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(54) Title: CAMK2D ANTISENSE OLIGONUCLEOTIDES AND USES THEREOF

(57) Abstract: The present disclosure relates to antisense oligonucleotides, which target CAMK2D mRNA in a cell, leading to reduced expression of CAMK2D protein. Reduction of CAMK2D protein expression is beneficial for the treatment of certain medical disorders, e.g., cardiovascular-related diseases or disorders.



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CAMK2D ANTISENSE OLIGONUCLEOTIDES AND USES THEREOF

REFERENCE TO SEQUENCE LISTING SUBMITTED
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[0001] The content of the electronically submitted sequence listing (Name: 3338_102PC04_SequenceListing_ST25.txt, Size: 746,302 bytes; and Date of Creation: February 20, 2019) submitted in this application is incorporated herein by reference in its entirety.

FIELD OF DISCLOSURE

[0002] The present disclosure relates to antisense oligomeric compounds (ASOs) that target calcium/calmodulin-dependent protein kinase type II delta (*CAMK2D*) transcript in a cell, leading to reduced expression of CAMK2D protein. Reduction of CAMK2D protein expression can be beneficial for a range of medical disorders, such as cardiovascular-related diseases or disorders.

BACKGROUND

[0003] Calcium/calmodulin ($\text{Ca}^{2+}/\text{CaM}$)-dependent serine/threonine kinases (CaMKs) constitute a family of 81 proteins in the human proteasome that play a central role in cellular signaling by transmitting Ca^{2+} signals. Four CaMKII isozymes (α , β , γ , and δ), in addition to about 30 splice variants, are expressed in humans. Braun, A.P., *et al.*, *Annual Review of Physiology* 57:417-445 (1995). Of these, CaMKII δ ("CAMK2D") protein is the most abundant isoform in the heart and plays an important role in the excitation-contraction coupling (ECC) and relaxation processes of normal cardiac physiology. Mattiazzi A., *et al.*, *Am J Physiol Heart Circ Physiol* 308:H1177-H1191 (2015). CAMK2D activity has also been described as being important in the recovery process after certain heart related injury (*e.g.*, ischemia-reperfusion injury). Said M., *et al.*, *Am J Physiol Heart Circ Physiol* 285:H1198-205 (2003).

[0004] Despite various scientific advancements, heart-related diseases remain the leading cause of death for both men and women worldwide. The American Heart Association estimates that by 2030, nearly 40% of the U.S. population would have some form of a cardiovascular disease and the direct medical costs are projected to reach \$818 billion.

See Benjamin, E.J., *et al.*, *Circulation* 135:e146-e603 (2017). However, Mattiazzi *et al.* notes that "[t]he ubiquitous nature of CaMKII and its effects on different protein targets challenge the use of CaMKII inhibitors as a therapeutic tool." *Am J Physiol Heart Circ Physiol* 308:H1177-H1191 (2015). Therefore, new treatment options that are much more robust and cost-effective are highly desirable.

SUMMARY OF DISCLOSURE

[0005] The present disclosure is directed to an antisense oligonucleotide (ASO) comprising, consisting essentially of, or consisting of the contiguous nucleotide sequence of 10 to 30 nucleotides in length that is complementary, such as fully complementary, to a nucleic acid sequence within a calcium/calmodulin-dependent protein kinase type II delta (CAMK2D) transcript. In some embodiments, the ASO of the present disclosure, or contiguous nucleotide sequence thereof, is at least about 80%, at least about 85%, at least about 90%, at least about 95%, or about 100% complementary to the nucleic acid sequence within the *CAMK2D* transcript. In some embodiments, the *CAMK2D* transcript is selected from the group consisting of SEQ ID NO: 1 and SEQ ID NO: 2.

[0006] In some embodiments, the ASO described herein is capable of reducing CAMK2D protein expression in a human cell (*e.g.*, HEK293 cell) which is expressing the CAMK2D protein. In some embodiments, the CAMK2D protein expression is reduced by at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or about 100% compared to CAMK2D protein expression in a human cell that is not exposed to the ASO.

[0007] In some embodiments, the ASO is capable of reducing *CAMK2D* transcript (*e.g.*, mRNA) expression in a human cell (*e.g.*, HEK293 cell), which is expressing the CAMK2D transcript. In some embodiments, the *CAMK2D* transcript expression is reduced by at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or about 100% compared to *CAMK2D* transcript expression in a human cell that is not exposed to the ASO.

