active compound such that the active compound will be regenerated upon in vivo administration. The prodrug can be designed to alter the metabolic stability or the transport characteristics of a drug, to mask side effects or toxicity, to improve the flavor of a drug or to alter other characteristics or properties of a drug. By virtue of knowledge of pharmacodynamic processes and drug metabolism in vivo, those of skill in this art, once a pharmaceutically active compound is known, can design prodrugs of the compound (see, e.g., Nogrady (1985) Medicinal Chemistry A Biochemical Approach, Oxford University Press, New York, pages 388-392).

In certain embodiments, a pharmaceutical composition comprising one or more pharmaceutical agents of the present invention is useful for treating a conditions or disorders in a mammalian, and particularly in a human, subject. Suitable administration routes include, but are not limited to, oral, rectal, transmucosal, intestinal, enteral, topical, suppository, through inhalation, intrathecal, intraventricular, intraperitoneal, intranasal, intraocular and parenteral (e.g., intravenous, intramuscular, intramedullary, and subcutaneous). In certain embodiments, pharmaceutical intrathecals are administered to achieve local rather than systemic exposures. For example, pharmaceutical compositions may be injected directly in the area of desired effect (e.g., in the renal or cardiac area).

In certain embodiments, short antisense compounds, compared to their parent oligonucleotides, make them particularly suited to oral administration. In certain embodiments, short antisense compounds are better suited for oral administration than their parent oligonucleotides because they have increased potency compared to those parent oligonucleotides. In certain embodiments, short antisense compounds are better suited for oral administration than their parent oligonucleotides because they have better stability, availability or solubility properties compared to those parent oligonucleotides.

In a further aspect, a pharmaceutical agent is sterile lyophilized oligonucleotide that is reconstituted with a suitable diluent, e.g., sterile water for injection. The reconstituted product is administered as a subcutaneous injection or as an intravenous infusion after dilution into saline. The lyophilized drug product consists of the oligonucleotide which has been prepared in water for injection, adjusted to pH 7.0-9.0 with acid or base during preparation, and then lyophilized. The lyophilized oligonucleotide may be 25-800 mg of the oligonucleotide. It is understood that this encompasses 25, 50, 75, 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 425, 450, 475, 500, 525, 550, 575, 600, 625, 650, 675, 700, 725, 750, 775, and 800 mg of lyophilized oligonucleotide. The lyophilized drug product may be packaged in a 2 mL Type I, clear glass vial (ammonium sulfate-treated), stoppered with a bromobutyl rubber closure and sealed with an aluminum FLIP-OFF® overseal.

The compositions of the present invention may additionally comprise other adjunct components conventionally found in pharmaceutical compositions, at their art-established usage levels. Thus, for example, the compositions may comprise additional, compatible, pharmaceutically-active materials such as, for example, antipruritics, astringents, local anesthetics or anti-inflammatory agents, or may comprise additional materials useful in physically formulating various dosage forms of the compositions of the present invention, such as dyes, flavoring agents, preservatives, antioxidants, opacifiers, thickening agents and stabilizers. However, such materials, when added, should not unduly interfere with the biological activities of the components of the compositions of the present invention. The formulations can be sterilized and, if desired, mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, colorings, flavorings and/or aromatic substances and the like which do not deleteriously interact with the oligonucleotide(s) of the formulation.

The antisense compounds provided herein may also be admixed, encapsulated, conjugated or otherwise associated with other molecules, molecule structures or mixtures of compounds.

Also described herein are pharmaceutical compositions and formulations which include the antisense compounds provided herein. The pharmaceutical compositions may be administered in a number of ways depending upon whether local or systemic treatment is desired and upon the area to be treated. In a preferred embodiment, administration is topical to the surface of the respiratory tract, particularly pulmonary, e.g., by nebulization, inhalation, or insufflation of powders or aerosols, by mouth and/or nose.

The pharmaceutical formulations described herein, which may conveniently be presented in unit dosage form, may be prepared according to conventional techniques well known in the pharmaceutical industry. Such techniques include the step of bringing into association the active ingredients with the pharmaceutical carrier(s) or excipient(s). In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers, finely divided solid carriers, or both, and then, if necessary, shaping the product (e.g., into a specific particle size for delivery). In a preferred embodiment, the pharmaceutical formulations are prepared for pulmonary administration in an appropriate solvent, e.g., water or normal saline, possibly in a sterile formulation, with carriers or other agents to allow for the formation of droplets of the desired diameter for delivery using inhalers, nasal delivery devices, nebulizers, and other devices for pulmonary delivery. Alternatively, the pharmaceutical formulations may be formulated as dry powders for use in dry powder inhalers.

A "pharmaceutical carrier" or "excipient" can be a pharmaceutically acceptable solvent, suspending agent or any other pharmacologically inert vehicle for delivering one or more nucleic acids to an individual and are known in the art. The excipient may be liquid or solid and is selected, with the planned manner of administration in mind, so as to provide for the desired bulk, consistency, etc., when combined with a nucleic acid and the other components of a given pharmaceutical composition.

H. Certain Therapeutic Uses

In certain embodiments, antisense compounds are used to modulate the expression of a target gene in an animal, such as a human. In certain embodiments, such compounds can be used to treat metabolic disorders or modulate one or more disease indications. For example, the methods comprise the step of administering to said animal in need of therapy for a disease or condition associated with a target gene an effective amount of an antisense compound that modulates expression of the target gene. Antisense compounds provided herein which effectively modulate expression of a target RNA or protein products of expression are considered active antisense compounds. Active antisense compounds also include compounds which effectively modulate one or more of a number of disease indications, including metabolic and cardiovascular disease indications, examples of which are described below.

Modulation of expression of a target gene can be measured in a bodily fluid, which may or may not contain cells; tissue; or organ of the animal. Methods of obtaining samples for analysis, such as body fluids (e.g., sputum, serum, urine), tissues (e.g., biopsy), or organs, and methods of preparation of the samples to allow for analysis are well known to those skilled in the art. Methods for analysis of RNA and protein levels are discussed above and are well known to those skilled in the art. The effects of treatment can be assessed by measuring biomarkers, or disease indications, associated with the target gene expression in the aforementioned fluids, tissues or organs, collected from an animal contacted with one or more compounds described herein, by routine clinical methods known in the art. These biomarkers include but are not limited to: liver transaminases, bilirubin, albumin, blood urea nitrogen, creatine and other markers of kidney and liver function; interleukins, tumor necrosis factors, intracellular adhesion molecules, C-reactive protein, chemokines, cytokines, and other markers of inflammation.

The antisense compounds provided herein can be utilized in pharmaceutical compositions by adding an effective amount of a compound to a suitable pharmaceutically acceptable diluent or carrier. Acceptable carriers and diluents are well known to those skilled in the art. Selection of a diluent or carrier is based on a number of factors, including, but not limited to, the solubility of the compound and the route of administration. Such considerations are well understood by those skilled in the art. In one aspect, the antisense compounds described herein inhibit expression of a target gene. The compounds can also be used in the manufacture of a medicament for the treatment of diseases and disorders related to a target gene.

Methods whereby bodily fluids, organs or tissues are contacted with an effective amount of one or more of the antisense compounds or compositions provided herein are also contemplated. Bodily fluids, organs or tissues can be contacted with one or more of the compounds resulting in modulation of target gene expression in the cells of bodily fluids, organs or tissues. An effective amount can be determined by monitoring the modulatory effect of the antisense compound or compounds or compositions on target nucleic acids or their products by methods routine to the skilled artisan.

Co-administration

In certain embodiments, two or more antisense compounds are co-administered. In certain embodiments, pharmaceutical compositions include one or more antisense compounds, particularly oligonucleotides, targeted to a first nucleic acid and one or more antisense compounds targeted to a second nucleic acid target. One or more of those antisense compounds may be a short antisense compound. In certain embodiments, pharmaceutical compositions include two or more antisense compounds targeted to different regions of the same nucleic acid target. One or more of such antisense compounds may be a short antisense compound. Two or more combined compounds may be used together or sequentially.

In certain embodiments, one or more pharmaceutical compositions are co-administered with one or more other pharmaceutical agents. In certain embodiments, such one or more other pharmaceutical agents are designed to treat the same disease or condition as the one or more pharmaceutical compositions of the present invention. In certain embodiments, such one or more other pharmaceutical agents are designed to treat a different disease or condition as the one or more pharmaceutical compositions of the present invention. In certain embodiments, such one or more other pharmaceutical agents are designed to treat an undesired effect of one or more pharmaceutical compositions of the present invention. In certain embodiments, one or more pharmaceutical compositions of the present invention are co-administered with another pharmaceutical agent to treat an undesired effect of that other pharmaceutical agent. In certain embodiments, one or more pharmaceutical compositions of the present invention and one or more other pharmaceutical agents are administered at the same time. In certain embodiments, one or more pharmaceutical compositions of the present invention and one or more other pharmaceutical agents are administered at different times. In certain embodiments, one or more pharmaceutical compositions of the present invention and one or more other pharmaceutical agents are prepared together in a single formulation. In certain embodiments, one or more pharmaceutical compositions of the present invention and one or more other pharmaceutical agents are prepared separately.

In certain embodiments, pharmaceutical agents that may be co-administered with a pharmaceutical composition of the present invention include lipid-lowering agents. In certain such embodiments, pharmaceutical agents that may be co-administered with a pharmaceutical composition of the present invention include, but are not limited to atorvastatin, simvastatin, rosuvastatin, and ezetimibe. In certain such embodiments, the lipid-lowering agent is administered prior to administration of a pharmaceutical composition of the present invention. In certain such embodiments, the lipid-lowering agent is administered following administration of a pharmaceutical composition of the present invention. In certain such embodiments the lipid-lowering agent is administered at the same time as a pharmaceutical composition of the present invention. In certain such embodiments the dose of a co-administered lipid-lowering agent is the same as the dose that would be administered if the lipid-lowering agent was administered alone. In certain such embodiments the dose of a co-administered lipid-lowering agent is lower than the dose that would be administered if the lipid-lowering agent was administered alone. In certain such embodiments the dose of a co-administered lipid-lowering agent is greater than the dose that would be administered if the lipid-lowering agent was administered alone.

In certain embodiments, a co-administered lipid-lowering agent is a HMG-CoA reductase inhibitor. In certain such embodiments the HMG-CoA reductase inhibitor is a statin. In certain such embodiments the statin is selected from atorvastatin, simvastatin, pravastatin, fluvastatin, and rosuvastatin. In certain embodiments, a co-administered lipid-lowering agent is a cholesterol absorption inhibitor. In certain such embodiments, cholesterol absorption inhibitor is ezetimibe. In certain embodiments, a co-administered lipid-lowering agent is a co-formulated HMG-CoA reductase inhibitor and cholesterol absorption inhibitor. In certain such embodiments the co-formulated lipid-lowering agent is ezetimibe/simvastatin. In certain embodiments, a co-administered lipid-lowering agent is a microsomal triglyceride transfer protein inhibitor.

In certain embodiments, a co-administered pharmaceutical agent is a bile acid sequestrant. In certain such embodiments, the bile acid sequestrant is selected from cholestyramine, colestipol, and colesevelam.

In certain embodiments, a co-administered pharmaceutical agent is a nicotinic acid. In certain such embodiments, the nicotinic acid is selected from immediate release nicotinic acid, extended release nicotinic acid, and sustained release nicotinic acid.

In certain embodiments, a co-administered pharmaceutical agent is a fibric acid. In certain such embodiments, a fibric acid is selected from gemfibrozil, fenofibrate, clofibrate, bezafibrate, and ciprofibrate.

Further examples of pharmaceutical agents that may be co-administered with a pharmaceutical composition of the present invention include, but are not limited to, corticosteroids, including but not limited to prednisone; immunoglobulins, including, but not limited to intravenous immunoglobulin (IVIg); analgesics (e.g., acetaminophen); anti-inflammatory agents, including, but not limited to non-steroidal anti-inflammatory drugs (e.g., ibuprofen, COX-1 inhibitors, and COX-2, inhibitors); salicylates; antibiotics; antivirals; antifungal agents; antidiabetic agents (e.g., biguanides, glucosidase inhibitors, insulins, sulfonylureas, and thiazolidenediones); adrenergic modifiers; diuretics; hormones (e.g., anabolic steroids, androgen, estrogen, calcitonin, progestin, somatostan, and thyroid hormones); immunomodulators; muscle relaxants; antihistamines; osteoporosis agents (e.g., biphosphonates, calcitonin, and estrogens); prostaglandins, antineoplastic agents; psychotherapeutic agents; sedatives; poison oak or poison sumac products; antibodies;

and vaccines.

In certain embodiments, the pharmaceutical compositions of the present invention may be administered in conjuction with a lipid-lowering therapy. In certain such embodiments, a lipid-lowering therapy is therapeutic lifestyle change. In certain such embodiments, a lipid-lowering therapy is LDL apheresis.

I. Kits, Research Reagents and Diagnostics

The antisense compounds provided herein can be utilized for diagnostics, and as research reagents and kits. Furthermore, antisense compounds, which are able to inhibit gene expression or modulate gene expression with specificity, are often used by those of ordinary skill to elucidate the function of particular genes or to distinguish between functions of various members of a biological pathway.

For use in kits and diagnostics, the antisense compounds described herein, either alone or in combination with other compounds or therapeutics, can be used as tools in differential and/or combinatorial analyses to elucidate expression patterns of a portion or the entire complement of genes expressed within cells and tissues. Methods of gene expression analysis are well known to those skilled in the art.

J. Certain Advantages of Short Antisense Compounds

In certain embodiments, short antisense compounds have advantages when compared to their parent oligonucleotides. For example, in certain embodiments, short antisense compounds have greater affinity for a target nucleic acid than their parent oligonucleotide. In certain embodiments, short antisense compounds have greater potency in vitro than their parent oligonucleotide. In certain such embodiments, that increased in vitro potency is not entirely explained by increased affinity. In certain embodiments, such increased in vitro potency may be attributable to increased ability of short antisense compounds to penetrate cells and/or increased ability to access target nucleic acids in a cell. In certain embodiments, short antisense compounds have greater potency in vivo than their parent oligonucleotides. In certain embodiments, such greater in vivo potency is not attributable to increased in vitro potency or increased affinity. In certain embodiments, short antisense compounds have even greater in vivo potency compared to their parent oligonucleotides than would be predicted based on in vitro potencies or on affinities. In certain embodiments, such increased in vivo potency may be attributable to increased bioavailability, better penetration into the cell, better access to target nucleic acid once in the cell, or other factors.

In certain embodiments, one would expect short antisense compounds to be less specific for their target nucleic acid compared to their parent oligonucleotides. In certain such embodiments, one would expect increased side-effects, including potential for toxic effects, from short antisense compounds. In certain embodiments, such additional side-effects are not observed. In certain embodiments, non-target nucleic acids to which a particular short antisense compound may bind are not available to the short antisense compound. In such embodiments, side-effects, including toxicity, are less problematic than would be predicted.

In certain embodiments, because they are smaller, short antisense compounds are less likely to bind proteins. In certain such embodiments, such less binding of proteins results in lower toxicity, since protein binding may have undesired consequences. In certain embodiments, such less binding of proteins results in greater potency, since it leaves more antisense compound available for therapeutic effect. In certain embodiments, less binding of proteins results in decreased drug-drug interaction toxicity.

Nonlimiting disclosure and incorporation by reference

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.

Example 1

Cell culture and treatment with short antisense compounds

The effect of short antisense compounds on target nucleic acid expression can be tested in any one of a number of cultured or primary cell lines. Cells lines can be obtained from publicly available sources, such as the American Type Culture Collection (Manassas, VA). Cells are cultured according to methods well known to those of ordinary skill in the art.

When cells reached appropriate confluency, they were treated with oligonucleotide using LIPOFECTIN® as described. When cells reached 65-75% confluency, they were treated with oligonucleotide. Oligonucleotide was mixed with LIPOFECTIN® Invitrogen Life Technologies, Carlsbad, CA) in Opti-MEM®-1 reduced serum medium (Invitrogen Life Technologies, Carlsbad, CA) to achieve the desired concentration of oligonucleotide and a LIPOFECTIN® concentration of 2.5 or 3 μg/mL per 100 nM oligonucleotide. This transfection mixture was incubated at room temperature for approximately 0.5 hours. For cells grown in 96-well plates, wells were washed once with 100 μL OPTI-MEM®-1 and then treated with 130 μL of the transfection mixture. Cells grown in 24-well plates or other standard tissue culture plates were treated similarly, using appropriate volumes of medium and oligonucleotide. Cells were treated and data were obtained in duplicate or triplicate. After approximately 4-7 hours of treatment at 37°C, the medium containing the transfection mixture was replaced with fresh culture medium. Cells were harvested 16-24 hours after oligonucleotide treatment.