- [0008] In some embodiments, the ASO disclosed herein is a gapmer. In some embodiments, the ASO has a design of $LLLD_nLLL$, $LLLLD_nLLLL$, or $LLLLLD_nLLLLL$, wherein the L is a nucleoside analog, the D is DNA, and n can be any integer between 4 and 24. In some embodiments, n can be any integer between 6 and 14. In some embodiments, n can be any integer between 8 and 12.
- [0009] In some embodiments, the nucleoside analog of the ASO disclosed herein comprises a 2'-O-alkyl-RNA; 2'-O-methyl RNA (2'-OMe); 2'-alkoxy-RNA; 2'-O-methoxyethyl-RNA (2'-MOE); 2'-amino-DNA; 2'-fluoro-RNA; 2'-fluoro-DNA; arabino nucleic acid (ANA); 2'-fluoro-ANA; or bicyclic nucleoside analog (LNA). In some embodiments, one or more of the nucleoside analog of the ASO is a sugar modified nucleoside. In some embodiments, the sugar modified nucleoside is an affinity enhancing 2' sugar modified nucleoside. In some embodiments, one or more of the nucleoside analog comprises a nucleoside comprising a bicyclic sugar. In some embodiments, the affinity enhancing 2' sugar modified nucleoside is an LNA. In some embodiments, the LNA is selected from the group consisting of constrained ethyl nucleoside (cEt), 2',4'-constrained 2'-O-methoxyethyl (cMOE), α -L-LNA, β -D-LNA, 2'-O,4'-C-ethylene-bridged nucleic acids (ENA), amino-LNA, oxy-LNA, thio-LNA, or any combination thereof. In some embodiments, the ASO comprises one or more 5'-methyl-cytosine nucleobases.
- [0010] In some embodiments, the ASO described herein is capable of (i) reducing an mRNA level encoding CAMK2D in human Inducible Pluripotent Stem Cell-Derived Cardiomyocytes (hiPSC-CM); (ii) reducing a protein level of CAMK2D in hiPSC-CM; (iii) reducing, ameliorating, or treating one or more symptoms of a cardiovascular disease or disorder, and (iv) any combination thereof.
- [0011] In some embodiments, the contiguous nucleotide sequence of the ASO is complementary to a nucleic acid sequence comprising (i) nucleotides 625 – 842 of SEQ ID NO: 1; (ii) nucleotides 1,398 – 59,755 of SEQ ID NO: 1; (iii) nucleotides 61,817 – 104,725 of SEQ ID NO: 1; (iv) nucleotides 112,162 – 118,021 of SEQ ID NO: 1; (v) nucleotides 119,440 – 135,219 of SEQ ID NO: 1; (vi) nucleotides 137,587 – 157,856 of SEQ ID NO: 1; (vii) nucleotides 159,191 – 266,174 of SEQ ID NO: 1; or (viii) nucleotides 272,788 – 310,949 of SEQ ID NO: 1. In some embodiments, the contiguous nucleotide sequence of the ASO is complementary to a nucleic acid sequence comprising (i) nucleotides 675 – 792 of SEQ ID NO: 1; (ii) nucleotides 1,448 – 59,705 of SEQ ID NO: 1; (iii) nucleotides 61,867 – 104,675 of SEQ ID NO: 1; (iv) nucleotides 112,212 –

117,971 of SEQ ID NO: 1; (v) nucleotides 119,490 – 135,169 of SEQ ID NO: 1; (vi) nucleotides 137,637 – 157,806 of SEQ ID NO: 1; (vii) nucleotides 159,241 – 266,124 of SEQ ID NO: 1; or (viii) nucleotides 272,838 – 310,899 of SEQ ID NO: 1. In some embodiments, the contiguous nucleotide sequence of the ASO is complementary to a nucleic acid sequence comprising (i) nucleotides 725 – 742 of SEQ ID NO: 1; (ii) nucleotides 1,498 – 59,655 of SEQ ID NO: 1; (iii) nucleotides 61,917 – 104,625 of SEQ ID NO: 1; (iv) nucleotides 112,262 – 117,921 of SEQ ID NO: 1; (v) nucleotides 119,540 – 135,119 of SEQ ID NO: 1; (vi) nucleotides 137,687 – 157,756 of SEQ ID NO: 1; (vii) 159,291 – 266,074 of SEQ ID NO: 1; or (viii) nucleotides 272,888 – 310,849 of SEQ ID NO: 1.

[0012] In some embodiments, the contiguous nucleotide sequence of the ASO comprises SEQ ID NO: 4 to SEQ ID NO: 1713 with one or two mismatches. In some embodiments, the contiguous nucleotide sequence of the ASO comprises the nucleotide sequence selected from the sequences in FIGs. 1A and 1B (SEQ ID NO: 4 to SEQ ID NO: 1713). In some embodiments, the contiguous nucleotide sequence of the ASO comprises SEQ ID NO: 25, SEQ ID NO: 27, SEQ ID NO: 114, SEQ ID NO: 158, SEQ ID NO: 190, SEQ ID NO: 327, SEQ ID NO: 463, SEQ ID NO: 513, SEQ ID NO: 516, SEQ ID NO: 519, SEQ ID NO: 657, SEQ ID NO: 659, SEQ ID NO: 827, SEQ ID NO: 1249, SEQ ID NO: 1326, SEQ ID NO: 1409, SEQ ID NO: 1524, SEQ ID NO: 1530, SEQ ID NO: 1662, or SEQ ID NO: 1676. In some embodiments, the contiguous nucleotide sequence of the ASO comprises SEQ ID NO: 55, SEQ ID NO: 61, SEQ ID NO: 63, SEQ ID NO: 71, SEQ ID NO: 75, SEQ ID NO: 79, SEQ ID NO: 84, SEQ ID NO: 85, SEQ ID NO: 92, SEQ ID NO: 102, SEQ ID NO: 105, SEQ ID NO: 128, SEQ ID NO: 130, SEQ ID NO: 133, SEQ ID NO: 138, SEQ ID NO: 161, SEQ ID NO: 178, SEQ ID NO: 180, SEQ ID NO: 186, SEQ ID NO: 195, SEQ ID NO: 200, SEQ ID NO: 202, SEQ ID NO: 234, SEQ ID NO: 264, SEQ ID NO: 387, SEQ ID NO: 390, SEQ ID NO: 396, SEQ ID NO: 441, SEQ ID NO: 446, SEQ ID NO: 457, SEQ ID NO: 467, SEQ ID NO: 523, SEQ ID NO: 524, SEQ ID NO: 636, SEQ ID NO: 640, SEQ ID NO: 700, SEQ ID NO: 740, SEQ ID NO: 832, SEQ ID NO: 965, SEQ ID NO: 1015, SEQ ID NO: 1065, SEQ ID NO: 1071, SEQ ID NO: 1155, SEQ ID NO: 1475, SEQ ID NO: 1508, SEQ ID NO: 1685, SEQ ID NO: 1686, SEQ ID NO: 1687, SEQ ID NO: 1688, or SEQ ID NO: 1690.

[0013] In some embodiments, the ASO of the present disclosure has a design selected from the group consisting of the designs in FIG. 3, wherein the upper letter is a sugar modified nucleoside and the lower case letter is DNA.