Control oligonucleotides are used to determine the optimal oligomeric compound concentration for a particular cell line. Furthermore, when oligomeric compounds are tested in oligomeric compound screening experiments or phenotypic assays, control oligonucleotides are tested in parallel.

The concentration of oligonucleotide used varies from cell line to cell line. To determine the optimal oligonucleotide concentration for a particular cell line, the cells are treated with a positive control oligonucleotide at a range of concentrations. The concentration of positive control oligonucleotide that results in 80% inhibition of the target mRNA is then utilized as the screening concentration for new oligonucleotides in subsequent experiments for that cell line. If 80% inhibition is not achieved, the lowest concentration of positive control oligonucleotide that results in 60% inhibition of the target mRNA is then utilized as the oligonucleotide screening concentration in subsequent experiments for that cell line. If 60% inhibition is not achieved, that particular cell line is deemed as unsuitable for oligonucleotide transfection experiments. The concentrations of antisense oligonucleotides used herein are from 50 nM to 300 nM when the antisense oligonucleotide is transfected using a liposome reagent and 1 nM to 40 nM when the antisense oligonucleotide is transfected by electroporation.

Example 2: Real-time Quantitative PCR Analysis of Target mRNA Levels

Quantitation of target mRNA levels was accomplished by real-time quantitative PCR using the ABI

PRISM® 7600, 7700, or 7900 Sequence Detection System (PE-Applied Biosystems, Foster City, CA) according to manufacturer's instructions.

Prior to quantitative PCR analysis, primer-probe sets specific to the target gene being measured were evaluated for their ability to be "multiplexed" with a GAPDH amplification reaction. After isolation the RNA is subjected to sequential reverse transcriptase (RT) reaction and real-time PCR, both of which are performed in the same well. RT and PCR reagents were obtained from Invitrogen Life Technologies (Carlsbad, CA). RT, real-time PCR was carried out in the same by adding 20 µL PCR cocktail (2.5x PCR buffer minus $MgCl_2$, 6.6 mM $MgCl_2$, 375 µM each of dATP, dCTP, dCTP and dGTP, 375 nM each of forward primer and reverse primer, 125 nM of probe, 4 Units RNAse inhibitor, 1.25 Units PLATINUM® Taq, 5 Units MuLV reverse transcriptase, and 2.5x ROX dye) to 96-well plates containing 30 µL total RNA solution (20-200 ng). The RT reaction was carried out by incubation for 30 minutes at 48°C. Following a 10 minute incubation at 95°C to activate the PLATINUM® Taq, 40 cycles of a two-step PCR protocol were carried out: 95°C for 15 seconds (denaturation) followed by 60°C for 1.5 minutes (annealing/extension).

Gene target quantities obtained by RT, real-time PCR were normalized using either the expression level of GAPDH, a gene whose expression is constant, or by quantifying total RNA using RiboGreen® (Molecular Probes, Inc. Eugene, OR). GAPDH expression was quantified by RT, real-time PCR, by being run simultaneously with the target, multiplexing, or separately. Total RNA was quantified using RiboGreen® RNA quantification reagent (Molecular Probes, Inc. Eugene, OR).

170 µL of RiboGreen® working reagent (RiboGreen® reagent diluted 1:350 in 10mM Tris-HCl, 1 mM EDTA, pH 7.5) was pipetted into a 96-well plate containing 30 µL purified cellular RNA. The plate was read in a CytoFluor® 4000 (PE Applied Biosystems) with excitation at 485nm and emission at 530nm.

The GAPDH PCR probes have JOE covalently linked to the 5' end and TAMRA or MGB covalently linked to the 3' end, where JOE is the fluorescent reporter dye and TAMRA or MGB is the quencher dye. In some cell types, primers and probe designed to a GAPDH sequence from a different species are used to measure GAPDH expression. For example, a human GAPDH primer and probe set is used to measure GAPDH expression in monkey-derived cells and cell lines.

Probes and primers for use in real-time PCR were designed to hybridize to target nucleic acids using routine methods. For example, PrimerExpress® (Applied Biosystems, Foster City, CA) software is routinely used to design probes and primers for use in real-time PCR. Examples of primer and probe sequences and the target nucleic acids to which they hybridize are presented in Table 24. The target-specific PCR probes have FAM covalently linked to the 5' end and TAMRA or MGB covalently linked to the 3' end, where FAM is the fluorescent dye and TAMRA or MGB is the quencher dye.

Table 24

Target-specific primers and probes for use in real-time PCR

Target Name	Species	Sequence Description	Sequence (5' to 3')	SEQ ID NO
ApoB	Mouse	Forward Primer	CGTGGGCTCCAGCATTCTA	1524
ApoB	Mouse	Reverse Primer	AGTCATTTCTGCCTTTGCGTC	1525
ApoB	Mouse	Probe	CCAATGGTCGGGCACTGCTCAA	1526
ApoB	Mouse	Forward Primer	GAAAATAGACTTCCTGAATAACTATGCATT	1527
ApoB	Mouse	Reverse Primer	ACTCGCTTGCCAGCTTGC	1528
ApoB	Mouse	Probe	TTTCTGAGTCCCCGTGCCCAACA	1529
GCGR	Mouse	Forward Primer	TGAGCCTTGCCACCTTCTCT	1530
GCGR	Mouse	Reverse Primer	GCGCACCCCAGCCAA	1531
GCGR	Mouse	Probe	AGAGGAGCTTCTTTTCCCTCTACCTGGGC	1532
GCGR	Mouse	Forward Primer	ATTTCCTGCCCCTGGTACCT	1533
GCGR	Mouse	Reverse Primer	CGGGCCCACACCTCTTG	1534
GCGR	Mouse	Probe	CCACAAAGTGCAGCACCGCCTAGTGT	1535
PTEN	Mouse	Forward Primer	GCCACAGGCTCCCAGACAT	1536
PTEN	Mouse	Reverse Primer	TCCATCCTCTTGATATCTCCTTTTG	1537
PTEN	Mouse	Probe	ACAGCCATCATCAAAGAGATCGTTAGCAGAA	1538
PTEN	Mouse	Forward Primer	ATGACAATCATGTTGCAGCAATTC	1539
PTEN	Mouse	Reverse Primer	CGATGCAATAAATATGCACAAATCA	1540
PTEN	Mouse	Probe	CTGTAAAGCTGGAAAGGGACGGACTGGT	1541

Example 3: Short Antisense Compounds Targeted to an ApoB nucleic acid and having 2'-MOE or methyleneoxy (4'-CH_2-O-2') BNA modifications

Six-week old male Balb/c mice (Jackson Laboratory, Bar Harbor, ME) were injected intraperitoneally (i.p.) with antisense compounds targeted to ApoB, at a frequency of twice per week for three weeks. Antisense compound doses included 2.4, 1.2, 0.6, 0.3 and 0.15 μmol/kg. For antisense compounds 14 nucleotides in length, these doses equate to approximately 12, 6, 3, 1.5 or 0.75 mg/kg, respectively. Shown in Table 25 are the sequences and motifs of the antisense compounds used in this study. The antisense compounds are either 20 or 14 nucleotides in length and have a central "gap" region consisting of ten 2'-deoxynucleotides flanked by wings having 2'-O-methoxyethyl (2'-MOE) or BNA modified "wings." For example, the 2-10-2 MOE gapmer motif indicates an antisense compound with a gap of ten nucleotides flanked by 2 nucleotide wings with 2'-MOE modifications. Bolded residues indicate 2'-O-methoxyethyl moieties and italicized residues indicate methyleneoxy (4'-CH_2-O-2') BNAs. The internucleoside linkages of each compound are phosphorothioate throughout. All cytosine residues of ISIS 147764 and ISIS 372938 are replaced by 5-methyl cytosines. For ISIS 387462, only the cytosine residue in the wing of the compound is replaced by 5-methyl cytosine. ApoB antisense compounds are targeted to publicly available ApoB-100 sequences, including Genbank Accession No. XM_137955.5 (SEQ ID NO: 2).

Table 25: Antisense Compounds Targeted to an ApoB nucleic acid

ISIS NO	Target SEQ ID NO	5' Target Site	Sequence (5'-3')	Gapmer Motif	SEQ ID NO
147764	2	8865	**GTCCCTGAAGATGTCAATGC**	5-10-5 MOE	1561
372938	2	8235	**GGTACATGGAAGTC**	2-10-2 MOE	190
387462	2	8235	*GG*TACATGGAAG*TC*	2-10-2 methyleneoxy (4'-CH_2-O-2') BNA	190

Forty-eight hours following the final injection, mice were sacrificed to evaluate transaminases (Table 26); liver and kidney weight (Table 27); triglyceride, LDL, HDL and free fatty acid levels (Table 28); target mRNA level in liver (Table 29); target protein level in plasma; and oligonucleotide tissue concentration (Table 30). These endpoints were determined using methods described herein and well known to those of ordinary skill in the art.

Table 26: ALT and AST Levels (IU/L)

ISIS NO	Dose µmol/kg	ALT	AST
Saline	N/A	27.8	46.3
147764	2.4	29.5	64.0
372938	2.4	26.0	49.0
372938	1.2	24.8	49.5
372938	0.6	28.0	79.3
372938	0.3	28.3	60.0
372938	0.15	28.3	50.3
387462	2.4	41.3	84.0
387462	1.2	35.3	63.5
387462	0.6	32.0	77.3

ISIS NO	Dose µmol/kg	ALT	AST
387462	0.3	27.8	55.0
387462	0.15	29.3	68.3

Table 27: Liver and Kidney Weight (% of saline control)

ISIS NO	Dose µmol/kg	Liver	Kidney
Saline	N/A	100	100
147764	2.4	102	105
372938	2.4	100	100
372938	1.2	90	101
372938	0.6	96	112
372938	0.3	91	107
372938	0.15	96	98
387462	2.4	116	90
387462	1.2	113	90
387462	0.6	106	97
387462	0.3	101	126
387462	0.15	95	100

Total body weight and food consumption did not differ significantly between saline-treated or oligonucleotide-treated animals. Glucose levels also were similar among all treatment groups.

Table 28: Triglyceride (TRIG), Total Cholesterol (CHOL), HDL, LDL and Free Fatty Acid (FFA) Levels

ISIS NO	Dose µmol/kg	TRIG (mg/dL)	CHOL (mg/dL)	HDL (mg/dL)	LDL (mg/dL)	FFA (mg/dL)
Saline	N/A	167	107	81.8	11.0	1.76
147764	2.4	167	107	81.3	10.3	1.29
372938	2.4	153	104	79.0	10.3	1.28
372938	1.2	136	101	77.8	9.5	1.70

ISIS NO	Dose µmol/kg	TRIG (mg/dL)	CHOL (mg/dL)	HDL (mg/dL)	LDL (mg/dL)	FFA (mg/dL)
372938	0.6	184	110	83.3	10.8	1.66
372938	0.3	138	109	84.3	11.0	1.53
372938	0.15	151	106	82.8	10.8	1.57
387462	2.4	49	14	9.0	1.5	0.74
387462	1.2	71	23	16.5	2.0	0.76
387462	0.6	150	55	39.3	3.7	1.43
387462	0.3	136	92	72.8	7.5	1.14
387462	0.15	163	104	81.5	9.3	1.47

Table 29: % ApoB mRNA Level (relative to saline control)

ISIS NO	2.4 µmol/kg	1.2 µmol/kg	0.6 µmol/kg	0.3 µmol/kg	0.15 µmol/kg
147764	57.7	ND	ND	ND	ND
372938	77.0	90.0	87.3	92.6	93.1
387462	1.5	8.5	27.4	58.9	75.8

Treatment with ISIS 387462 resulted in a significant and dose-dependent decrease in triglycerides, total cholesterol, HDL, LDL and free fatty acids. In accordance with these phenotypic findings, treatment with ISIS 387462 also led to a dose-dependent reduction in ApoB mRNA (Table 29) and protein (not shown) levels in mouse plasma. To determine whether the observed increase in efficiency with the methyleneoxy (4'-CH_2-O-2') BNA gapmer is due to an increase in oligonucleotide accumulation, full-length and total oligonucleotide concentration in the liver and kidney were determined.

Table 30: Full-length and Total Antisense Compound Tissue Concentration (µM) Relative to ApoB mRNA level (% of saline control)

ISIS NO	Dose µmol/kg	Kidney Full-Length	Liver Full-Length	Kidney Total	Liver Total	ApoB mRNA
147764	2.4	28.6	22.9	33.5	31.3	58
372938	2.4	32.0	5.49	34.0	7.76	77
387462	2.4	37.2	5.69	38.9	7.31	1.5

ISIS NO	Dose µmol/kg	Kidney Full-Length	Liver Full-Length	Kidney Total	Liver Total	ApoB mRNA
387462	1.2	29.8	3.71	31.3	4.91	8.5
387462	0.6	18.9	1.97	20.0	2.57	27
387462	0.3	9.11	0.73	9.49	0.78	59
387462	0.15	6.97	0.19	7.43	0.24	76

Levels of the 2-10-2 methyleneoxy (4'-CH2-O-2') BNA gapmer were similar to the 5-10-5 and 2-10-2 MOE gapmers in the kidney, but significantly reduced in the liver. The EC_{50} for ISIS 387462 in the liver was determined by comparing oligonucleotide concentration in the liver to inhibition of ApoB mRNA. The approximate EC_{50} for ISIS 387462 is 1 µM. In contrast, an effective 5-10-5 MOE gapmer compound typically has an EC_{50} of approximately 15 µM in the liver.

Taken together, these results demonstrate that the ApoB short gapmer having methyleneoxy (4'-CH_2-O-2') in the wings is a potent inhibitor of target mRNA expression and can effectively lower triglycerides, cholesterol and free fatty acids. The potency of the short antisense compound does not appear to be a result of increased tissue accumulation since similar levels of the compound were observed in kidney and reduced levels were found in the liver, relative to the 5-10-5 MOE gapmer. In addition, the methyleneoxy (4'-CH_2-O-2') BNA gapmer exhibited little to no adverse side effects.

Example 4: Short Antisense Compounds Targeted to a GCGR nucleic acid and having 2'-MOE Modifications

Eight-week old male C57/BL6 mice (Jackson Laboratory, Bar Harbor, ME) were administered a single dose of GCGR oligonucleotide by intraperitoneal injection at a concentration of 6.25, 12.5, 25 or 50 mg. Each dose group consisted of four animals. Shown in Table 31 are the sequences, motifs and conjugates of the GCGR antisense compounds used in this study. Bolded residues indicate 2'-O-methoxyethyl (2'-MOE) moieties. All compounds comprise phosphorothioate internucleoside linkages throughout and each cytosine is replaced with 5-methylcytosine. ISIS 386626, ISIS 386627 and ISIS 386628 further comprise a C_{16} conjugate group attached to the 2'-O position of the sugar via a diamide linkage (2'-$OCH_2C(=O)N(H)(CH_2)_4N(H)C(=O)-(CH_2)_{15}CH_3$). GCGR antisense compounds target published GCGR sequences, including Genbank® Accession No. BC031885.1 (SEQ ID NO: 7).

Table 31: Short antisense compounds targeted to a GCGR nucleic acid

ISIS NO	Target SEQ ID NO	5' Target Site	Sequence (5'-3')	Gapmer Motif	Conjugate	SEQ ID NO
148364	7	393	TGCACTTTGTGGTACCAAGG	5-10-5 MOE	None	1562
386626	7	1768	G_{C16}CTTCTCCATCATA	2-10-2 MOE	C16	1563
386627	7	1244	G_{C16}GGCATGCTCGTCA	2-10-2 MOE	C16	653
386593	7	1244	GGGCATGCTCGTCA	2-10-2 MOE	None	649
386628	7	1680	T_{C16}GTCTTGCTGCTTT	2-10-2 MOE	C16	1564
386594	7	1680	TGTCTTGCTGCTTT	2-10-2 MOE	None	1565

Mice were sacrificed 48 hours following injection to determine serum transaminase levels (Table 32); liver, white adipose tissue (WAT), spleen and kidney weight (Table 33); cholesterol, triglyceride and glucose levels (Table 34); GCGR mRNA levels (Tables 35-41); and full-length and total oligonucleotide concentration in liver and kidney (Table 42). Endpoints were assessed using methods described herein and well known to those of ordinary skill in the art. Data is included from a pre-treatment bleed (Pre-Bleed) and post-treatment bleed (Post-Bleed).

Table 32: ALT & AST Levels (IU/L)

ISIS NO	Dose (mg/kg)	ALT Pre-Bleed	ALT Post-Bleed	AST Pre-Bleed	AST Post-Bleed
Saline	N/A	36	51	55	85
148364	50	24	40	40	115
148364	25	26	35	42	87
148364	12.5	23	32	44	69
148364	6.25	28	34	47	76
386626	50	28	40	48	120
386626	25	30	36	44	92
386626	12.5	28	34	44	90
386626	6.25	26	42	46	69
386627	50	27	457	42	451
386627	25	29	97	45	142
386627	12.5	29	62	46	81
386627	6.25	23	87	38	96
386593	50	23	33	46	58
386593	25	25	32	41	95

ISIS NO	Dose (mg/kg)	ALT Pre-Bleed	ALT Post-Bleed	AST Pre-Bleed	AST Post-Bleed
386593	12.5	26	33	43	74
386593	6.25	28	31	43	53
386628	50	28	68	44	76
386628	25	24	32	40	57
386628	12.5	28	35	42	75
386628	6.25	22	29	40	59
386594	50	29	34	46	92
386594	25	27	31	47	82
386594	12.5	28	33	45	74
386594	6.25	23	48	42	67

Table 33: Organ Weights (% saline control)

ISIS NO	Dose (mg/kg)	Liver	WAT	Kidney	Spleen
Saline	N/A	100	100	100	100
148364	50	103	80	108	123
148364	25	103	75	112	115
148364	12.5	100	84	108	96
148364	6.25	101	89	104	113
386626	50	112	77	104	130
386626	25	109	97	103	120
386626	12.5	96	73	97	114
386626	6.25	100	90	100	95
386627	50	90	113	102	165
386627	25	99	87	99	143
386627	12.5	109	93	102	136
386627	6.25	103	96	102	131
386593	50	96	98	102	118
386593	25	83	94	100	104
386593	12.5	99	82	101	129
386593	6.25	96	77	98	144
386628	50	104	100	99	126
386628	25	102	97	109	113

ISIS NO	Dose (mg/kg)	Liver	WAT	Kidney	Spleen
386628	12.5	101	111	99	114
386628	6.25	98	106	102	151
386594	50	90	80	99	131
386594	25	93	76	99	128
386594	12.5	94	98	100	113
386594	6.25	102	85	101	119

Overall, the GCGR antisense compounds exhibited little to no adverse side effects.

Table 34: Triglyceride (TRIG), Cholesterol (CHOL) and Glucose Levels (IU/L)

ISIS NO	Dose (mg/kg)	TRIG Pre-Bleed	TRIG Post-Bleed	CHOL Pre-Bleed	CHOL Post-Bleed	Glucose Pre-Bleed	Glucose Post-Bleed
Saline	N/A	132	181	91	96	208	285
148364	50	110	177	81	94	207	228
148364	25	115	200	83	96	219	239
148364	12.5	106	179	85	89	198	256
148364	6.25	86	162	86	89	226	215
386626	50	87	163	79	57	239	179
386626	25	100	187	87	72	235	186
386626	12.5	100	148	82	76	232	185
386626	6.25	86	162	85	90	222	221
386627	50	106	120	83	126	227	150
386627	25	101	148	90	115	218	203
386627	12.5	99	203	86	98	237	219
386627	6.25	111	165	88	104	238	228
386593	50	130	128	100	95	244	213
386593	25	119	135	83	77	206	208
386593	12.5	122	128	83	79	222	233
386593	6.25	120	138	84	78	214	219
386628	50	102	98	88	95	209	232
386628	25	102	129	84	85	210	223
386628	12.5	90	123	90	94	231	240
386628	6.25	117	121	83	85	228	229

ISIS NO	Dose (mg/kg)	TRIG Pre-Bleed	TRIG Post-Bleed	CHOL Pre-Bleed	CHOL Post-Bleed	Glucose Pre-Bleed	Glucose Post-Bleed
386594	50	93	99	84	85	203	274
386594	25	106	94	90	86	219	272
386594	12.5	118	133	85	95	200	292
386594	6.25	112	146	78	94	222	275

GCGR 2-10-2 MOE gapmers exhibited a trend toward lower post-bleed triglyceride levels, relative to the 5-10-5 MOE gapmer, with ISIS 386628 and ISIS 386594 having the greatest dose-dependent effect. Glucose levels also were decreased in a dose-dependent manner following treatment with ISIS 386626 and ISIS 386627. Treatment with ISIS 386628, ISIS 386593 and ISIS 386594 also generally led to a decrease in post-bleed glucose levels. Cholesterol levels did not appear to significantly differ among treatment groups.

To determine whether the phenotypic changes shown above correlated with a decrease in GCGR mRNA, treated animals were evaluated for levels of target mRNA in liver by real time PCR according to methods described herein. Tables 35 to 41 show results from direct comparisons of the antisense compounds targeting GCGR nucleic acid for their effect on target expression. Results are expressed as percent of saline control.

Table 35: GCGR mRNA levels following treatment with ISIS 148364 & ISIS 386626

ISIS NO	50 mg/kg	25 mg/kg	12.5 mg/kg	6.25 mg/kg
148364	36	79	87	62
386626	0	8	3	7

Table 36: GCGR mRNA levels following treatment with ISIS 148364 & ISIS 386627

ISIS NO	50 mg/kg	25 mg/kg	12.5 mg/kg	6.25 mg/kg
148364	63	87	105	86
386627	3	30	57	74

Table 37: GCGR mRNA levels following treatment with ISIS 148364 & ISIS 386593

ISIS NO	50 mg/kg	25 mg/kg	12.5 mg/kg	6.25 mg/kg
148364	56	74	105	86
386593	9	38	74	90

Table 38: GCGR mRNA levels following treatment with ISIS 148364 & ISIS 386628

ISIS NO	50 mg/kg	25 mg/kg	12.5 mg/kg	6.25 mg/kg
148364	42	77	98	101
386628	2	18	53	77

Table 39: GCGR mRNA levels following treatment with ISIS 148364 & ISIS 386594

ISIS NO	50 mg/kg	25 mg/kg	12.5 mg/kg	6.25 mg/kg
148364	59	98	102	96
386594	25	47	50	96

Table 40: GCGR mRNA levels following treatment with ISIS 386627 & ISIS 386593

ISIS NO	50 mg/kg	25 mg/kg	12.5 mg/kg	6.25 mg/kg
386627	5	40	58	42
386593	10	29	34	71

Table 41: GCGR mRNA levels following treatment with ISIS 386628 & ISIS 386594

ISIS NO	50 mg/kg	25 mg/kg	12.5 mg/kg	6.25 mg/kg
386628	4	13	38	97
386594	19	50	56	99

Treatment with the 2-10-2 MOE gapmers led to a significant dose-dependent decrease in GCGR mRNA expression. ISIS 386626 exhibited the greatest decrease in target mRNA. To determine whether the observed increase in efficiency with the short antisense compounds is due to an increase in antisense compound accumulation, full-length and total antisense compound concentration in the liver and kidney were determined.

Table 42: Total and Full-length Antisense Compound Concentrations in Liver and Kidney (μg/g)

ISIS NO	Total Kidney	Total Liver	Full-length Kidney	Full-length Liver
148364	90	54	58	46
386626	757	274	355	125
386593	91	12	77	12
386628	496	286	305	202

The results shown in Table 42 demonstrate that short antisense compounds comprising a C_{16}

conjugate exhibit a significant increase in antisense compound accumulation in both liver and kidney. However, ISIS 386593, which was effective at reducing target mRNA, triglycerides and glucose levels, accumulates to a level similar to the 5-10-5 MOE gapmer in liver and to a lower level in kidney. These results suggest that while conjugation with C_{16} can increase liver and kidney antisense compound concentration, it does not entirely account for the effectiveness of the short antisense compounds.

Taken together, these results demonstrate that GCGR short antisense compounds are capable of significantly inhibiting target mRNA expression while also lowering triglyceride and glucose levels. In addition, with the exception of ISIS 386627, the short MOE gapmers exhibited little to no toxic effects.

Example 5: Short antisense compounds targeting to a GCGR nucleic acid and having 2'-MOE and Methyleneoxy (4'-CH_2-O-2') BNA modifications

Eight-week old male C57/BL6 mice (Jackson Laboratory, Bar Harbor, ME) were administered a single dose of GCGR antisense compound by intraperitonel (i.p.) injection at a concentration of 10, 3.2, 1, and 0.32 μmol.kg. Each dose group consisted of four animals. Shown in Table 43 are the sequences, motifs and conjugates of the GCGR antisense compounds used in this study. Bolded residues indicate 2'-O-methoxyethyl (2'-MOE) modifications and the italicized residues indicate methyleneoxy (4'-CH_2-O-2') BNA modifications. All antisense compounds comprise phosphorothioate internucleoside linkages throughout and each cytosine is replaced with 5-methylcytosine. GCGR antisense compounds target published GCGR nucleic acids, including Genbank Accession No. BC031885.1 (SEQ ID NO: 7).

Table 43: Antisense Compounds targeted to a GCGR nucleic acid

ISIS NO	Target SEQ ID NO	5' Target Site	Sequence (5'-3')	Gapmer Motif	SEQ ID NO
148364	7	393	**TGCAC**TTTGTGGTAC**CAAGG**	5-10-5 MOE	1562
396144	7	1768	**GC**TTCTCCATCA**TA**	2-10-2 MOE	1566
396148	7	1768	*GC*TTCTCCATCA*TA*	2-10-2 Methyleneoxy (4'-CH_2-O-2') BNA	1567
396145	7	1765	**ATGGC**TTCTCCATCA**TATCC**	5-10-5 MOE	1568
396146	7	1244	**GG**GCATGCTCGT**CA**	2-10-2 MOE	650
396149	7	1244	*GG*GCATGCTCGT*CA*	2-10-2 Methyleneoxy (4'-CH_2-O-2') BNA	652
396147	7	1241	**CTTGG**GCATGCTCGT**CAGTC**	5-10-5 MOE	1569

To determine whether the phenotypic changes shown above correlated with a decrease in GCGR mRNA, treated animals were evaluated for levels of target mRNA in liver by RT, real time PCR according to methods described herein. Table 44 show results from direct comparisons of the antisense compounds targeting GCGR nucleic acid for their effect on target expression. Results are expressed as percent of saline control.

TABLE 44: GCGR mRNA levels

ISIS NO.	0.32 µmol/kg	1 µmol/kg	3.2 µmol/kg	10 µmol/kg
148364	105	106	73	38
396144	122	117	40	35
396148	20	6	2	1
396145	nd	Nd	33	8
396146	98	135	95	35
396149	91	41	30	7
396147	nd	Nd	68	28

As shown in Table 44, each short antisense compound having methyleneoxy (4'-CH_2-O-2') BNA modifications demonstrated a dose-dependent reduction in GCGR mRNA levels. Furthermore, the short antisense compounds were more effective at target reduction than the 5-10-5 MOE gapmer. Each short antisense compound comprising methyleneoxy (4'-CH_2-O-2') BNA in the wings resulted in a significant reduction in GCGR protein relative to both saline control and ISIS 148364 treatment. Next, estimated ED_{50} concentrations for each antisense were calculated using Graphpad Prism; ED_{50} is the dose at which 50% mRNA reduction is observed. The results are shown below in Table 45.

Table 45: Estimated ED_{50} Concentration

Gapmer Motif	ISIS NO	ED_{50} (µmole/kg)	ED_{50} (mg/kg)
5-10-5 MOE	148364	7	50.6
2-10-2 MOE	396144	4	18.1
2-10-2 methyleneoxy BNA	396148	0.1	0.4
5-10-5 MOE	396145	2.1	9.3
2-10-2 MOE	396146	8.3	40
2-10-2 methylenexy BNA	396149	1.1	5
5-10-5 MOE	396147	5.2	37.5

Example 6: Short Antisense Compounds Targeting a PTEN nucleic acid and having methyleneoxy (4'-CH_2-O-2') BNA Modifications

Six-week old male Balb/c mice (Jackson Laboratory, Bar Harbor, ME) were administered a single i.p. injection of PTEN antisense compound at a dose of 8 µmol/kg. Each dose group consisted of four animals. Shown in Table 46 are the sequences and motifs of the PTEN antisense compounds used in this study. Bolded residues indicate 2'-O-methoxyethyl moieties (2'-MOE) and italicized residues indicate Methyleneoxy BNA nucleotides. Each antisense compound comprises phosphorothioate linkages throughout. In addition, the cytosine residues in the gap of ISIS 384073 and in the wings of ISIS 392056, ISIS 392057, ISIS 392061 and ISIS 392063 are replaced with 5-methylcytosines. Antisense compounds target published PTEN nucleic acids, including Genbank Accession No. U92437.1 (SEQ ID NO: 13).

Table 46: Antisense Compounds targeted to a PTEN nucleic acid

ISIS NO	Target SEQ ID NO	5' Target Site	Sequence (5'-3')	Gapmer Motif	SEQ ID NO
141923	Control	N/A	**CCTTC**CCTGAAGGTT**CCTCC**	5-10-5 MOE	1570
116847	29	2011	**TCAAA**TCCAGAGGCTA**GCAG**	5-10-5 MOE	1571
384073	29	2013	*AAA*TCCAGAGGCT*AGC*	3-10-3 methyleneoxy (4'-CH_2-O-2') BNA	1428
391172	29	2013	*AA*ATCCAGAGGC*TAG*	2-10-3 methyleneoxy (4'-CH_2-O-2') BNA	1429
392056	29	140	*AG*CTGCAGCCAT*GA*	2-10-2 methyleneoxy (4'-CH_2-O-2') BNA	1263
392057	29	807	*GG*TCCAGGGCCA*AG*	2-10-2 methyleneoxy (4'-CH_2-O-2') BNA	1162
392061	29	2014	*AA*TCCAGAGGCT*AG*	2-10-2 methyleneoxy (4'-CH_2-O-2') BNA	1431
392063	29	3099	*AG*GCCAGTGCTA*AG*	2-10-2 methyleneoxy (4'-CH_2-O-2') BNA	1226

Mice were sacrificed 72 hours following injection to determine serum transaminase levels (Table 47); liver and spleen weights (Table 47); and PTEN mRNA levels in liver, kidney and fat (Table 48), according to procedures described herein and well know to one of ordinary skill in the art.

Table 47: Transaminase Levels and Organ Weights

ISIS NO	AST (IU/L)	ALT (IU/L)	Liver Weight % Saline	Spleen Weight % Saline
Saline	98.5	37.5	100	100
141923	89.5	34.8	101	108
116847	59.8	29.5	109	108
384073	57.8	29.3	115	111
391172	48.5	32.8	120	112
392056	516	892	125	167
392057	63.8	34.5	125	101

ISIS NO	AST (IU/L)	ALT (IU/L)	Liver Weight % Saline	Spleen Weight % Saline
392061	189	42.0	123	111
392063	67.3	21.8	127	134

Overall, the short antisense compounds with methyleneoxy (4'-CH_2-O-2') BNA modifications exhibited little to no adverse effects. In addition, total body weight did not significantly differ between treatment groups.

Table 48: %PTEN mRNA levels in Liver, Kidney and Fat

ISIS NO	Liver	Kidney	Fat
Saline	100	100	100
141923	102	133	118
116847	37	96	85
384073	24	74	77
391172	18	63	101
392056	27	88	74
392057	33	79	96
392061	24	61	85
392063	6.5	52	72

As shown in Table 48, each antisense compound targeted to a PTEN nucleic acid led to a significant reduction in target mRNA levels in liver as compared with saline treated and control treated animals. The antisense compounds had various effects on target mRNA levels in kidney and fat.

Example 7: Short Antisense Compounds Targeting a PTEN nucleic acid and having BNA Modifications

Six-week old male Balb/c mice (Jackson Laboratory, Bar Harbor, ME) were administered a single intraperitoneal (i.p.) injection of antisense compound targeted a PTEN nucleic acid at a dose of 8, 4, 2 or 1 µmol/kg. Each dose group consisted of four animals. Shown in Table 49 are the sequence, wing chemistry and motif of each antisense compound used in this study. Bold residues indicate 2'-MOE modified nucleotides, italicized letters indicate methyleneoxy (4'-CH_2-O-2') BNA modifications. All antisense compounds comprise phosphorothioate linkages at each position. Each cytosine of ISIS 116847 and the cytosine residues in the methyleneoxy (4'-CH_2-O-2') BNA wings of ISIS 392063 are replaced with 5-

methylcytosines, while the thymidine residues in the methyleneoxy (4'-CH_2-O-2') BNA wings of ISIS 392745 are replaced with 5-methyl thymidines. Antisense compounds target published PTEN nucleic acids, including Genbank Accession No. U92437.1 (SEQ ID NO: 13).