- [0014] In some embodiments, the ASO disclosed herein is capable of reducing expression of CAMK2D protein in a hiPSC-CM cell which is expressing the CAMK2D protein. In some embodiments, the expression of CAMK2D protein is reduced by at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100% compared to a cell not exposed to the ASO. In some embodiments, the ASO is capable of reducing expression of *CAMK2D* transcript (*e.g.*, mRNA) in a hiPSC-CM cell which is expressing the *CAMK2D* transcript. In some embodiments, the expression of *CAMK2D* transcript is reduced by at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100% compared to a cell not exposed to the ASO.
- [0015] In some embodiments, the ASO has from 14 to 20 nucleotides in length. In some embodiments, the nucleotide sequence of the ASO comprises one or more modified internucleoside linkage. In some embodiments, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or 100% of internucleoside linkages are modified. In certain embodiments, each of the internucleotide linkages in the ASO of the present disclosure is a phosphorothioate linkage.
- [0016] The present disclosure also provides a conjugate comprising the ASO as disclosed herein, wherein the ASO is covalently attached to at least one non-nucleotide or non-polynucleotide moiety. In some embodiments, the non-nucleotide or non-polynucleotide moiety comprises a protein, a fatty acid chain, a sugar residue, a glycoprotein, a polymer, or any combinations thereof.
- [0017] Also provided herein is a pharmaceutical composition comprising the ASO or the conjugate as disclosed herein and a pharmaceutically acceptable diluent, carrier, salt, or adjuvant. In certain embodiments, a pharmaceutically acceptable salt comprises a sodium salt, a potassium salt, or an ammonium salt. In some embodiments, the pharmaceutical composition further comprises at least one further therapeutic agent. In some embodiments, the further therapeutic agent is a CAMK2D antagonist. In some embodiments, the CAMK2D antagonist is an anti-CAMK2d antibody or fragment thereof.
- [0018] The present disclosure further provides a kit comprising the ASO, the conjugate, or the pharmaceutical composition as disclosed herein, and instructions for use. Also disclosed is a diagnostic kit comprising the ASO, the conjugate, or the pharmaceutical composition of the present disclosure, and instructions for use.

[0019] The present disclosure is also directed method of inhibiting or reducing CAMK2D protein expression in a cell, comprising administering the ASO, the conjugate, or the pharmaceutical composition disclosed herein to the cell expressing CAMK2D protein, wherein the CAMK2D protein expression in the cell is inhibited or reduced after the administration. In some aspect, the present disclosure is directed to an *in vitro* method of inhibiting or reducing CAMK2D protein expression in a cell, comprising contacting the ASO, the conjugate, or the pharmaceutical composition disclosed herein to the cell expressing CAMK2D protein, wherein the CAMK2D protein expression in the cell is inhibited or reduced after the contacting. In some embodiments, the ASO inhibits or reduces expression of *CAMK2D* transcript (*e.g.*, mRNA) in the cell after the administration. In some embodiments, the expression of *CAMK2D* transcript (*e.g.*, mRNA) is reduced by at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100% after the administration compared to a cell not exposed to the ASO. In some embodiments, the expression of CAMK2D protein is reduced by at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% after the administration compared to a cell not exposed to the ASO. In some embodiments, the cell is a cardiac cell, *e.g.*, hiPSC-CM.

[0020] Provided herein is a method of reducing, ameliorating, or treating one or more symptoms of a cardiovascular disease or disorder in a subject in need thereof, comprising administering an effective amount of the ASO, the conjugate, or the pharmaceutical composition of the present disclosure to the subject. The present disclosure also provides the use of the ASO, the conjugate, or the pharmaceutical composition disclosed herein for the manufacture of a medicament. In some embodiments, the medicament is for the treatment of a cardiovascular disease or disorder in a subject in need thereof. In some embodiments, the ASO, the conjugate, or the pharmaceutical composition of the present disclosure is for use in therapy. In some embodiments, the ASO, the conjugate, or the pharmaceutical composition disclosed herein is for use in therapy of a cardiovascular disease or disorder in a subject in need thereof.

[0021] In some embodiments, the cardiovascular disease or disorder comprises a coronary artery disease, stroke, heart failure, hypertensive heart disease, rheumatic heart disease, cardiomyopathy, heart arrhythmia, congenital heart disease, valvular heart disease, carditis, aortic aneurysms, peripheral artery disease, thromboembolic disease, venous

thrombosis, or any combination thereof. In some embodiments, the cardiovascular disease or disorder is a heart failure. In some embodiments, the heart failure comprises a left-sided heart failure, a right-sided heart failure, a congestive heart failure, a heart failure with reduced ejection fraction (HFrEF), a heart failure with preserved ejection fraction (HFpEF), a heart failure with mid-range ejection fraction (HFmrEF), a hypertrophic cardiomyopathy (HCM), a hypertensive heart disease (HHD), or hypertensive hypertrophic cardiomyopathy.

[0022] In some embodiments, the subject is a human. In some embodiments, the ASO, the conjugate, or the pharmaceutical composition of the present disclosure is administered intracardially, orally, parenterally, intrathecally, intra-cerebroventricularly, pulmorarily, topically, or intraventricularly.

BRIEF DESCRIPTION OF FIGURES

[0023] FIGs. 1A and 1B show exemplary ASOs targeting the *CAMK2D* pre-mRNA. FIG. 1A shows the ASOs targeting a single site within the *CAMK2D* pre-mRNA. FIG. 1B shows the ASOs targeting multiple sites (*i.e.*, two or three) within the *CAMK2D* pre-mRNA. Each column of FIGs. 1A and 1B show the SEQ ID number designated for the sequence only of the ASO, the target start and end positions on the *CAMK2D* pre-mRNA sequence (for FIG. 1B, the multiple target sites are identified as #1, #2, or #3), the ASO sequence without any particular design or chemical structure, the ASO number (ASO No.), and the ASO sequence with a chemical structure.

[0024] FIG. 2 shows both the percent reduction of *CAMK2D* mRNA expression in HEK293 cells (y-axis) and the relative position of the ASOs on the *CAMK2D* transcript (x-axis). Each circle represents an individual ASO. As further described in Example 2, the HEK293 cells were treated with 25 μ M of ASO and the *CAMK2D* mRNA expression (normalized to GAPDH) is shown as a percent of the control.

[0025] FIG. 3 shows certain exemplary ASOs with their design. Each column of FIG. 3 shows the SEQ ID NO for the ASO sequence only, the target start and end positions on the *CAMK2D* pre-mRNA sequence (where the ASO binds to multiple sites (*see* FIG. 1B), exemplary target start and end positions are provided), the ASO design number (DES No.), the ASO sequence with a design, and the ASO number (ASO No.).

[0026] FIG. 4 shows the percent reduction of *CAMK2D* mRNA expression in both HEK293 cells and human inducible pluripotent stem cell-derived cardiomyocytes

(hiPSC-CM) after *in vitro* culture with various ASOs as described in Examples 2 and 3. The cells were treated with 25 μ M (HEK293) or 500 nM (hiPSC-CM) of ASO and the *CAMK2D* mRNA expression (normalized to GAPDH) is shown as a percent of the control. Where no value is provided, the particular ASO was not tested under the particular conditions.

[0027] FIG. 5 shows the potency of exemplary ASOs on *CAMK2D* mRNA expression level in C57BL/6JBom mice one week after subcutaneous administration. *CAMK2D* mRNA expression level was normalized to GAPDH and then shown relative to the control group (*i.e.*, saline treated samples).

DETAILED DESCRIPTION OF DISCLOSURE

I. Definitions

[0028] It is to be noted that the term "a" or "an" entity refers to one or more of that entity; for example, "a nucleotide sequence," is understood to represent one or more nucleotide sequences. As such, the terms "a" (or "an"), "one or more," and "at least one" can be used interchangeably herein.

[0029] Furthermore, "and/or" where used herein is to be taken as specific disclosure of each of the two specified features or components with or without the other. Thus, the term "and/or" as used in a phrase such as "A and/or B" herein is intended to include "A and B," "A or B," "A" (alone), and "B" (alone). Likewise, the term "and/or" as used in a phrase such as "A, B, and/or C" is intended to encompass each of the following aspects: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

[0030] It is understood that wherever aspects are described herein with the language "comprising," otherwise analogous aspects described in terms of "consisting of" and/or "consisting essentially of" are also provided.

[0031] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure is related. For example, the Concise Dictionary of Biomedicine and Molecular Biology, Juo, Pei-Show, 2nd ed., 2002, CRC Press; The Dictionary of Cell and Molecular Biology, 3rd ed., 1999, Academic Press; and the Oxford Dictionary Of Biochemistry And Molecular Biology, Revised, 2000, Oxford University Press, provide one of skill with a general dictionary of many of the terms used in this disclosure.

- [0032] Units, prefixes, and symbols are denoted in their Système International de Unites (SI) accepted form. Numeric ranges are inclusive of the numbers defining the range. Unless otherwise indicated, nucleotide sequences are written left to right in 5' to 3' orientation. Amino acid sequences are written left to right in amino to carboxy orientation. The headings provided herein are not limitations of the various aspects of the disclosure, which can be had by reference to the specification as a whole. Accordingly, the terms defined immediately below are more fully defined by reference to the specification in its entirety.
- [0033] The term "about" is used herein to mean approximately, roughly, around, or in the regions of. When the term "about" is used in conjunction with a numerical range, it modifies that range by extending the boundaries above and below the numerical values set forth. In general, the term "about" can modify a numerical value above and below the stated value by a variance of, *e.g.*, 10 percent, up or down (higher or lower). For example, if it is stated that "the ASO reduces expression of CAMK2d protein in a cell following administration of the ASO by at least about 60%," it is implied that the CAMK2D levels are reduced by a range of 50% to 70%.
- [0034] The term "nucleic acids" or "nucleotides" is intended to encompass plural nucleic acids. In some embodiments, the term "nucleic acids" or "nucleotides" refers to a target sequence, *e.g.*, pre-mRNAs, mRNAs, or DNAs *in vivo* or *in vitro*. When the term refers to the nucleic acids or nucleotides in a target sequence, the nucleic acids or nucleotides can be naturally occurring sequences within a cell. In other embodiments, "nucleic acids" or "nucleotides" refer to a sequence in the ASOs of the disclosure. When the term refers to a sequence in the ASOs, the nucleic acids or nucleotides are not naturally occurring, *i.e.*, chemically synthesized, enzymatically produced, recombinantly produced, or any combination thereof. In one embodiment, the nucleic acids or nucleotides in the ASOs are produced synthetically or recombinantly, but are not a naturally occurring sequence or a fragment thereof. In another embodiment, the nucleic acids or nucleotides in the ASOs are not naturally occurring because they contain at least one nucleotide analog that is not naturally occurring in nature. The term "nucleic acid" or "nucleoside" refers to a single nucleic acid segment, *e.g.*, a DNA, an RNA, or an analog thereof, present in a polynucleotide. "Nucleic acid" or "nucleoside" includes naturally occurring nucleic acids or non-naturally occurring nucleic acids. In some embodiments, the terms "nucleotide", "unit" and "monomer" are used interchangeably. It will be recognized that when referring

to a sequence of nucleotides or monomers, what is referred to is the sequence of bases, such as A, T, G, C or U, and analogs thereof.

[0035] The term "nucleotide" as used herein, refers to a glycoside comprising a sugar moiety, a base moiety and a covalently linked group (linkage group), such as a phosphate or phosphorothioate internucleotide linkage group, and covers both naturally occurring nucleotides, such as DNA or RNA, and non-naturally occurring nucleotides comprising modified sugar and/or base moieties, which are also referred to as "nucleotide analogs" herein. Herein, a single nucleotide (unit) can also be referred to as a monomer or nucleic acid unit. In certain embodiments, the term "nucleotide analogs" refers to nucleotides having modified sugar moieties. Non-limiting examples of the nucleotides having modified sugar moieties (*e.g.*, LNA) are disclosed elsewhere herein. In other embodiments, the term "nucleotide analogs" refers to nucleotides having modified nucleobase moieties. The nucleotides having modified nucleobase moieties include, but are not limited to, 5-methyl-cytosine, isocytosine, pseudoisocytosine, 5-bromouracil, 5-propynyluracil, 6-aminopurine, 2-aminopurine, inosine, diaminopurine, and 2-chloro-6-aminopurine.