Table 49: Antisense Compounds Targeted to a PTEN Nucleic Acid

ISIS NO	Target SEQ ID NO	Target Site	Sequence (5'-3')	Gapmer Motif	SEQ ID NO
116847	13	2011	**TCAAA**TCCAGAGGCTA**GCAG**	5-10-5 MOE	1571
392063	13	3099	*CT*TAGCACTGGC*CT*	2-10-2 Methyleneoxy BNA	1226
392745	13	3099	*CT*TAGCACTGGC*CT*	2-10-2 methyleneoxy BNA	1226

Mice were sacrificed 72 hours following injection to determine serum transaminase levels (Table 50); liver, kidney and spleen weights (Table 50); PTEN mRNA levels in liver (Table 51); and estimated ED_{50} oligonucleotide concentration (Table 52). These endpoints were measured using methods described herein and well known to those of ordinary skill in the art.

Table 50: AST, ALT and Bilirubin Levels and Organ Weights

ISIS NO	Dose µmol/kg	AST (IU/L)	ALT (IU/L)	Bilirubin (mg/dL)	Liver Weight % Saline	Kidney Weight % Saline	Spleen Weight % Saline
Saline	N/A	64.0	31.8	0.15	100	100	100
116847	8	73.0	32.0	0.1	114	92	106
392063	8	50.3	17.3	0.1	115	98	115
392063	4	100.8	31.3	0.15	122	94	116
392063	2	60.5	32.8	0.1	112	99	106
392063	1	57.5	29.3	0.1	104	95	107
392745	8	75.5	23.5	0.13	125	99	100
392745	4	77.0	29.3	0.13	121	100	96
392745	2	69.0	32.0	0.13	110	98	103
392745	1	52.0	27.3	0.1	109	97	104

Overall, the PTEN antisense compounds did not show significant signs of toxicity. Kidney, liver and spleen weights were all within normal ranges. Total body weight did not significantly differ between treatment groups.

Table 51: % PTEN mRNA levels in Liver (relative to saline control)

ISIS NO	8 μmol/kg	4 μmol/kg	2 μmol/kg	1 μmol/kg
116847	36	ND	ND	ND
392063	7.4	16	32	60
392745	5.2	11	31	60

As shown in Table 51, each short antisense compound having methyleneoxy (4'-CH_2-O-2') BNA modifications demonstrated a dose-dependent reduction in PTEN mRNA levels. Furthermore, the short antisense compounds were more effective at target reduction than the 5-10-5 MOE gapmer. Levels of PTEN protein in liver were also determined following administration of each antisense compound at a dose of 8 μmol/kg. Each short antisense compound comprising methyleneoxy (4'-CH_2-O-2') BNA in the wings resulted in a significant reduction in PTEN protein relative to both saline control and ISIS 116847 treatment. Next, estimated ED_{50} concentrations for each oligonucleotide were calculated using Graphpad Prism. The results are shown below in Table 52.

Table 52: Estimated ED_{50} Concentration

Wing Chemistry	ISIS NO	ED_{50} (μmole/kg)	ED_{50} (mg/kg)
MOE (with 5-MeC)	116847	6.3	45.2
methyleneoxy BNA (with 5-MeC)	392063	1.3	5.8
methyleneoxy BNA	392745	1.2	5.6

To further investigate different types of bicyclic nucleic acid compounds, an additional set of short antisense compounds targeting a PTEN nucleic acid was designed and tested. Six-week old male Balb/c mice (Jackson Laboratory, Bar Harbor, ME) were administered a single intraperitoneal (i.p.) injection of antisense compound at a dose of 8, 4, 2 or 1 μmol/kg. Each dose group consisted of four animals. Shown in Table 53 are the sequence, wing chemistry and motif of each antisense compound used in this study. All antisense compounds comprise phosphorothioate linkages at each position. The cytosine residues in the methyleneoxy (4'-CH_2-O-2') BNA wings of ISIS 392063 are replaced with 5-methylcytosines. The antisense compound target published PTEN nucleic acids, including Genbank Accession No. U92437.1 (SEQ ID NO: 13).

Table 53: Antisense Compounds Targeting a PTEN Nucleic Acid

ISIS NO	Target SEQ ID NO	5' Target Site	Sequence (5'-3')	Gapmer Motif	SEQ ID NO
392063	29	3099	*CT*TAGCACTGGC*CT*	2-10-2 Methyleneoxy BNA	1226
396564	29	3099	CTTAGCACTGGCCT	2-10-2 Oxyamino (4'-CH_2-N(R)-O-2') BNA	1226
396006	29	3099	CTTAGCACTGGCCT	2-10-2 α-L-Methyleneoxy BNA	1226

Mice were sacrificed 72 hours following injection to determine serum transaminase levels (Table 54); liver and spleen weights (Table 54); and PTEN mRNA levels in liver (Table 55), according to methods described herein and well known to those of ordinary skill in the art.

Table 54: AST and ALT Levels and Organ Weights

ISIS NO	Dose µmol/kg	AST (IU/L)	ALT (IU/L)	Liver Weight	Spleen Weight
Saline	N/A	71	33	100	100
392063	8	97	38	118	103
392063	4	179	36	115	107
392063	2	67	32	109	116
392063	1	68	27	102	105
396564	8	67	25	100	104
396564	4	96	30	102	106
396564	2	68	27	100	119
396564	1	79	39	97	109
396006	8	56	28	110	104
396006	2	139	36	97	105

Table 55: % PTEN mRNA levels in Liver (relative to saline control)

ISIS NO	8 µmol/kg	4 µmol/kg	2 µmol/kg	1 µmol/kg
392063	6.9	18	39	71
396564	86	97	100	96
396006	6.5	ND	ND	70

As shown above, short antisense compounds having α-L-methyleneoxy (4'-CH_2-O-2') BNA modifications led to a dose-dependent reduction in target mRNA levels. Treatment with the short antisense compound having oxyamino BNA modifications led to a modest reduction in target expression.

Example 8. Single Dose Administration Dose Response Study with Short Antisense Compounds Targeting ApoB and PTEN nucleic acids

Six-week old male Balb/c mice (Jackson Laboratory, Bar Harbor, ME) were administered a single intraperitoneal (i.p.) injection of antisense compound at a dose of 8, 4, 2 or 1 μmol/kg. Each dose group consisted of four animals. Shown in Table 56 are the sequence, wing chemistry and motif of each antisense compound used in this study. Italicized residues indicate methyleneoxy (4'-CH_2-O-2') BNA modifications, underlined residues indicate *N*-methyl-oxyamino (4'-CH_2-N(CH_3)-O-2') BNA modifications, and boxed residues indicate α-L-methyleneoxy (4'-CH_2-O-2') BNA modifications. All antisense compounds comprise phosphorothioate linkages at each position. Each cytosine of ISIS 116847 and the cytosine residues in the methyleneoxy (4'-CH_2-O-2') BNA wings of ISIS 392063 are replaced with 5-methylcytosines, while the thymidine residues in the methyleneoxy (4'-CH_2-O-2') BNA wings of ISIS 392745 are replaced with 5-methyl thymidines. PTEN antisense compounds target published PTEN nucleic acid, including Genbank Accession No. U92437.1 (SEQ ID NO: 13). ApoB antisense compounds target published ApoB nucleic acid, including Genbank Accession No. XM_137955.5 (SEQ ID NO: 2).

Table 56: Short Antisense Compounds Targeted to ApoB and PTEN Nucleic Acids

ISIS NO	Target	Target Seq ID	5' Target Site	SEQUENCE	Gapmer	SEQ ID NO
387462	ApoB	19	8235	*GG*TACATGGAAG*TC*	2-10-2 Methyleneoxy BNA	193
392063	PTEN	29	3099	*CT*TAGCACTGGC*CT*	2-10-2 Methyleneoxy BNA	1226
396565	PTEN	29	3099	CUTAGCACTGGCCU	2-10-2 N-Me-oxyamino BNA	1226
396006	PTEN	29	3099	CUTAGCACTGGCCU	2-10-2 α-L-methyleneoxy BNA	1226

Table 57: %ApoB and PTEN mRNA Reduction (relative to saline control)

ISIS	Dose	%ApoB mRNA Reduction	%PTEN mRNA Reduction

NO	(μmol/kg)	(relative to saline)	(relative to saline)
387462	8	0.62	92.8
	4	6.55	103
	2	18.6	105
	1	42.0	98.0
392063	8	126	6.79
	4	111	18.1
	2	112	42.4
	1	114	62.3
396565	8	116	23.8
	4	1.04	46.6
	2	94.4	76.1
	1	115	89.5
396006	8	94.3	62.9
	4	101	18.2
	2	79.7	52.4
	1	111	82.4

As shown in Table 57, each short antisense compound having Methyleneoxy BNA modifications demonstrated a dose-dependent reduction in target mRNA levels. Notably, the short antisense compound with N-methyl-oxyamino BNA wings (ISIS 396565) also demonstrated dose-dependent reduction in PTEN expression similar to both the β-D-methyleneoxy BNA and α-L-methyleneoxy BNA short antisense compounds. Next, estimated ED_{50} concentrations for each antisense were calculated using Graphpad Prism. The results are shown below in Table 58.

Table 58: Estimated ED_{50} Concentrations

Wing Chemistry	ISIS NO	ED_{50} (μmole/kg)	ED_{50} (mg/kg)
Methyleneoxy BNA	387462	0.8	3.9
Methyleneoxy BNA	392063	1.5	7
N-Me-oxyamino BNA	396565	3.8	17.4
α-L-methyleneoxy BNA	396006	2.1	9.3

EXAMPLE 9: Administration of a Parent and Parent Mixed Backbone Antisense Compound

Targeting SGLT-2 mRNA.

ISIS 257016 was administered to *db/db* mice (Charles River Laboratories, Wilmington, MA) intraperitoneally at a dose of 1, 7.5, 14 or 17 mg/kg twice a week. Control groups included a group receiving saline on the same dosing schedule and a group receiving ISIS 145733. ISIS 257016 and ISIS 145733 both comprise the sequence GAAGTAGCCACCAACTGTGC (SEQ ID NO: 1572) further comprising a central "gap" region consisting of ten 2'-deoxynucleotides, which is flanked on both sides (5' and 3' directions) by five-nucleotide "wings". The wings are composed of 2'-methoxyethyl (2'-MOE) nucleotides. All cytidine residues are 5-methylcytidines. The internucleoside (backbone) linkages are phosphorothioate (P=S) throughout the oligonucleotide for ISIS 145733; however ISIS 257016 has a mixed backbone. The internucleoside linkages for ISIS 257016 are phosphodiester (P=O) in the wings and phosphorothioate in the gap. Forty-eight hours following administration of the last dose the mice were sacrificed and kidney tissue was analyzed for SGLT-2 mRNA levels. The results are shown below in Table 59.

Table 59: Antisense inhibition of SGLT2 mRNA expression in vivo by 5-10-5 MOE gapmers

	% change in SGLT2 expression relative to saline	
Dose of oligonucleotide nmol/kg	**ISIS 145733**	**ISIS 257016**
17	-37.5	-76
14	-31.25	-74
7.5	-12.5	-62.5
1	+3	-44

Both ISIS 257016 and ISIS 145733 markedly reduced SGLT-2 levels compared to saline control. (mRNA levels determined using RT, real-time PCR as described above) However, ISIS 257016 has been shown to be about 20-50 times more potent for reducing SGLT-2 mRNA compared to ISIS 145733. An associated reduction in plasma glucose levels was seen for the treatment groups (661 ±14 for the saline group compared to 470 ±23 for the group receiving ISIS 257016). Accumulation of ISIS 257016 and ISIS 145733 in the kidney was similar over the dose range, however little of the full length 257016 antisense was detected in the kidney which supports the theory that a degradation product is responsible for the increased activity. Also the onset of action following a single dose of 25 mg/kg correlated to a time pint were little intact 257016 antisense compound was left.

Similar studies were performed in lean mice, *ob/ob* mice and in ZDF rats (Charles Rivers Laboratories) using ISIS 257016, ISIS 145733 or saline in a similar same dosing schedule as described above. The sequence of the binding site for ISIS 145733 and ISIS 257016 is conserved between mouse and rat (see Table 60). Reduction of SGLT-2 mRNA in the kidney was similar to that seen above. In a study utilizing rats, at a dose of 10 mg/kg given two times a week for two weeks, ISIS 145733 was shown to reduce SGLT-2 mRNA levels by about 40% whereas the reduction achieved with ISIS 257016 was greater than 80%. ISIS 257016 reduces SGLT2 expression maximally at a low dose of 12.5 mg/kg. Additional studies at lower dosing ranges show significant reduction of SGLT2 mRNA levels with the mixed backbone antisense compound at doses less than 1 mg/kg/wk .

EXAMPLE 10: Administration of a Parent and Short Antisense Compound Targeting SGLT-2 mRNA

Pharmacokinetic studies indicated that ISIS 257016 was acting as a prodrug that was metabolized to a 12 nucleobase pharmacophore. In a next study, ZDF rats were dosed intraperitoneally twice per week with 1.5 mg/kg of either ISIS 257016 or ISIS 370717, or with saline at a similar dosing schedule. ISIS 370717 is a 12 nucleobase antisense compound targeted to SGLT-2 nucleic acid comprising the sequence TAGCCACCAACT (SEQ ID NO: 154) and further comprising central "gap" region consisting of ten 2'-deoxynucleotides, which is flanked on both sides (5' and 3' directions) by one-nucleotide "wings". The wings are composed of 2'-methoxyethyl (2'-MOE) nucleotides. All cytidine residues are 5-methylcytidines. The internucleoside (backbone) linkages are phosphorothioate (P=S) throughout the oligonucleotide.

Following five weeks of dosing the animals were sacrificed and kidney tissue was analyzed for SGLT-2 mRNA levels. The pharmacological activity of ISIS 257016 and ISIS 370717 were similar, however, the 12 nucleotide antisense compound displayed a faster onset of action. ISIS 370717 displayed nearly 80% inhibition of SGLT2 expression in kidney on day two after a single dose of 2.8 umoles/kg whereas ISIS 257016 displayed only about 25% inhibition on day 2 after the same single dose administration. The date support that ISIS 257016 is a prodrug having a 12 nucleotide pharmacophore.

EXAMPLE 11: Potency and Bioavailability of a Short Antisense Compound

The improved potency displayed by ISIS 370717 and the improved oral bioavailability for these short antisense compounds makes these compounds useful for oral administration. Normal rats received ISIS 370717, ISIS 145733 or saline at 100 mg/kg twice per week via intrajejunal administration. About 48 hours following the last dose, the animals were sacrificed and kidney tissue was analyzed for antisense compound concentration and SGLT-2 mRNA levels. There was a significantly higher accumulation of ISIS 370717 in the kidney tissue (approximately 500 micro grams per gram of tissue) compared to the controls. Moreover, SGLT-2 mRNA was reduced by more than 80% over the controls.

EXAMPLE 12: Wing, Gap and Total Length Variations Around a 12 nucleotide short antisense compound

ISIS 370717 1-10-1 MOE gapmer was used as a template to make sequence related oligos with varying motifs. These variations are provided in Table 60. The antisense compounds were designed to target different regions of the mouse or rat SGLT2 nucleic acid, using published sequences (GenBank accession number U29881.1, incorporated herein as SEQ ID NO: 1575, and GenBank accession number AJ292928.1, incorporated herein as SEQ ID NO: 1576, respectively).

Table 60: Short Antisense compounds targeting SGLT2 nucleic acids

ISIS NO	5' Target Site on mouse SEQ ID NO: 1575	5' Target Site on rat SEQ ID NO: 1576	Gapmer Motif	Sequence (5'-3')	SEQ ID NO
257016	2680	148	5-10-5 MOE	GAAGTAGCCACCAACTGTGC	1553
370717	2684	152	1-10-1 MOE	TAGCCACCAACT	1554
386169	2684	152	2-8-2 MOE	TAGCCACCAACT	1555
386176	2685	153	1-8-1 MOE	AGCCACCAAC	1556
386196	2684	152	3-6-3 MOE	TAGCCACCAACT	1557

The antisense compounds were analyzed for their effect on mouse SGLT2 mRNA levels. Data are ranges taken from three experiments in which mice were dosed twice per week for three weeks with 2.5, 0.5 or 0.1 umol/kg of the above MOE gapmers given by intraperitoneal injection. Mice were sacrificed 48 hours following last administration and evaluated for SGLT2 levels in kidney. SGLT2 mRNA levels were determined by RT, real-time PCR as described by other examples herein. PCR results were normalized to an internal ISIS control. The results are shown below in Table 61.