[0036] The term "nucleoside" as used herein is used to refer to a glycoside comprising a sugar moiety and a base moiety, and can therefore be used when referring to the nucleotide units, which are covalently linked by the internucleotide linkages between the nucleotides of the ASO. In the field of biotechnology, the term "nucleotide" is often used to refer to a nucleic acid monomer or unit. In the context of an ASO, the term "nucleotide" can refer to the base alone, *i.e.*, a nucleobase sequence comprising cytosine (DNA and RNA), guanine (DNA and RNA), adenine (DNA and RNA), thymine (DNA) and uracil (RNA), in which the presence of the sugar backbone and internucleotide linkages are implicit. Likewise, particularly in the case of oligonucleotides where one or more of the internucleotide linkage groups are modified, the term "nucleotide" can refer to a "nucleoside." For example the term "nucleotide" can be used, even when specifying the presence or nature of the linkages between the nucleosides.

[0037] The term "nucleotide length" as used herein means the total number of the nucleotides (monomers) in a given sequence. For example, the sequence of tacatattatattactctc (SEQ ID NO: 158) has 20 nucleotides; thus the nucleotide length of the sequence is 20. The term "nucleotide length" is therefore used herein interchangeably with "nucleotide number."

- [0038] As one of ordinary skill in the art would recognize, the 5' terminal nucleotide of an oligonucleotide does not comprise a 5' internucleotide linkage group, although it can comprise a 5' terminal group.
- [0039] As used herein, the term "alkyl", alone or in combination, signifies a straight-chain or branched-chain alkyl group with 1 to 8 carbon atoms, particularly a straight or branched-chain alkyl group with 1 to 6 carbon atoms and more particularly a straight or branched-chain alkyl group with 1 to 4 carbon atoms. Examples of straight-chain and branched-chain C₁-C₈ alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, the isomeric pentyls, the isomeric hexyls, the isomeric heptyls and the isomeric octyls, particularly methyl, ethyl, propyl, butyl and pentyl. Particular examples of alkyl are methyl. Further examples of alkyl are mono, di or trifluoro methyl, ethyl or propyl, such as cyclopropyl (cPr), or mono, di or tri fluoro cyclopropyl.
- [0040] The term "alkoxy", alone or in combination, signifies a group of the formula alkyl-O- in which the term "alkyl" has the previously given significance, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec.butoxy and tert.butoxy. Particular "alkoxy" are methoxy.
- [0041] The term "oxy", alone or in combination, signifies the -O- group.
- [0042] The term "alkenyl", alone or in combination, signifies a straight-chain or branched hydrocarbon residue comprising an olefinic bond and up to 8, preferably up to 6, particularly preferred up to 4 carbon atoms. Examples of alkenyl groups are ethenyl, 1-propenyl, 2-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl and isobutenyl.
- [0043] The term "alkynyl", alone or in combination, signifies a straight-chain or branched hydrocarbon residue comprising a triple bond and up to 8, preferably up to 6, particularly preferred up to 4 carbon atoms.
- [0044] The terms "'halogen'" or "'halo'", alone or in combination, signifies fluorine, chlorine, bromine or iodine and particularly fluorine, chlorine or bromine, more particularly fluorine and chlorine, such as fluorine. The term "halo", in combination with another group, denotes the substitution of said group with at least one halogen, particularly substituted with one to five halogens, particularly one to four halogens, *i.e.*, one, two, three or four halogens. The terms "hydroxyl" and "hydroxy", alone or in combination, signify the -OH group.
- [0045] The terms "thiohydroxyl" and "thiohydroxy", alone or in combination, signify the -SH group.
- [0046] The term "carbonyl", alone or in combination, signifies the -C(O)- group.

- [0047] The term "carboxy" or "carboxyl", alone or in combination, signifies the -COOH group.
- [0048] The term "amino", alone or in combination, signifies the primary amino group (-NH₂), the secondary amino group (-NH-), or the tertiary amino group (-N-).
- [0049] The term "alkylamino", alone or in combination, signifies an amino group as defined above substituted with one or two alkyl groups as defined above.
- [0050] The term "aminocarbonyl", alone or in combination, signifies the -C(O)-NH₂ group.
- [0051] The term "sulfonyl", alone or in combination, means the -SO₂ group.
- [0052] The term "sulfinyl", alone or in combination, signifies the -SO- group.
- [0053] The term "sulfanyl", alone or in combination, signifies the -S- group.
- [0054] The term "cyano", alone or in combination, signifies the -CN group.
- [0055] The term "azido", alone or in combination, signifies the -N₃ group.
- [0056] The term "nitro", alone or in combination, signifies the NO₂ group.
- [0057] The term "formyl" alone or in combination, signifies the -C(O)H group.
- [0058] The term "aryl", alone or in combination, denotes a monovalent aromatic carbocyclic mono- or bicyclic ring system comprising 6 to 10 carbon ring atoms, optionally substituted with 1 to 3 substituents independently selected from halogen, hydroxyl, alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, alkenyloxy, carboxyl, alkoxycarbonyl, alkylcarbonyl and formyl. Examples of aryl include phenyl and naphthyl. in particular phenyl.
- [0059] The term "heteroaryl", alone or in combination, denotes a monovalent aromatic heterocyclic mono- or bicyclic ring system of 5 to 12 ring atoms, comprising 1, 2, 3 or 4 heteroatoms selected from N, O and S, the remaining ring atoms being carbon, optionally substituted with 1 to 3 substituents independently selected from halogen, hydroxyl, alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, alkenyloxy, carboxyl, alkoxycarbonyl, alkylcarbonyl and formyl. Examples of heteroaryl include pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, triazinyl, azepinyl, diazepinyl, isoxazolyl, benzofuranyl, isothiazolyl, benzothienyl, indolyl, isoindolyl, isobenzofuranyl, benzimidazolyl, benzoxazolyl, benzoisoxazolyl, benzothiazolyl, benzoisothiazolyl, benzooxadiazolyl, benzothiadiazolyl, benzotriazolyl, purinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, carbazolyl, or acridinyl.
- [0060] The term "heterocycle", alone or in combination, denotes a monovalent non-aromatic heterocyclic mono- or bicyclic ring system of 5 to 12 ring atoms, comprising 1,

2, 3 or 4 heteroatoms selected from N, O and S, the remaining ring atoms being carbon, optionally substituted with 1 to 3 substituents independently selected from halogen, hydroxyl, alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, alkenyloxy, carboxyl, alkoxycarbonyl, alkylcarbonyl and formyl.

[0061] The term "protecting group", alone or in combination, signifies a group which selectively blocks a reactive site in a multifunctional compound such that a chemical reaction can be carried out selectively at another unprotected reactive site. Protecting groups can be removed. Exemplary protecting groups are amino-protecting groups, carboxy-protecting groups or hydroxy-protecting groups.

[0062] If one of the starting materials or compounds of the invention contain one or more functional groups which are not stable or are reactive under the reaction conditions of one or more reaction steps, appropriate protecting groups (as described *e.g.*, in "Protective Groups in Organic Chemistry" by T. W. Greene and P. G. M. Wuts, 3rd Ed., 1999, Wiley, New York) can be introduced before the critical step applying methods well known in the art. Such protecting groups can be removed at a later stage of the synthesis using standard methods described in the literature. Examples of protecting groups are tert-butoxycarbonyl (Boc), 9-fluorenylmethyl carbamate (Fmoc), 2-trimethylsilylethyl carbamate (Teoc), carbobenzyloxy (Cbz) and p-methoxybenzyloxycarbonyl (Moz).

[0063] The compounds described herein can contain several asymmetric centers and can be present in the form of optically pure enantiomers, mixtures of enantiomers such as, for example, racemates, mixtures of diastereoisomers, diastereoisomeric racemates or mixtures of diastereoisomeric racemates.

[0064] The term "asymmetric carbon atom" means a carbon atom with four different substituents. According to the Cahn-Ingold-Prelog Convention an asymmetric carbon atom can be of the "R" or "S" configuration.

[0065] As used herein, the term "bicyclic sugar" refers to a modified sugar moiety comprising a 4 to 7 membered ring comprising a bridge connecting two atoms of the 4 to 7 membered ring to form a second ring, resulting in a bicyclic structure. In some embodiments, the bridge connects the C2' and C4' of the ribose sugar ring of a nucleoside (*i.e.*, 2'-4' bridge), as observed in LNA nucleosides.

[0066] As used herein, a "coding region" or "coding sequence" is a portion of polynucleotide which consists of codons translatable into amino acids. Although a "stop codon" (TAG, TGA, or TAA) is typically not translated into an amino acid, it can be considered to be part of a coding region, but any flanking sequences, for example

promoters, ribosome binding sites, transcriptional terminators, introns, untranslated regions ("UTRs"), and the like, are not part of a coding region. The boundaries of a coding region are typically determined by a start codon at the 5' terminus, encoding the amino terminus of the resultant polypeptide, and a translation stop codon at the 3' terminus, encoding the carboxyl terminus of the resulting polypeptide.

[0067] The term "non-coding region" as used herein means a nucleotide sequence that is not a coding region. Examples of non-coding regions include, but are not limited to, promoters, ribosome binding sites, transcriptional terminators, introns, untranslated regions ("UTRs"), non-coding exons and the like. Some of the exons can be wholly or part of the 5' untranslated region (5' UTR) or the 3' untranslated region (3' UTR) of each transcript. The untranslated regions are important for efficient translation of the transcript and for controlling the rate of translation and half-life of the transcript.

[0068] The term "region" when used in the context of a nucleotide sequence refers to a section of that sequence. For example, the phrase "region within a nucleotide sequence" or "region within the complement of a nucleotide sequence" refers to a sequence shorter than the nucleotide sequence, but longer than at least 10 nucleotides located within the particular nucleotide sequence or the complement of the nucleotides sequence, respectively. The term "sub-sequence" or "subsequence" can also refer to a region of a nucleotide sequence.

[0069] The term "downstream," when referring to a nucleotide sequence, means that a nucleic acid or a nucleotide sequence is located 3' to a reference nucleotide sequence. In certain embodiments, downstream nucleotide sequences relate to sequences that follow the starting point of transcription. For example, the translation initiation codon of a gene is located downstream of the start site of transcription.

[0070] The term "upstream" refers to a nucleotide sequence that is located 5' to a reference nucleotide sequence.

[0071] As used herein, the term "regulatory region" refers to nucleotide sequences located upstream (5' non-coding sequences), within, or downstream (3' non-coding sequences) of a coding region, and which influence the transcription, RNA processing, stability, or translation of the associated coding region. Regulatory regions can include promoters, translation leader sequences, introns, polyadenylation recognition sequences, RNA processing sites, effector binding sites, UTRs, and stem-loop structures. If a coding region is intended for expression in a eukaryotic cell, a polyadenylation signal and transcription termination sequence will usually be located 3' to the coding sequence.