Table 61: Antisense inhibition of SGLT2 in vivo by 1-10-1 and 1-10-2 MOE gapmers

	% change in SGLT2 expression relative to saline				
Dose of oligonucleotide umol/kg	**ISIS 370717**	**ISIS 386169**	**ISIS 386176**	**ISIS 386196**	**ISIS 386197**
2.5	-82	-85	-80	-50	-20
0.5	-70	-80	-68	-30	-15
0.1	-55	-70	-65	-35	-20

These results illustrate that all the various motifs tested inhibit the expression of SGLT2 *in vivo* in a dose-dependent manner. The 1-10-1, 2-8-2 and 1-8-1 gapmers were found to be particularly potent.

EXAMPLE 13: Antisense Inhibition of Rat SGLT-2 by 1-10-1 and 1-10-2 MOE Gapmers

1-10-1 and 1-10-2 MOE gapmer antisense compounds, provided in Table 62, were designed to target different regions of the mouse or rat SGLT2 RNA. All short antisense compounds in Table 62 are chimeric oligonucleotides ("gapmers") either 12 or 13 nucleotides in length, composed of a central "gap" segment consisting of ten 2'-deoxynucleotides, which are flanked on the 5' side by a one-nucleoside "wing" and on the 3' side by a two or one-nucleotide "wing". The wings are composed of 2'-methoxyethyl (2'-MOE) nucleotides. The internucleoside (backbone) linkages are phosphorothioate (P=S) throughout the oligonucleotide. All cytidine residues are 5-methylcytidines.

Table 62: Antisense compounds targeting SGLT2 nucleic acid

ISIS NO	5' Target Site on SEQ ID NO: XXX (mouse)	5' Target Site on SEQ ID NO: XXX (rat)	Gapmer Motif	Sequence (5'-3')	SEQ ID NO
370717	2684	152	1-10-1 MOE	TAGCCACCAACT	1554
382675	2683	151	1-10-1 MOE	TAGCCACCAACTG	1559
379692		508	1-10-1 MOE	TGTTCCAGCCCA	246
382676		507	1-10-2 MOE	TGTTCCAGCCCAG	246
379699		1112	1-10-2 MOE	GGCATGAGCTTC	281
382677		1111	1-10-2 MOE	GGCATGAGCTTCA	281
382677		958	1-10-2 MOE	GGCATGAGCTTCA	281

The short antisense compounds were analyzed for their effect on rat SGLT2 mRNA levels. Data are ranges taken from three experiments in which Male Sprague-Dawley rats (170-200g) were dosed twice per week for three weeks with 450, 150 or 50 nmol/kg of either a 1-10-1 or 1-10-2 MOE gapmer given by intraperitoneal injection. Rats were sacrificed 48 hours following last administration and evaluated for SGLT2 mRNA levels in kidney. Target levels were determined by RT, real-time PCR as described by other examples herein. PCR results were normalized to an internal ISIS control. The results are shown below in Table 63.

Table 63: Antisense inhibition of SGLT2 mRNA *in vivo* by 1-10-1 and 1-10-2 MOE gapmers

	% change in SGLT2 expression relative to saline					
Dose of oligonucleotide	**ISIS**	**ISIS**	**ISIS**	**ISIS**	**ISIS**	**ISIS**

nmol/kg	370717 1-10-1	382675 1-10-2	379692 1-10-1	382676 1-10-2	379699 1-10-1	382677 1-10-2
450	-70	-80	-90	-85	-83	-75
150	-70	-65	-85	-80	-75	-60
50	-55	-50	-80	-65	-60	-40

These results illustrate that both the 1-10-1 and 1-10-2 MOE gapmers reduce SGLT2 mRNA *in vivo* in a dose-dependent manner.

Rats were further evaluated for total body weight, liver, spleen and kidney weight. Significant changes in spleen, liver or body weight can indicate that a particular compound causes toxic effects. All changes were within the margin of error of the experiment. No significant changes in body weight were observed during the treatment or at study termination. No significant changes in liver or spleen weights were observed.

Toxic effects of short antisense compounds administered *in vivo* can also be assessed by measuring the levels of enzymes and proteins associated with disease or injury of the liver or kidney. Elevations in the levels of the serum transaminases aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are often indicators of liver disease or injury. Serum total bilirubin is an indicator of liver and biliary function, and albumin and blood urea nitrogen (BUN) are indicators of renal function. Glucose and triglyceride levels are sometimes altered due to toxicity of a treatment. Serum glucose also depends in part upon the activity of SGLT2. The levels of ALT, AST, total bilirubin, albumin, BUN, glucose and triglyceride were measured in rats treated with the short antisense compounds. The levels of routine clinical indicators of liver and kidney injury and disease were within normal ranges and are not significantly changed relative to saline-treated animals, demonstrating that the short antisense compounds do not significantly affect renal or hepatic function. Triglyceride and glucose levels were not significantly elevated relative to saline-treated animals.

EXAMPLE 14: Antisense Inhibition of Mouse and Rat SGLT2 by 1-10-1 MOE Gapmers

1-10-1 MOE gapmer antisense compounds designed to target different regions of mouse SGLT2 mRNA are shown in Table 64.

Table 64: Composition of Antisense Compounds Targeting SGLT2 mRNA

ISIS NO	5' Target Site on SEQ ID NO: XXX (mouse)	5' Target Site on SEQ ID NO: XXX (rat)	Motif	Sequence (5'-3')	SEQ ID NO
370717	2684	152	1-10-1 MOE	TAGCCACCAACT	1554
379692		508	1-10-1 MOE	TGTTCCAGCCCA	246

379699		1112	1-10-1 MOE	GGCATGAGCTTC	281
379702		1525	1-10-1 MOE	GCACACAGCTGC	293
381408	3034**		1-10-1 MOE	TACCGAACACCT	1560

** indicates 3 mismatches to a target sequence

The short antisense compounds were analyzed for their effect on mouse SGLT2 mRNA levels. Data was taken from three experiments in which Male 6-week old Balb/c mice were dosed twice per week for two weeks with 450, 150, or 50 nmol/kg of one of the above 1-10-1 MOE gapmers given by intraperitoneal injection. Mice were sacrificed 48 hours following last administration and evaluated for SGLT2 mRNA levels in kidney. Target levels were determined by RT, real-time PCR as described by other examples herein. PCR results were normalized to an internal ISIS control. The results are shown below in Table 65.

Table 65: Antisense inhibition of SGLT2 mRNA *in vivo* by 1-10-1 MOE gapmers

	% change in SGLT2 expression relative to saline				
Dose of oligonucleotide nmol/kg	**ISIS 370717**	**ISIS 379692**	**ISIS 379699**	**ISIS 379702**	**ISIS 381408**
450	-65	-80	-80	-75	-
150	-55	-70	-62.5	-72.5	-
50	-47.5	-52.5	-42.5	-52.5	-

These results illustrate that all the 1-10-1 MOE gapmers except, ISIS 381408, inhibit the expression of SGLT2 in vivo in a dose-dependent manner in mouse. Activity of ISIS 381408 has been shown in Rat studies (See Table 65).

Evaluation of 1-10-1 Gapmers in Rat

The effect of the above 1-10-1 gapmers (see Table 64 above) on rat SGLT2 mRNA levels. Data are taken from four experiments in which male Sprague-Dawley rats (170-200g) were dosed twice per week for three weeks with 250 nmol/kg given by intraperitoneal injection. Rats were sacrificed 48 hours following last administration and evaluated for SGLT2 mRNA levels in kidney. Target levels were determined by RT, real-time PCR as described by other examples herein. PCR results were normalized to an internal ISIS control. The results are shown below in Table 66.

Table 66: Antisense inhibition of SGLT2 mRNA *in vivo* by 1-10-1 MOE gapmers

Dose of oligonucleotide nmol/kg	% change in SGLT2 expression relative to saline				
	ISIS 370717	ISIS 379692	ISIS 379699	ISIS 379702	ISIS 381408
250	-70	-85	-75	-25	-5

These results illustrate that all the 1-10-1 MOE gapmers inhibit the expression of SGLT2 in *in vivo* rat studies.

EXAMPLE 15: Antisense Inhibition of Mouse and Rat SGLT2 Expression by Additional 1-10-1 and 2-8-2 MOE Gapmers

1-10-1 and 2-8-2 MOE gapmer short antisense compounds were designed to target different regions of the mouse SGLT2 RNA but have complementarity across species. The short antisense compounds are shown in Table 67. All short antisense compounds in Table 67 are gapmers 12 nucleotides in length, composed of a central "gap" segment consisting of 2'-deoxynucleotides, which are flanked on both sides (5' and 3' directions) by wing segments having 2'-modifications. The wings are composed of 2'-methoxyethyl (2'-MOE) nucleotides. The internucleoside (backbone) linkages are phosphorothioate (P=S) throughout the oligonucleotide. All cytidine residues are 5-methylcytidines.

Table 67: Short Antisense Compounds Targeting SGLT2 nucleic acid

ISIS NO	5' Target Site (rat)	Target SEQ ID (rat)	Gapmer Motif	Sequence (5'-3')	SEQ ID NO
379692	508		1-10-1 MOE	TGTTCCAGCCCA	246
388625	508		1-10-1 MOE	TGTTCCAGCCCA	246
379699	1112		1-10-1 MOE	GGCATGAGCTTC	281
388626	1112		2-8-2 MOE	GGCATGAGCTTC	281
379702	1525		2-8-2 MOE	GCACACAGCTGC	293
388627	1525		2-8-2 MOE	GCACACAGCTGC	293

The short antisense compounds were analyzed for their effect on mouse SGLT2 mRNA levels *in vivo*. Data was taken from three experiments in which male 6-week old Balb/c mice were dosed twice per week for three weeks with 0.5, 0.1, or 0.02 umol/kg of either a 1-10-1 or 2-8-2 MOE gapmer given by intraperitoneal injection. Mice were sacrificed 48 hours following last administration and evaluated for

SGLT2 levels in kidney. Target levels were determined by RT, real-time PCR as described by other examples herein. PCR results were normalized to an internal ISIS control. The results are shown below in Table 68.

Table 68: Antisense inhibition of SGLT2 mRNA *in vivo* by 1-10-1 and 2-8-2 MOE gapmers

	% change in SGLT2 expression relative to saline					
Dose of oligonucleotide umol/kg	**ISIS 379692 1-10-1**	**ISIS 388625 2-8-2**	**ISIS 379699 1-10-1**	**ISIS 388626 2-8-2**	**ISIS 379702 1-10-1**	**ISIS 388627 2-8-2**
0.5	-85	-90	-75	-80	-70	-65
0.1	-75	-88	-60	-60	-65	-50
0.02	-55	-65	-30	-45	-40	-38

These results illustrate that both the 1-10-1 and 2-8-2 MOE gapmers inhibit the expression of SGLT2 in vivo in a dose-dependent manner.

Mice were further evaluated for total body weight, liver, spleen and kidney weight. All changes were within the margin of error of the experiment. No significant changes in body weight were observed during the treatment or at study termination. No significant changes in liver or spleen weights were observed.

The levels of ALT, AST, BUN, transaminases, plasma creatinine, glucose and triglyceride were measured in mice treated with the short antisense compounds. The levels of routine clinical indicators of liver and kidney injury and disease were within normal ranges and are not significantly changed relative to saline-treated animals, demonstrating that the short antisense compounds do not significantly affect renal or hepatic function. Triglyceride and glucose levels were not significantly elevated relative to saline-treated animals.

Evaluation of ISIS 379692 1-10-1 MOE Gapmer, ISIS 392170 1-10-1 Methyleneoxy BNA Gapmer, ISIS 388625 2-8-2 MOE Gapmer and ISIS 392173 2-8-2 Methyleneoxy BNA Gapmer in Mice

The effect of ISIS 379692 1-10-1 MOE gapmer and ISIS 388625 2-8-2 MOE gapmer are compared with the effect of ISIS 392170 1-10-1 Methyleneoxy BNA Gapmer and ISIS 392173 2-8-2 Methyleneoxy BNA Gapmer (see Table 69) on mouse SGLT2 mRNA levels *in vivo*. Data are taken from three experiments in which male 6-week old Balb/c mice were dosed twice per week for three weeks with 5, 25 and 125 nmol/kg of either the ISIS 379692 1-10-1 MOE gapmer or the ISIS 388625 2-8-2 MOE gapmer given by intraperitoneal injection. Mice were sacrificed 48 hours following last administration and evaluated for

SGLT2 mRNA levels in kidney. Target levels were determined by RT, real-time PCR as described by other examples herein. PCR results were normalized to an internal ISIS control. The data are expressed as percent change ("+" indicates an increase, "-" indicates a decrease) relative to saline treated animals and are illustrated in Table 69.

Table 69: Antisense inhibition of SGLT2 mRNA *in vivo* by a 1-10-1 and a 2-8-2 MOE gapmer

Dose of oligonucleotide nmol/kg	ISIS 379692 1-10-1 MOE	ISIS 392170 1-10-1 Methyleneoxy BNA	ISIS 388625 2-8-2 MOE	ISIS 392173 2-8-2 Methyleneoxy BNA
125	-58	-69	-70	-75
25	-46	-54	-47	-57
5	-7	-23	-18	-44

These results illustrate that both the 1-10-1 and 2-8-2 MOE gapmer inhibit the expression of SGLT2 *in vivo* at the highest three dosing ranges in a dose-dependent manner. The results also illustrate that the Methyleneoxy BNA constructs are more potent then the MOE constructs. No significant changes in body weight were observed during the treatment or at study termination. No significant changes in liver or spleen weights were observed. The toxicity parameters including levels of ALT, AST, BUN, and creatinine were within normal ranges and are not significantly changed relative to saline-treated animals, demonstrating that the compounds do not significantly affect renal or hepatic function.

Evaluation of ISIS 379692 1-10-1 MOE Gapmer and ISIS 388625 2-8-2 MOE Gapmer in Rat

The effect of ISIS 379692 1-10-1 MOE gapmer and ISIS 388625 MOE 2-8-2 gapmer (see Table 70) on rat SGLT2 mRNA levels *in vivo*. Data are taken from four experiments in which male Sprague-Dawley rats (170-200g) were dosed twice per week for three weeks with 200, 50, 12.5, or 3.125 nmol/kg of either the ISIS 379692 1-10-1 MOE gapmer or the ISIS 388625 2-8-2 MOE gapmer given by intraperitoneal injection. Rats were sacrificed 48 hours following last administration and evaluated for SGLT2 levels in kidney. Target levels were determined by RT, real-time PCR as described by other examples herein. PCR results were normalized to an internal ISIS control. The results are shown below in Table 70.

Table 70: Antisense inhibition of SGLT2 mRNA *in vivo* by a 1-10-1 and a 2-8-2 MOE gapmer

% change in SGLT2 expression relative to saline

Dose of oligonucleotide umol/kg	ISIS 379692 1-10-1	ISIS 388625 2-8-2
200	-80	-80
50	-65	-65
12.5	-15	-15
3.125	+30	+25

These results illustrate that both the 1-10-1 and 2-8-2 MOE gapmer inhibit the expression of SGLT2 in vivo at the highest three dosing ranges in a dose-dependent manner.

Rats were further evaluated for total body weight, liver, spleen and kidney weight. All changes were within the margin of error of the experiment. No significant changes in body weight were observed during the treatment or at study termination. No significant changes in liver or spleen weights were observed.

The levels of ALT, AST, BUN, cholesterol, plasma creatinine and triglycerides were measured in rats treated with the short antisense compounds. The levels of routine clinical indicators of liver and kidney injury and disease were within normal ranges and are not significantly changed relative to saline-treated animals, demonstrating that the short antisense compounds do not significantly affect renal or hepatic function.

EXAMPLE 16: Antisense Inhibition of SGLT2 Expression in ZDF rat

ISIS 388625, 388626 and control oligo ISIS 388628 were analyzed for their effect on ZDF rat plasma glucose levels and HbA1c. The leptin receptor deficient Zucker diabetic fatty (ZDF) rat is a useful model for the investigation of type 2 diabetes. Diabetes develops spontaneously in these male rats at ages 8-10 weeks, and is associated with hyperphagia, polyuria, polydipsia, and impaired weight gain, symptoms which parallel the clinical symptoms of diabetes (Phillips MS, et al., 1996, Nat Genet 13, 18-19). Six week old ZDF rats were injected intraperitoneally with short antisense compound at a dose of 40 0nM/kg once a week for twelve weeks. Data are illustrated in Tables 71 and 72.

Table 71: Plasma glucose

ISIS NO.	Seq ID NO	Sequence (5'-3')	Motif	Plasma glucose levels recorded on specific dates (mg/dl)			
				Day 10	Day 40	Day 55	Day 66
PBS		n/a	n/a	450.7	478.5	392.8	526.2
388625	246	TGTTCCAGCCCA	2-8-2 MOE	435.5	278.7	213.8	325.5

388626	281	GGCATGAGCTTC	2-8-2 MOE	434.7	300.5	219.8	379.8
388628	226	TAGCCGCCCACA	2-8-2 MOE	436.0	502.0	411.2	668.8

Table 72: HbA1c Status

ISIS NO.	Seq ID NO	Sequence (5'-3')	Motif	Percentage HbA1c on specific dates (%) $p < 0.001$		
				Day 40	Day 55	Day 68
PBS		n/a	n/a	8.0	8.9	10.0
388625	246	TGTTCCAGCCCA	2-8-2 MOE	6.5	5.8	4.3
388626	281	GGCATGAGCTTC	2-8-2 MOE	6.6	5.9	4.0
388628	226	TAGCCGCCCACA	2-8-2 MOE	8.0	9.1	7.8

ISIS 388625 and 388626 significantly reduced plasma glucose levels and HbA1C compared to PBS and control treated animals.

EXAMPLE 17: Antisense Inhibition of SGLT2 Expression in Dog Kidney (ISIS 388625)

ISIS 388625 is a 2-8-2 MOE Gapmer with sequence TGTTCCAGCCCA (SEQ ID NO: 246) (e.g. see Table 71). The effect of ISIS 388625 on dog SGLT2 mRNA levels. Data are taken from two dosing groups in which a total of nine male beagle dogs were dosed with either one or ten mg/kg/week of ISIS 388625 or saline given by subcutaneous injection twice weekly. On day 46 of the study all dogs were sacrificed and evaluated for SGLT2 levels in kidney. Target levels were determined by quantitative RT, real-time PCR as described by other examples herein. PCR results were normalized to an internal ISIS control. The results are shown below in Table 73.

Table 73: Antisense inhibition of SGLT2 mRNA *in vivo* by ISIS 388625

	% change in SGLT2 expression Relative to saline
Dose of oligonucleotide mg/kg/wk	**ISIS 388625**
1	-85
10	-95

These results illustrate that greater than 80% reduction of SGLT2 mRNA can be achieved at a 1 mg/kg/wk dose of ISIS 388625. Even greater reduction can be achieved at slightly higher doses. Administration of ISIS 388625 in dog was also shown to improve glucose tolerance. Peak plasma glucose levels were decreased by over 50% on average and the subsequent drop in glucose was lessened compared to saline controls in a standard glucose tolerance test. Urinary glucose excretion was also increased.

EXAMPLE 18: In vivo testing of short antisense compounds targeted to SGLT2 nucleic acid

Twenty 1-10-1 MOE gapmers that are complementary to human/monkey/mouse/rat SGLT2 were designed, synthesized and tested *in vivo* for suppression of SGLT2 mRNA levels in kidney. Target sites for mouse and rat are indicated in Table 74. Target sites for human are indicated in Tables 4 and 5. Data are averages from two experiments in which male 6-week old Balb/c mice were administered intraperitoneal injections of 350 nmol/kg of oligonucleotide, twice per week, over a period of two weeks (a total of four injections). Mice were sacrificed 48 hours following the last administration and evaluated for SGLT2 mRNA levels in kidney. SGLT2 mRNA levels were determined by quantitative real-time PCR analysis according to standard procedures, using two different PCR primer probe sets, primer probe set (PPS) 534 and PPS 553. SGLT2 mRNA levels were normalized to cyclophilin mRNA levels, which were also measured by quantitative real-time PCR. The results are shown below in Table 74.

Table 74: Antisense inhibition of SGLT2 *in vivo*

ISIS NO	5' Target Site on SEQ ID NO: XXX (mouse)	5' Target Site on SEQ ID NO: XXX (rat)	Sequence (5'-3')	Motif	PPS 534 % Saline	PPS 553 % Saline	SEQ ID NO
PBS			N/A		---	---	
370717	2684	152	TAGCCACCAACT	1-10-1 MOE	-84.4	-84.3	1554
379684	2070	64	TGTCAGCAGGAT	1-10-1 MOE	-45.0	-43.2	214
379685	2103	97	TGACCAGCAGGA	1-10-1 MOE	-10.3	-20.5	219
379686	2121*	115	ACCACAAGCCAA	1-10-1 MOE	-71.9	-75.1	225
379687	2824	216	GATGTTGCTGGC	1-10-1 MOE	-47.1	-52.1	230
379688	2876	268	CCAAGCCACTTG	1-10-1 MOE	-62.6	-70.4	240
379689		298	AGAGCGCATTCC	1-10-1 MOE	-17.5	-30.4	241
379690		415	ACAGGTAGAGGC	1-10-1 MOE	-18.9	-22.5	242
379691		454	AGATCTTGGTGA	1-10-1 MOE	-35.0	-48.6	243

379692		508	TGTTCCAGCCCA	1-10-1 MOE	-88.1	-88.5	246
379693		546	CATGGTGATGCC	1-10-1 MOE	-51.6	-59.9	254
379694		609	GACGAAGGTCTG	1-10-1 MOE	-42.1	-54.4	264
379695		717	GGACACCGTCAG	1-10-1 MOE	-52.5	-64.1	266
379696		954	CAGCTTCAGGTA	1-10-1 MOE	-24.6	-36.2	267
379697		982	CTGGCATGACCA	1-10-1 MOE	-32.0	-46.3	272
379698		1071	GCAGCCCACCTC	1-10-1 MOE	-11.8	-27.0	275
379699		1112	GGCATGAGCTTC	1-10-1 MOE	-83.5	-85.8	281
379700		1138	CCAGCATGAGTC	1-10-1 MOE	-2.8	-16.4	285
379701		1210	CCATGGTGAAGA	1-10-1 MOE	-0.3	-11.9	288
379702		1525	GCACACAGCTGC	1-10-1 MOE	-87.8	-89.5	293
379703		1681	GCCGGAGACTGA	1-10-1 MOE	-44.2	-45.9	295

* indicates 1 or 2 mismatches to a target sequence

Example 19: Antisense inhibition of human PCSK9 in Hep3B cells

Short antisense compounds targeted to a PCSK9 nucleic acid were tested for their effects on PCSK9 mRNA *in vitro*. The short antisense compounds are presented in Table 6. The Isis No, gapmer motif and SEQ ID NO of each short antisense compound are shown again in Table 75. Cultured Hep3B cells were treated with 100 nM of short antisense compound. 5-10-5 MOE gapmers targeted to a PCSK9 nucleic acid were used as positive controls. After the treatment period, RNA was isolated from the cells and PCSK9 mRNA levels were measured by quantitative real-time PCR, as described herein. PCSK9 mRNA levels were adjusted according to total RNA content as measured by RIBOGREEN®. Results are presented in Table 75 as percent inhibition of PCSK9 (%Inhib), relative to untreated control cells. In the "% Inhib" column, a "0" indicates that no reduction of PCSK9 mRNA was observed with that particular short antisense compound.

Table 75: Antisense inhibition of PCSK9 by short antisense compounds

ISIS No.	SEQ ID NO	5' Target Site on SEQ ID NO: 4	3' Target Site on SEQ ID NO: 4	Gapmer Motif	% Inhibition Range	% Inhib

400297	329	695	708	2-10-2 MOE		0
400298	330	696	709	2-10-2 MOE		0
400299	331	697	710	2-10-2 MOE		0
400300	332	742	755	2-10-2 MOE		9
400301	333	757	770	2-10-2 MOE	20-30%	27
400302	334	828	841	2-10-2 MOE		0
400303	335	829	842	2-10-2 MOE		0
400304	336	830	843	2-10-2 MOE	10-20%	11
400305	337	937	950	2-10-2 MOE	30-40%	38
400306	338	952	965	2-10-2 MOE	40-50%	40
400307	339	988	1001	2-10-2 MOE	70-80%	76
400308	340	989	1002	2-10-2 MOE	50-60%	55
400309	341	990	1003	2-10-2 MOE	40-50%	44
400310	342	991	1004	2-10-2 MOE		8
400311	343	992	1005	2-10-2 MOE	10-20%	18
400312	344	993	1006	2-10-2 MOE	20-30%	28
400313	345	994	1007	2-10-2 MOE	10-20%	10
400314	346	1057	1070	2-10-2 MOE	20-30%	26
400315	347	1075	1088	2-10-2 MOE		0
400316	348	1076	1089	2-10-2 MOE		8
400317	349	1077	1090	2-10-2 MOE		7
400318	350	1078	1091	2-10-2 MOE	20-30%	26
400319	351	1093	1106	2-10-2 MOE		0
400320	352	1094	1107	2-10-2 MOE		0
400321	353	1095	1108	2-10-2 MOE		0
400322	354	1096	1109	2-10-2 MOE		0
400323	355	1147	1160	2-10-2 MOE		0
400324	356	1255	1268	2-10-2 MOE		7
400325	357	1334	1347	2-10-2 MOE		4
400326	358	1335	1348	2-10-2 MOE		0
400327	359	1336	1349	2-10-2 MOE	30-40%	36
400328	360	1453	1466	2-10-2 MOE	10-20%	13
400329	361	1454	1467	2-10-2 MOE	10-20%	14
400330	362	1455	1468	2-10-2 MOE	40-50%	43
400331	363	1456	1469	2-10-2 MOE	30-40%	35
400332	364	1569	1582	2-10-2 MOE		0
400333	365	1570	1583	2-10-2 MOE		0
400334	366	1571	1584	2-10-2 MOE		0
400335	367	1572	1585	2-10-2 MOE		0
400336	368	1573	1586	2-10-2 MOE		4

400337	369	1574	1587	2-10-2 MOE		0
400338	370	1575	1588	2-10-2 MOE		9
400339	371	1576	1589	2-10-2 MOE		0
400340	372	1577	1590	2-10-2 MOE		0
400341	373	1578	1591	2-10-2 MOE		0
400342	374	1621	1634	2-10-2 MOE		0
400343	375	1622	1635	2-10-2 MOE		0
400344	376	1623	1636	2-10-2 MOE		0
400345	377	1624	1637	2-10-2 MOE		0
400346	378	1738	1751	2-10-2 MOE		5
400347	379	1739	1752	2-10-2 MOE		0
400348	380	1740	1753	2-10-2 MOE		0
400349	381	1741	1754	2-10-2 MOE	10-20%	13
400350	382	1834	1847	2-10-2 MOE	10-20%	15
400351	383	1835	1848	2-10-2 MOE	10-20%	14
400352	384	1836	1849	2-10-2 MOE	20-30%	29
400353	385	1837	1850	2-10-2 MOE	10-20%	19
400354	386	1838	1851	2-10-2 MOE	10-20%	19
400355	387	1839	1852	2-10-2 MOE		0
400356	388	1840	1853	2-10-2 MOE		0
400357	389	2083	2096	2-10-2 MOE		0
400358	390	2084	2097	2-10-2 MOE	10-20%	12
400359	391	2085	2098	2-10-2 MOE		0
400360	392	2086	2099	2-10-2 MOE	30-40%	38
400361	393	2316	2329	2-10-2 MOE		2
400362	394	2317	2330	2-10-2 MOE	10-20%	16
400363	395	2318	2331	2-10-2 MOE		8
400364	396	2319	2332	2-10-2 MOE		0
400365	397	2320	2333	2-10-2 MOE	20-30%	25
400366	398	2321	2334	2-10-2 MOE	10-20%	15
400367	399	2322	2335	2-10-2 MOE	10-20%	12
400368	400	2323	2336	2-10-2 MOE	10-20%	11
400369	401	2324	2337	2-10-2 MOE		0
400370	402	2325	2338	2-10-2 MOE	10-20%	13
400371	403	3543	3556	2-10-2 MOE		0

As illustrated in Table 75, short antisense compounds targeted to a PCSK9 nucleic acid, having a 2-10-2 MOE gapmer motif, reduced PCSK9 mRNA in cultured cells.

Short antisense compounds targeted to a PCSK9 nucleic acid were tested in a dose response experiment Hep3B cells. Cells were treated as described herein with nM concentrations of short antisense compound as indicated in Tables 76. After the treatment period, RNA was isolated from the cells and PCSK9 mRNA levels were measured by quantitative real-time PCR, as described herein. PCSK9 mRNA levels were normalized to cyclophilin mRNA levels, as measured by real-time PCR using a cyclophilin-specific primer probe set. Results are presented as percent inhibition of PCSK9, relative to untreated control cells. Also shown is the EC_{50} (concentration at which 50% reduction of mRNA is observed) for each short antisense compound tested in the dose response experiment, as calculated using Graphpad Prism. As illustrated in the following table, PCSK9 mRNA levels were reduced in a dose-dependent manner.

Table 76: Dose-dependent antisense inhibition of PCSK9 by short antisense compounds

	% Inhibition					
	160 nM	80 nM	40 nM	20 nM	10 nM	5 nM
5-10-5	95	96	85	78	58	38
400307	93	92	56	45	39	35
400308	86	77	40	26	10	31
400309	78	72	12	38	23	49
400327	55	43	49	23	37	5
400330	71	82	69	40	32	8
400331	82	75	63	47	40	29
400352	64	63	44	40	16	7
400353	48	54	43	23	27	15

Example 20: Antisense inhibition of PCSK9 by short antisense compounds comprising BNAs

Short antisense compounds targeted to a PCSK9 nucleic acid were tested in dose response experiments, in both mouse and human cultured cells. The compounds tested included ISIS 403739 and ISIS 403740. ISIS 403739 is a short antisense compound consisting of the nucleotide sequence of SEQ ID NO: 404 and having a 2-10-2 gapmer motif, where the nucleotides in the wings comprise (6'S)-6'methyl BNA. ISIS 403740 is a short antisense compound consisting of the nucleotide sequence of SEQ ID NO: 405 and having a 2-10-2 gapmer motif, where the nucleotides in the wings comprise (6'S)-6'methyl BNA. Also tested was a 5-10-5 MOE gapmer targeted to a PCSK9 nucleic acid.

Mouse hepatocytes were plated and treated as described herein with nM concentrations of short antisense compound as indicated in Table 77. After the treatment period, RNA was isolated from the cells and PCSK9 mRNA levels were measured by quantitative real-time PCR, as described herein. PCSK9 mRNA levels were normalized to cyclophilin mRNA levels, as measured by real-time PCR using a cyclophilin-specific primer probe set. Results are presented as percent inhibition of PCSK9, relative to untreated control cells. Where present, "0" indicates no observed reduction in PCSK9 mRNA. ISIS 403739 exhibited dose-dependent reduction of mouse PCSK9 mRNA at the doses of 30 nM and higher. ISIS 403740 exhibited reduction of mouse PCSK9 mRNA at the two highest doses of short antisense compound.

Table 77: Antisense inhibition of mouse PCSK9 by short antisense compounds comprising BNAs

	% Inhibition						
	3.75 nM	7.5 nM	15 nM	30 nM	60 nM	120 nM	240 nM
5-10-5	10	15	21	18	44	43	77
403739	40	19	29	29	32	49	57
403740	3	0	29	13	0	40	33

Human Hep3B cells were treated with nM concentrations of short antisense compound as described herein. After the treatment period, RNA was isolated from the cells and PCSK9 mRNA levels were measured by quantitative real-time PCR, as described herein. PCSK9 mRNA levels were normalized to cyclophilin mRNA levels, as measured by real-time PCR using a cyclophilin-specific primer probe set. Results are presented as percent inhibition of PCSK9, relative to untreated control cells. The data are shown in Table 78 and demonstrate a dose-dependent reduction in human PCSK9 mRNA following treatment with ISIS 403740. ISIS 403739 exhibited dose-dependent reduction at higher doses.

Table 78: Antisense inhibition of mouse PCSK9 by short antisense compounds comprising BNAs

	% Inhibition						
	2.5 nM	5 nM	10 nM	20 nM	40 nM	80 nM	160 nM
5-10-5	7	2	21	33	30	59	71
403739	10	5	7	6	25	52	65
403740	6	12	16	29	45	48	59

Example 21: Antisense inhibition of GCGR in HepG2 cells

Short antisense compounds targeted to a GCGR nucleic acid were tested for their effects on GCGR mRNA *in vitro.*

HepG2 Cells

Cultured HepG2 cells at a density of 10000 cells per well in a 96-well plate were treated as described herein with 25, 50, 100 or 200 nM of antisense oligonucleotide. After the treatment period, RNA was isolated from the cells and GCGR mRNA levels were measured by quantitative real-time PCR, as described herein. GCGR mRNA levels were adjusted according to total RNA content as measured by RIBOGREEN®. Results are presented as percent reduction in GCGR mRNA, relative to untreated control cells.