- [0072] The term "transcript" as used herein can refer to a primary transcript that is synthesized by transcription of DNA and becomes a messenger RNA (mRNA) after processing, *i.e.*, a precursor messenger RNA (pre-mRNA), and the processed mRNA itself. The term "transcript" can be interchangeably used with "pre-mRNA" and "mRNA." After DNA strands are transcribed to primary transcripts, the newly synthesized primary transcripts are modified in several ways to be converted to their mature, functional forms to produce different proteins and RNAs such as mRNA, tRNA, rRNA, lncRNA, miRNA and others. Thus, the term "transcript" can include exons, introns, 5' UTRs, and 3' UTRs.
- [0073] The term "expression" as used herein refers to a process by which a polynucleotide produces a gene product, for example, a RNA or a polypeptide. It includes, without limitation, transcription of the polynucleotide into messenger RNA (mRNA) and the translation of an mRNA into a polypeptide. Expression produces a "gene product." As used herein, a gene product can be either a nucleic acid, *e.g.*, a messenger RNA produced by transcription of a gene, or a polypeptide which is translated from a transcript. Gene products described herein further include nucleic acids with post transcriptional modifications, *e.g.*, polyadenylation or splicing, or polypeptides with post translational modifications, *e.g.*, methylation, glycosylation, the addition of lipids, association with other protein subunits, or proteolytic cleavage.
- [0074] The terms "identical" or percent "identity" in the context of two or more nucleic acids refer to two or more sequences that are the same or have a specified percentage of nucleotides or amino acid residues that are the same, when compared and aligned (introducing gaps, if necessary) for maximum correspondence, not considering any conservative amino acid substitutions as part of the sequence identity. The percent identity can be measured using sequence comparison software or algorithms or by visual inspection. Various algorithms and software are known in the art that can be used to obtain alignments of amino acid or nucleotide sequences.
- [0075] One such non-limiting example of a sequence alignment algorithm is the algorithm described in Karlin *et al.*, 1990, *Proc. Natl. Acad. Sci.*, 87:2264-2268, as modified in Karlin *et al.*, 1993, *Proc. Natl. Acad. Sci.*, 90:5873-5877, and incorporated into the NBLAST and XBLAST programs (Altschul *et al.*, 1991, *Nucleic Acids Res.*, 25:3389-3402). In certain embodiments, Gapped BLAST can be used as described in Altschul *et al.*, 1997, *Nucleic Acids Res.* 25:3389-3402. BLAST-2, WU-BLAST-2 (Altschul *et al.*, 1996, *Methods in Enzymology*, 266:460-480), ALIGN, ALIGN-2 (Genentech, South San Francisco, California) or Megalign (DNASTAR) are additional publicly available

software programs that can be used to align sequences. In certain embodiments, the percent identity between two nucleotide sequences is determined using the GAP program in the GCG software package (*e.g.*, using a NWSgapdna.CMP matrix and a gap weight of 40, 50, 60, 70, or 90 and a length weight of 1, 2, 3, 4, 5, or 6). In certain alternative embodiments, the GAP program in the GCG software package, which incorporates the algorithm of Needleman and Wunsch (*J. Mol. Biol.* (48):444-453 (1970)) can be used to determine the percent identity between two amino acid sequences (*e.g.*, using either a BLOSUM 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5). Alternatively, in certain embodiments, the percent identity between nucleotide or amino acid sequences is determined using the algorithm of Myers and Miller (*CABIOS*, 4:11-17 (1989)). For example, the percent identity can be determined using the ALIGN program (version 2.0) and using a PAM120 with residue table, a gap length penalty of 12 and a gap penalty of 4. One skilled in the art can determine appropriate parameters for maximal alignment by particular alignment software. In certain embodiments, the default parameters of the alignment software are used.

[0076] In certain embodiments, the percentage identity "X" of a first nucleotide sequence to a second nucleotide sequence is calculated as $100 \times (Y/Z)$, where Y is the number of amino acid residues scored as identical matches in the alignment of the first and second sequences (as aligned by visual inspection or a particular sequence alignment program) and Z is the total number of residues in the second sequence. If the length of a first sequence is longer than the second sequence, the percent identity of the first sequence to the second sequence will be higher than the percent identity of the second sequence to the first sequence.

[0077] Different regions within a single polynucleotide target sequence that align with a polynucleotide reference sequence can each have their own percent sequence identity. It is noted that the percent sequence identity value is rounded to the nearest tenth. For example, 80.11, 80.12, 80.13, and 80.14 are rounded down to 80.1, while 80.15, 80.16, 80.17, 80.18, and 80.19 are rounded up to 80.2. It also is noted that the length value will always be an integer.

[0078] As used herein, the terms "homologous" and "homology" are interchangeable with the terms "identity" and "identical."

[0079] The term "naturally occurring variant thereof" refers to variants of the CAMK2D polypeptide sequence or *CAMK2D* nucleic acid sequence (*e.g.*, transcript) which exist

naturally within the defined taxonomic group, such as mammalian, such as mouse, monkey, and human. Typically, when referring to "naturally occurring variants" of a polynucleotide the term also can encompass any allelic variant of the *CAMK2D*-encoding genomic DNA which is found at Chromosomal position 4q26 (*i.e.*, residues 113,451,032 to 113,761,927 of GenBank Accession No. NC_000004.12) by chromosomal translocation or duplication, and the RNA, such as mRNA derived therefrom. "Naturally occurring variants" can also include variants derived from alternative splicing of the *CAMK2D* mRNA. When referenced to a specific polypeptide sequence, *e.g.*, the term also includes naturally occurring forms of the protein, which can therefore be processed, *e.g.*, by co- or post-translational modifications, such as signal peptide cleavage, proteolytic cleavage, glycosylation, *etc.*

[0080] In determining the degree of "complementarity" between the ASOs of the disclosure (or regions thereof) and the target region of the nucleic acid which encodes mammalian *CAMK2D* (*e.g.*, the *CAMK2D* gene), such as those disclosed herein, the degree of "complementarity" (also, "homology" or "identity") is expressed as the percentage identity (or percentage homology) between the sequence of the ASO (or region thereof) and the sequence of the target region (or the reverse complement of the target region) that best aligns therewith. The percentage is calculated by counting the number of aligned bases that are identical between the two sequences, dividing by the total number of contiguous monomers in the ASO, and multiplying by 100. In such a comparison, if gaps exist, it is preferable that such gaps are merely mismatches rather than areas where the number of monomers within the gap differs between the ASO of the disclosure and the target region.