Table 79 presents data following treatment with the indicated doses of ISIS 327161, a 3-10-3 MOE gapmer. ISIS 327161 reduced GCGR mRNA in a dose-dependent manner.

Table 79: Antisense inhibition of GCGR in HepG2 cells by a short antisense compound

ISIS NO.	Seq ID NO	Sequence (5'-3')	Gapmer Motif	25 nM	50 nM	100 nM	200 nM
327161	520	AGCTGCTGTACATC	3-8-3 MOE	-36	-30	-33	-64

Monkey hepatocytes

Additional short antisense compounds targeted to a GCGR nucleic acid were tested for their effects on monkey GCGR mRNA *in vitro*. Cultured primary monkey hepatocytes were treated as described herein with 25, 50, 100 or 200 nM of short antisense compound. After the treatment period, RNA was isolated from the cells and GCGR mRNA levels were measured by quantitative real-time PCR, as described herein. GCGR mRNA levels were adjusted according to total RNA content as measured by RIBOGREEN®. Results are presented in Table 80 as percent reduction in GCGR mRNA, relative to untreated control cells.

Table 80: Antisense inhibition of GCGR in primary monkey hepatocytes by short antisense compounds

ISIS NO.	Seq ID NO	Sequence (5'-3')	Gapmer Motif	25 nM	50 nM	100 nM	200 nM
327131	489	ATGTTGGCCGTGGT	3-8-3 MOE	0	-8	-36	-36
327161	520	AGCTGCTGTACATC	3-8-3 MOE	-19	-33	-55	-54

Example 22: Antisense inhibition of DGAT2 by short antisense compounds

Short antisense compounds targeted to a DGAT2 nucleic acid were tested for their effects on DGAT2 mRNA *in vitro*. Cultured A10 cells in a 96-well plate were treated with 75 nM of short antisense compound. After a treatment period of approximately 24 hours, RNA was isolated from the cells and DGAT2 mRNA levels were measured by quantitative real-time PCR, as described herein. DGAT2 mRNA levels were adjusted according to total RNA content as measured by RIBOGREEN®. Results are presented as percent inhibition of DGAT2, relative to untreated control cells in Table 81.

Table 81: Antisense inhibition of DGAT2 in A10 cells

ISIS NO.	Seq ID NO	Sequence (5'-3')	Gapmer Motif	% Control
372491	795	ACATGAGGATGACACT	3-10-3 MOE	80
372500	702	GTGTGTCTTCACCAGC	3-10-3 MOE	16
372501	704	TTGTGTGTCTTCACCA	3-10-3 MOE	28
372503	708	GCAGGTTGTGTGTCTT	3-10-3 MOE	35
372508	719	AGTTCCTGGTGGTCAG	3-10-3 MOE	35
372516	805	TACAGAAGGCACCCAG	3-10-3 MOE	27
372524	738	GCCAGGCATGGAGCTC	3-10-3 MOE	21
372530	746	TCGGCCCCAGGAGCCC	3-10-3 MOE	35
372546	825	TTGGTCTTGTGATTGT	3-10-3 MOE	34
372563	691	AGCCAGGTGACAGA	2-10-2 MOE	48
372569	796	CATGAGGATGACAC	2-10-2 MOE	104
372578	703	TGTGTCTTCACCAG	2-10-2 MOE	59
372580	707	GGTTGTGTGTCTTC	2-10-2 MOE	48
372586	720	GTTCCTGGTGGTCA	2-10-2 MOE	40
372594	806	ACAGAAGGCACCCA	2-10-2 MOE	77
372602	739	CCAGGCATGGAGCT	2-10-2 MOE	39
372618	765	GTGGTACAGGTCGA	2-10-2 MOE	29
372624	826	TGGTCTTGTGATTG	2-10-2 MOE	56

Additional short antisense compounds targeted to DGAT2 mRNA were tested *in vitro* in a dose-response experiment. A10 cells were prepared as described above and treated with 6.25, 12.5, 25.0, 50.0, 100.0, and 200.0 nM short antisense compounds to determine if DGAT2 inhibition occurs in a dose-dependent manner. The data demonstrate that each of the short antisense compounds presented in Table 82 reduces rat DGAT2 mRNA in a dose-dependent manner. Results are presented as percent inhibition, relative to untreated control cells. A "0" indicates that DGAT2 mRNA was not reduced.

Table 82: Dose-Dependent Inhibition of DGAT2 in A10 cells

ISIS NO.	Seq ID NO	Sequence (5'-3')	Gapmer Motif	6.25 nM	12.5 nM	25.0 nM	50.0 nM	100.0 nM	200.0 nM
372562	784	GTCTTGGAGGGCCG	2-10-2 MOE	0	0	0	36	48	75
372568	794	GACACTGCAGGCCA	2-10-2 MOE	0	0	15	26	72	69
372586	720	GTTCCTGGTGGTCA	2-10-2 MOE	19	0	7	22	45	77
372602	739	CCAGGCATGGAGCT	2-10-2 MOE	0	0	0	18	47	76
372618	765	GTGGTACAGGTCGA	2-10-2	0	5	0	27	65	80

			MOE						

Additional short antisense compounds targeted to DGAT2 mRNA were tested *in vitro*. A10 cells were prepared as described above and treated with 0.62, 1.85, 5.56, 16.67, 50.0, and 150.0 nM short antisense compounds to determine if DGAT2 inhibition occurs in a dose-dependent manner. DGAT2 mRNA was measured using quantitative real-time PCR, as described herein. The data demonstrate that each of the short antisense compounds presented in Table 83 below inhibit rat DGAT2 mRNA in a dose-dependent manner. Results are presented as percent inhibition of rat DGAT2, relative to untreated control cells. Where present, "0" indicates that no reduction in DGAT2 mRNA was observed.

Table 83: Dose-Dependent Inhibition of DGAT2 in A10 cells

ISIS NO.	Seq ID NO	Sequence (5'-3')	Gapmer Motif	0.62 nM	1.85 nM	5.56 nM	16.67 nM	50 nM	150 nM
372500	702	GTGTGTCTTCACCAGC	3-10-3 MOE	0	0	0	18	64	88
372501	704	TTGTGTGTCTTCACCA	3-10-3 MOE	1	5	10	11	25	68
372503	708	GCAGGTTGTGTGTCTT	3-10-3 MOE	7	10	4	25	54	80
372508	719	AGTTCCTGGTGGTCAG	3-10-3 MOE	0	0	6	14	39	71
372516	805	TACAGAAGGCACCCAG	3-10-3 MOE	1	10	0	4	35	81
372524	738	GCCAGGCATGGAGCTC	3-10-3 MOE	7	0	5	30	68	91
372530	746	TCGGCCCCAGGAGCCC	3-10-3 MOE	0	2	0	10	38	78
372546	825	TTGGTCTTGTGATTGT	3-10-3 MOE	0	2	11	4	48	78
372563	691	AGCCAGGTGACAGA	2-10-2 MOE	0	0	0	1	4	46
372578	703	TGTGTCTTCACCAG	2-10-2 MOE	0	0	0	2	7	42
372580	707	GGTTGTGTGTCTTC	2-10-2 MOE	0	5	5	3	16	42
372586	720	GTTCCTGGTGGTCA	2-10-2 MOE	0	0	0	0	7	55
372594	806	ACAGAAGGCACCCA	2-10-2 MOE	0	0	0	0	2	15
372602	739	CCAGGCATGGAGCT	2-10-2 MOE	0	0	10	0	19	51
372618	765	GTGGTACAGGTCGA	2-10-2 MOE	0	0	0	0	30	60
372624	826	TGGTCTTGTGATTG	2-10-2 MOE	0	0	0	1	16	38

Example 23: Antisense inhibition of human PTP1B in HuVEC cells

Short antisense compounds targeted to a PTP1B nucleic acid were tested for their effects on

PTP1B mRNA *in vitro*. Cultured HuVEC cells at a density of 5000 cells per well in a 96-well plate were treated as described herein with 3 nM of short antisense compound. After the treatment period, RNA was isolated from the cells and PTP1B mRNA levels were measured by quantitative real-time PCR, as described herein. PTP1B mRNA levels were adjusted according to total RNA content as measured by RIBOGREEN®. Results are presented as percent inhibition of PTP1B (% Inhib), relative to untreated control cells. The data demonstrated that short antisense compounds targeted to a PTP1B nucleic acid and having a 2-10-2 gapmer motif can inhibit PTP1B in HuVEC cells in Table 84.

Table 84: Antisense inhibition of PTP1B in HuVEC cells by short antisense compounds

ISIS NO.	SEQ ID NO	Gapmer Motif	% Inhib
399301	1542	2-10-2 OMe	55
404137	1053	2-10-2 MOE	76
404138	1054	2-10-2 MOE	76
404139	1052	2-10-2 MOE	80
404140	1051	2-10-2 MOE	73

Example 24: Antisense inhibition of human PTP1B in HepG2 cells

Short antisense compounds targeted to a PTP1B nucleic acid were tested for their effects on PTP1B mRNA *in vitro*. Cultured HepG2 cells at a density of 10000 cells per well in a 96-well plate were treated with 25 nM of antisense oligonucleotide. After the treatment period, RNA was isolated from the cells and PTP1B mRNA levels were measured by quantitative real-time PCR, as described herein. PTP1B mRNA levels were adjusted according to total RNA content as measured by RIBOGREEN®. Results are presented as percent inhibition (% Inhib) of PTP1B, relative to untreated control cells. The data demonstrated that short antisense compounds targeted to a PTP1B nucleic acid and having a 2-10-2 gapmer motif can inhibit PTP1B in HepG2 cells in Table 85.

Table 85: Antisense inhibition of PTP1B in HepG2 cells by short antisense compounds

ISIS NO.	SEQ ID NO	Gapmer Motif	% Inhib
399301	1542	2-10-2 OMe	43
404137	1053	2-10-2 MOE	71
404138	1054	2-10-2 MOE	86
404139	1052	2-10-2 MOE	45
404140	1051	2-10-2 MOE	93

Example 25: Antisense inhibition of PTP1B in HuVEC cells: Dose response experiment

Human vascular endothelial (HuVEC) cells were plated at a density of 5000 cells per well and treated as described herein with nM concentrations of short antisense compound as indicated in Table 86.

After the treatment period, RNA was isolated from the cells and PTP1B mRNA levels were measured by quantitative real-time PCR, as described herein. PTP1B mRNA levels were adjusted according to total RNA content as measured by RIBOGREEN®. Two different human PTP1B primer probe sets were used to measure mRNA levels. Results with Primer Probe Set (PPS) 198 are shown in Table 86, and results with Primer Probe Set (PPS) 3000 are shown in Table 87. Results are presented as percent inhibition of PTP1B mRNA expression relative to untreated control cells. Where present, "0" indicates that no PTP1B mRNA reduction was observed. As illustrated in Tables 86 and 87, PTP1B mRNA levels were reduced in a dose-dependent manner.

Table 86: Dose Response for Human PTP1B in HuVEC cells, using PPS 198

			% Inhibition			
ISIS NO.	Seq ID NO	Gapmer Motif	1.11 nM	3.33 nM	10.0 nM	30.0 nM
398105	1066	2-10-2 MOE	0	25	79	90
398112	1072	2-10-2 MOE	1	10	73	93
398120	1086	2-10-2 MOE	0	31	80	96
399096	1544	2-10-2 MOE	3	30	78	96
399102	1545	2-10-2 MOE	0	15	62	88
399113	1547	2-10-2 MOE	0	31	72	90
399132	1548	2-10-2 MOE	0	32	75	95
399173	1549	2-10-2 MOE	0	24	63	89
399208	1550	2-10-2 MOE	0	37	86	93
399276	1551	2-10-2 MOE	0	8	61	89
399301	1542	2-10-2 MOE	8	63	91	97
399315	1552	2-10-2 MOE	0	20	68	88
398173	1543	1-10-1 MOE	0	4	80	97

Table 87: Dose Response for Human PTP1B in HuVEC cells, using PPS 3000

			% Inhibition			
ISIS NO.	Seq ID NO	Gapmer Motif	1.11 nM	3.33 nM	10.0 nM	30.0 nM
398105	1066	2-10-2 MOE	0	35	79	93
398112	1072	2-10-2 MOE	0	26	77	94
398120	1086	2-10-2 MOE	0	35	79	93
399096	1544	2-10-2 MOE	0	23	75	94
399102	1545	2-10-2 MOE	0	9	60	87
399113	1547	2-10-2 MOE	0	9	65	90
399132	1548	2-10-2 MOE	0	26	76	91
399173	1549	2-10-2 MOE	0	11	59	92
399208	1550	2-10-2 MOE	0	47	85	96
399276	1551	2-10-2 MOE	0	14	64	86
399301	1542	2-10-2 MOE	16	65	93	99
399315	1552	2-10-2 MOE	0	25	71	93
398173	1543	1-10-1 MOE	0	18	80	90

Example 26: Antisense inhibition of ApoB by short antisense compounds

The short antisense compounds shown in Table 88 were tested for their effects in vivo. Six-week old male Balb/c mice (Jackson Laboratory, Bar Harbor, ME) were administered intraperitoneal doses of 3.2, 1, 0.32, or .1 umol/kg, twice per week for three weeks. A 5-10-5 MOE gapmer was used for a control treatment. Mice were sacrificed approximately 48 hours following the final dose. Liver tissue was collected for RNA isolation, and blood was collected for serum chemistry analyses. ApoB mRNA levels were measured by real-time PCR as described herein. ApoB mRNA levels were normalized to RNA levels as determined by RIBOGREEN, and are presented in Table 89 as percent inhibition relative to ApoB mRNA levels in saline-treated control animals.

Table 88: Short Antisense Compounds Targeting an ApoB nucleic acid

ISIS NO	Sequence (5'-3')	Gapmer Motif	SEQ ID NO
387462	GGTACATGGAAGTC	2-10-2 Methyleneoxy BNA	190
398296	GGTACATGGAAGTC	2-10-2 6'-(*S*)-methyl Methyleneoxy BNA	190

Table 89: Antisense inhibition of ApoB by Short Antisense Compounds Comprising BNA

Isis No	Dose (umol/kg)	% Inhib
379818	1	56
387462	0.1	33
	0.32	57
	1	93
	3.2	99
398296	0.1	17
	0.32	35
	1	80
	3.2	98

Table 89 shows that ApoB mRNA levels were reduced in a dose-dependent manner following treatment with short antisense compounds having a 2-10-2 gapmer motif and BNA modifications in the wings. At the 1 umol/kg dose, ApoB inhibition by the short antisense compounds was greater than observed with a 5-10-5 MOE gapmer at an equivalent dose. Cholesterol was reduced at the 1 and 3.2 umol/kg doses of short antisense compound.

The short antisense compounds exhibited little to no adverse side effects, as judged by organ and body weights, serum transaminases, bilirubin, blood urea nitrogen, and creatinine.

Example 27: Antisense inhibition of PTEN by short antisense compounds

The short antisense compounds shown in Table 90 were tested for their effects in vivo. Six-week old male Balb/c mice (Jackson Laboratory, Bar Harbor, ME) were administered intraperitoneal doses of 3.2, 1, 0.32, or .1 umol/kg, twice per week for three weeks. A 5-10-5 MOE gapmer was used for a control treatment. Mice were sacrificed approximately 48 hours following the final dose. Liver tissue was collected for RNA isolation, and blood was collected for serum chemistry analyses. PTEN mRNA levels were measured by real-time PCR as described herein. PTEN mRNA levels were normalized to RNA levels as determined by RIBOGREEN, and are presented in Table 91 as percent inhibition relative to PTEN mRNA levels in saline-treated control animals.

Table 90: Short Antisense Compounds targeted to a PTEN nucleic acid

ISIS NO	Sequence (5'-3')	Gapmer Motif	SEQ ID NO
392063	AGGCCAGTGCTAAG	2-10-2 Methyleneoxy BNA	1226
392749	AGGCCAGTGCTAAG	2-10-2 (6'S)-6'-methyl Methyleneoxy BNA	1226
396006	AGGCCAGTGCTAAG	2-10-2 alpha-L-methyleneoxy BNA	1226

Table 91: Antisense inhibition of PTEN by short antisense compounds comprising BNA modifications

Isis No	Dose (umol/kg)	% Inhib
116847	1	47
392063	0.1	26
	0.32	43
	1	74
	3.2	96
392749	0.1	17
	0.32	34
	1	64
	3.2	96
396006	0.1	20
	0.32	32
	1	67
	3.2	88

Table 91 shows that PTEN mRNA levels were reduced in a dose-dependent manner following treatment with short antisense compounds having a 2-10-2 gapmer motif and BNA modifications in the wings. At the 1 umol/kg dose, PTEN inhibition by the short antisense compounds was greater than observed with a 5-10-5 MOE gapmer at an equivalent dose.

With the exception of the highest dose of ISIS 392063, no significant increases in serum transaminases were observed. Overall, the short antisense compounds exhibited little to no adverse side effects.

Example 28: Single dose administration of short antisense compounds comprising BNA modifications

Six-week old male Balb/c mice (Jackson Laboratory, Bar Harbor, ME) were administered a single intraperitoneal injection of short antisense compound at a dose of 8, 4, 2 or 1 μmol/kg. The short antisense compounds tested were ISIS 387462 and ISIS 398296. Each dose group consisted of four animals. A 5-10-5 MOE gapmer was used for a control treatment. Mice were sacrificed approximately 48 hours following the final dose. Liver tissue was collected for RNA isolation, and blood was collected for serum chemistry analyses. ApoB mRNA levels were measured by real-time PCR as described herein. ApoB mRNA levels were normalized to RNA levels as determined by RIBOGREEN, and are presented in Table 92 as percent inhibition relative to ApoB mRNA levels in saline-treated control animals.

Table 92: Antisense inhibition of ApoB by Short Antisense Compounds Comprising BNA

Isis No	Dose (umol/kg)	% Inhib
379818	8	77
387462	8	99
	4	93
	2	81
	1	58
398296	8	97
	4	81
	2	54
	1	19

Table 92 shows that ApoB mRNA levels were reduced in a dose-dependent manner following a single administration of short antisense compounds having a 2-10-2 gapmer motif and BNA modifications in the wings. At the 8 umol/kg dose, ApoB inhibition by the short antisense compounds was greater than observed with a 5-10-5 MOE gapmer at an equivalent dose. The ED_{50} of ISIS 387462 was 3.9 mg/kg, and the ED_{50} of ISIS 398296 was 8.7 mg/kg. Cholesterol was also reduced in a dose-dependent manner. Triglycerides were reduced at the highest dose.

The short antisense compounds exhibited little to no adverse side effects, as judged by organ and body weights, serum transaminases, bilirubin, blood urea nitrogen, and creatinine.

In a similar single dose administration study, ISIS 392748, having SEQ ID NO: 1226, a 2-10-2 gapmer motif, where the nucleotides of the wings comprise (6'R)-6'-methyl methyleneoxy BNA modifications, reduced PTEN mRNA in a dose-dependent manner. Additionally, ISIS 392749, having SEQ ID NO: 1226, a 2-10-2 gapmer motif, where the nucleotides of the wings comprise (6'S)-6'-methyl methyleneoxy BNA modifications, reduced PTEN mRNA in a dose-dependent manner. A short antisense compound having 2-10-2 gapmer motifs, the sequence of SEQ ID NO: 1226, and 6-(S)-CH2-O-CH3-BNA modifications also reduced PTEN mRNA in a similar *in vivo* study. A short antisense compound having 2-10-2 gapmer motifs, the sequence of SEQ ID NO: 1226, and 6-(R)-CH2-O-CH3-BNA modifications also reduced PTEN mRNA in a similar *in vivo* study.

Example 29: Single dose administration of short antisense compounds comprising BNA modifications

Six-week old male Balb/c mice (Jackson Laboratory, Bar Harbor, ME) were administered a single intraperitoneal injection of antisense compound at a dose of 8, 4, 2 or 1 μmol/kg. Each dose group consisted of four animals. The compounds tested were ISIS 392063, ISIS 392749, and ISIS 366006. A 5-10-5 MOE gapmer was used for a control treatment. Mice were sacrificed approximately 48 hours following the final dose. Liver tissue was collected for RNA isolation, and blood was collected for serum chemistry analyses. ApoB mRNA levels were measured by real-time PCR as described herein. ApoB mRNA levels were normalized to RNA levels as determined by RIBOGREEN, and are presented in Table 93 as percent inhibition relative to ApoB mRNA levels in saline-treated control animals.

Table 93: Antisense inhibition of PTEN by short antisense compounds comprising BNA modifications

Isis No	Dose (umol/kg)	% Inhib
116847	8	62
392063	8	92
	4	82
	2	58
	1	38
396565	8	76
	4	38
	2	24
	1	11

396006	8	94
	4	82
	2	48
	1	18

Table 93 shows that PTEN mRNA levels were reduced in a dose-dependent manner following treatment with short antisense compounds having a 2-10-2 gapmer motif and BNA modifications in the wings. At the 8 umol/kg dose, PTEN inhibition by the short antisense compounds was greater than observed with a 5-10-5 MOE gapmer at an equivalent dose. The estimated ED_{50}s were 7 mg/kg for ISIS 392063, 17.4 mg/kg for ISIS 396565, and 9.3 mg/kg for ISIS 396006.

With the exception of the highest dose of ISIS 392063, no significant increases in serum transaminases were observed. Overall, the short antisense compounds exhibited little to no adverse side effects.

Example 30: Antisense inhibition of ApoB by short antisense compounds comprising palmitic acid conjugates

Six-week old male Balb/c mice (Jackson Laboratory, Bar Harbor, ME) were administered a single intraperitoneal injection of antisense compound at a dose of 2.5, 1.0. 0.4, and 0.16 umol/kg. Each dose group consisted of four animals. The compounds tested are shown in Table 94. A 5-10-5 MOE gapmer was used for a control treatment. Mice were sacrificed approximately 48 hours following the final dose. Liver tissue was collected for RNA isolation, and blood was collected for serum chemistry analyses. ApoB mRNA levels were measured by real-time PCR as described herein. ApoB mRNA levels were normalized to RNA levels as determined by RIBOGREEN, and are presented in Table 95 as percent inhibition relative to ApoB mRNA levels in saline-treated control animals.

Table 94: Short antisense compounds comprising palmitic conjugates

ISIS NO	Sequence (5'-3')	Gapmer Motif	SEQ ID NO
387462	GGTACATGGAAGTC	2-10-2 Methyleneoxy BNA	190
391871	GGTACATGGAAGTC	1-1-10-2 2'-(butylacetomido)-palmitamide/MOE/MOE Unmodified cytosines in gap (i.e., 2-10-2 MOE with 2'-(butylacetomido)-palmitamide substituted at 5' nucleotide	190
391872	GGTACATGGAAGTC	1-1-10-2 2'-(butylacetomido)-palmitamide Methyleneoxy BNA/Methyleneoxy BNA Unmodified cytosines in gap (i.e., 2-10-2 methyleneoxy BNA with 2'-(butylacetomido)-palmitamide substituted at 5' nucleotide)	190

Table 95: Antisense inhibition by short antisense compounds comprising palmitic acid conjugates

Isis No	Dose (umol/kg)	% Inhib
5-10-5	2.5	54
387462	2.5	99
	1.0	91
	0.4	65
	0.16	16
391871	2.5	49
	1.0	18
	0.4	5
	0.16	0
391872	2.5	99
	1.0	92
	0.4	50
	0.16	18

Table 95 shows that ApoB mRNA levels were reduced in a dose-dependent manner following treatment with short antisense compounds having a palmitic acid (C16) conjugate. At the 2.5 umol/kg dose, ApoB inhibition by the short antisense compounds was greater than observed with a 5-10-5 MOE gapmer at an equivalent dose. In this study, the estimated ED_{50}s were 1.5 mg/kg for ISIS 387462, 13.1 mg/kg for ISIS 391871, and 1.9 mg/kg for ISIS 391872. The estimated ED_{50} for the 5-10-5 MOE gapmer was 17.4 mg/kg. Triglycerides were reduced at the 2.5 and 1.0 mg/kg doses of ISIS 387462 and ISIS 391872. ISIS 387462 and ISIS 391872 markedly reduced total cholesterol, HDL-C and LDL-C in a dose-dependent manner; reduction in LDL-C was so marked that it fell below the limit of detection. Overall, the short antisense compounds exhibited little to no adverse effects.

Example 31: Antisense inhibition of PCSK9 in vivo by short antisense compounds comprising BNA modifications

Six-week old male Balb/c mice (Jackson Laboratory, Bar Harbor, ME) were administered a single intraperitoneal injection of antisense compound at a dose of 15, 4.7, 1.5 and .47 umol/kg of ISIS 403739 or 403740. Each dose group consisted of four animals. A 5-10-5 MOE gapmer was used for a control treatment. Mice were sacrificed approximately 72 hours following the final dose. Liver tissue was collected for RNA isolation, and blood was collected for serum chemistry analyses. PCSK9 mRNA levels were measured by real-time PCR as described herein. PCSK9 mRNA levels were normalized to cyclophilin mRNA levels as determined by real-time PCR. ISIS 403739 reduced PCSK9 mRNA by approximately 70%, relative to saline controls. ISIS 403740 reduced PCSK9 by approximately 13% relative to saline controls, however, the reduction was not statistically significant. The lower doses did not significantly reduce PCSK9 mRNA. Overall, the short antisense compounds exhibited little to no adverse side effects.

1. A short antisense compound 8 to 16 monomers in length, comprising a 2'-deoxyribonucleotide gap region flanked on each side by a wing, wherein each wing independently comprises 1 to 3 high-affinity modified monomers and wherein the short antisense compound is targeted to a nucleotide encoding ApoB.
2. The short antisense compound of claim 1, wherein said high-affinity modified monomers are sugar-modified nucleotides.
3. The short antisense compound of claim 2, wherein at least one of the sugar-modified nucleotides comprises a bridge between the 4' and the 2' position of the sugar.
4. The short antisense compound of claim 2, wherein each of said high-affinity modified nucleotides confers a T_m of 1 to 4 degrees per nucleotide.
5. The short antisense compound of claim 2, wherein each of said sugar-modified nucleotides comprises a 2'-substituent group that is other than H or OH.
6. The short antisense compound of claim 5, wherein at least one of said sugar-modified nucleotides is a 4' to 2' bridged bicyclic nucleotide.
7. The short antisense compound of claim 5, wherein each of the 2'-substituent groups is, independently, alkoxy, substituted alkoxy, or halogen.
8. The short antisense compound of claim 7, wherein each of the 2'-substituent groups is $OCH_2CH_2OCH_3$.
9. The short antisense compound claim 3, wherein the conformation of each of said sugar-modified nucleotides is, independently, β-D or α-L.
10. The short antisense compound claim 5, wherein each of said bridges independently comprises 1 or from 2 to 4 linked groups independently selected from $-[C(R_1)(R_2)]_n-$, $-C(R_1)=C(R_2)-$, $-C(R_1)=N-$, $-C(=NR_1)-$, $-C(=O)-$, $-C(=S)-$, $-O-$, $-Si(R_1)_2-$, $-S(=O)_x-$ and $-N(R_1)-$;

wherein

x is 0, 1, or 2;

n is 1, 2, 3, or 4;

each R_1 and R_2 is, independently, H, a protecting group, hydroxyl, C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, substituted C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, substituted C_2-C_{12} alkynyl, C_5-C_{20} aryl, substituted C_5-C_{20} aryl, 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.

11. The short antisense compound of claim 10, wherein each of said bridges is, independently, 4'-CH_2-2', 4'-$(CH_2)_2$-2', 4'-CH_2-O-2', 4'-$(CH_2)_2$-O-2', 4'-CH_2-O-N(R_1)-2' and 4'-CH_2-N(R_1)-O-2'- wherein each R_1 is, independently, H, a protecting group or C_1-C_{12} alkyl.
12. The short antisense compound of claim 1, wherein each of the high-affinity modified monomer is independently selected from bicyclic nucleotides or other 2'-modified nucleotides.
13. The short antisense compound of claim 12, wherein the 2'-modified nucleotides are selected from halogen, allyl, amino, azido, thio, O-allyl, O-C_1-C_{10} alkyl, -OCF_3, O-$(CH_2)_2$-O-CH_3, 2'-O$(CH_2)_2SCH_3$, O-$(CH_2)_2$-O-N(R_m)(R_n) or O-CH_2-C(=O)-N(R_m)(R_n), where each R_m and R_n is, independently, H or substituted or unsubstituted C_1-C_{10} alkyl.
14. The short antisense compound of claim 13, wherein the 2'-modified nucleotide is a 2'-$OCH_2CH_2OCH_3$ nucleotide.
15. The short antisense compound of claim 1, wherein at least one monomeric linkage is a modified monomeric linkage.
16. The antisense compound of claim 15, wherein the modified monomeric linkage is a phosphorothioate linkage.
17. The short antisense compound of claim 1, wherein each monomeric linkage is a phosphorothioate internucleoside linkage.
18. The short antisense compound of any of claims 1-17, that is 8-15 monomers in length.
19. The short antisense compound of claim 18 that is 9-15 monomers in length.
20. The short antisense compound of claim 18 that is 10-15 monomers in length.
21. The short antisense compound of claim 18 that is 9-14 monomers in length.
22. The short antisense compound of claim 18 that is 10-14 monomers in length.
23. The short antisense compound of claim 18 that is 9-13 monomers in length.
24. The short antisense compound of claim 18 that is 10-13 monomers in length.
25. The short antisense compound of claim 18 that is 9-12 monomers in length.
26. The short antisense compound of claim 18 that is 10-12 monomers in length.
27. The short antisense compound of claim 18 that is 9-11 monomers in length.
28. The short antisense compound of claim 18 that is 10-11 monomers in length.
29. The short antisense compound of claim 18 that is 8 monomers in length.
30. The short antisense compound of claim 18 that is 9 monomers in length.
31. The short antisense compound of claim 18 that is 10 monomers in length.
32. The short antisense compound of claim 18 that is 11 monomers in length.
33. The short antisense compound of claim 18 that is 12 monomers in length.
34. The short antisense compound of claim 18 that is 13 monomers in length.
35. The short antisense compound of claim 18 that is 14 monomers in length.
36. The short antisense compound of claim 18 that is 15 monomers in length.

37. The short antisense compound of claim 18 that is 16 monomers in length.
38. The short antisense compound of any of claims 1-18, having a motif selected from 1-12-1; 3-10-3; 2-10-3; 2-10-2; 1-10-1; 1-10-2; 3-8-3; 2-8-2; 1-8-1; 3-6-3; and 1-6-11 wherein, the first number represents the number of monomers in the 5'-wing, the second number represents the number of monomers in the gap, and the third number represents the number of monomers in the 3' wing.
39. The short antisense compound of claim 38 wherein the motif is selected from 1-10-1; 2-10-2; 3-10-3; and 1-9-2.
40. The short antisense compound of any of claims 1-18 having a motif selected from 1-1-10-2, 1-1-8-2, 1-1-6-3, and 1-2-8-2, wherein the first number represents the number of monomers in a first 5' wing, the second number represents the number of monomers in a second 5' wing, the third number represents the number of monomers in the gap, and the fourth number represents the number of monomers in the 3' wing.
41. The short antisense compound of any of claims 1-18 having a motif selected from 2-10-1-1, 2-8-1-1, 3-6-1-1,and 2-8-2-1, wherein the first number represents the number of monomers in the 5' wing, the second number represents the number of monomers in the gap, the third number represents the number of monomers in a first 3' wing, and the fourth number represents the number of monomers in a second 3' wing.
42. The short antisense compound of any of claims 1-18 having a motif selected from 1-2-10-1-1; 1-1-8-1-1; 2-1-6-1-1; and 1- 2-8-2-1, wherein the first number represents the number of monomers in a first 5' wing, the second number represents the number of monomers in a second 5' wing, the third number represents the number of monomers in the gap, the fourth number represents the number of monomers in a first 3' wing and the fifth number represents the number of monomers in a second 3'wing.
43. A method of modulating expression of a ApoB by contacting a nucleic acid encoding ApoB with a short antisense compound.
44. The method of claim 43 wherein the ApoB nucleic acid is in a cell.
45. The method of claim 44, wherein the ApoB nucleic acid is in an animal.
46. The method of claim 45, wherein the animal is a human.
47. The method of any of claims 43-48, wherein the short antisense compound is the short antisense compound of any of claims 1-38.
48. Use of the short antisense compound of any of claims 1-42 for the preparation of a medicament for reducing the expression of ApoB RNA in an animal.
49. The use of claim 48, wherein the medicament decreases total serum cholesterol, serum LDL, serum VLDL, serum HDL, serum triglycerides, serum apolipoprotein(a) and/or free fatty acids in an animal.
50. A method of inhibiting expression of ApoB RNA in an animal, comprising administering to said animal the short antisense compound of any of claims 1-42.

51. A method of treating a cardiovascular disorder in an animal, comprising administering to an animal in need of such therapy the short antisense compound of any of claims 1-42.