[0081] The term "complement" as used herein indicates a sequence that is complementary to a reference sequence. It is well known that complementarity is the base principle of DNA replication and transcription as it is a property shared between two DNA or RNA sequences, such that when they are aligned antiparallel to each other, the nucleotide bases at each position in the sequences will be complementary, much like looking in the mirror and seeing the reverse of things. Therefore, for example, the complement of a sequence of 5'ATGC'3' can be written as 3'TACG'5' or 5'GCAT'3'. The terms "reverse complement", "reverse complementary", and "reverse complementarity" as used herein are interchangeable with the terms "complement", "complementary", and "complementarity." In some embodiments, the term "complementary" refers to 100% match or complementarity (*i.e.*, fully complementary) to a contiguous nucleic acid

sequence within a *CAMK2D* transcript. In some embodiments, the term "complementary" refers to at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% match or complementarity to a contiguous nucleic acid sequence within a *CAMK2D* transcript.

[0082] The terms "corresponding to" and "corresponds to," when referencing two separate nucleic acid or nucleotide sequences can be used to clarify regions of the sequences that correspond or are similar to each other based on homology and/or functionality, although the nucleotides of the specific sequences can be numbered differently. For example, different isoforms of a gene transcript can have similar or conserved portions of nucleotide sequences whose numbering can differ in the respective isoforms based on alternative splicing and/or other modifications. In addition, it is recognized that different numbering systems can be employed when characterizing a nucleic acid or nucleotide sequence (*e.g.*, a gene transcript and whether to begin numbering the sequence from the translation start codon or to include the 5'UTR). Further, it is recognized that the nucleic acid or nucleotide sequence of different variants of a gene or gene transcript can vary. As used herein, however, the regions of the variants that share nucleic acid or nucleotide sequence homology and/or functionality are deemed to "correspond" to one another. For example, a nucleotide sequence of a *CAMK2D* transcript corresponding to nucleotides X to Y of SEQ ID NO: 1 ("reference sequence") refers to an *CAMK2d* transcript sequence (*e.g.*, *CAMK2D* pre-mRNA or mRNA) that has an identical sequence or a similar sequence to nucleotides X to Y of SEQ ID NO: 1, wherein X is the start site and Y is the end site (as shown in FIGs. 1A and 1B). A person of ordinary skill in the art can identify the corresponding X and Y residues in the *CAMK2D* transcript sequence by aligning the *CAMK2D* transcript sequence with SEQ ID NO: 1.

[0083] The terms "corresponding nucleotide analog" and "corresponding nucleotide" are intended to indicate that the nucleobase in the nucleotide analog and the naturally occurring nucleotide have the same pairing, or hybridizing, ability. For example, when the 2-deoxyribose unit of the nucleotide is linked to an adenine, the "corresponding nucleotide analog" contains a pentose unit (different from 2-deoxyribose) linked to an adenine.

[0084] The term "DES Number" or "DES No." as used herein refers to a unique number given to a nucleotide sequence having a specific pattern of nucleosides (*e.g.*, DNA) and

nucleoside analogs (*e.g.*, LNA). As used herein, the design of an ASO is shown by a combination of upper case letters and lower case letters. For example, DES-0231 refers to an ASO sequence of tacatattatattactctc (SEQ ID NO: 158) with an ASO design of LLLDDDDDDDDDDDDDDLL (i.e., TACatattatattactcCTC), wherein the L (*i.e.*, upper case letter) indicates a nucleoside analog (*e.g.*, LNA) and the D (*i.e.*, lower case letter) indicates a nucleoside (*e.g.*, DNA).

[0085] The annotation of ASO chemistry is as follows Beta-D-oxy LNA nucleotides are designated by OxyB where B designates a nucleotide base such as thymine (T), uridine (U), cytosine (C), 5-methylcytosine (MC), adenine (A) or guanine (G), and thus include OxyA, OxyT, OxyMC, OxyC and OxyG. DNA nucleotides are designated by DNA_b, where the lower case b designates a nucleotide base such as thymine (T), uridine (U), cytosine (C), 5-methylcytosine (Mc), adenine (A) or guanine (G), and thus include DNA_a, DNA_t, DNA and DNA_g. The letter M before C or c indicates 5-methylcytosine. The letter "s" indicates a phosphorothioate internucleotide linkage.

[0086] The term "ASO Number" or "ASO No." as used herein refers to a unique number given to a nucleotide sequence having the detailed chemical structure of the components, *e.g.*, nucleosides (*e.g.*, DNA), nucleoside analogs (*e.g.*, beta-D-oxy-LNA), nucleobase (*e.g.*, A, T, G, C, U, or MC), and backbone structure (*e.g.*, phosphorothioate or phosphodiester). For example, ASO-0231 can refer to OxyTs OxyAs OxyMCs DNA_as DNA_ts DNA_as DNA_ts DNA_as DNA_ts DNA_as DNA_ts DNA_as DNA_cs DNA_ts DNA_cs OxyMCs OxyTs OxyMC.

[0087] "Potency" is normally expressed as an IC₅₀ or EC₅₀ value, in μ M, nM or pM unless otherwise stated. Potency can also be expressed in terms of percent inhibition. IC₅₀ is the median inhibitory concentration of a therapeutic molecule. EC₅₀ is the median effective concentration of a therapeutic molecule relative to a vehicle or control (*e.g.*, saline). In functional assays, IC₅₀ is the concentration of a therapeutic molecule that reduces a biological response, *e.g.*, transcription of mRNA or protein expression, by 50% of the biological response that is achieved by the therapeutic molecule. In functional assays, EC₅₀ is the concentration of a therapeutic molecule that produces 50% of the biological response, *e.g.*, transcription of mRNA or protein expression. IC₅₀ or EC₅₀ can be calculated by any number of means known in the art.

[0088] As used herein, the term "inhibiting," *e.g.*, the expression of *CAMK2D* gene transcript and/or CAMK2D protein refers to the ASO reducing the expression of the *CAMK2D* gene transcript and/or CAMK2D protein in a cell or a tissue. In some

embodiments, the term "inhibiting" refers to complete inhibition (100% inhibition or non-detectable level) of *CAMK2D* gene transcript or CAMK2D protein. In other embodiments, the term "inhibiting" refers to at least 5%, 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 60%, at least 70%, at least 80%, at least 90%, at least 95% or at least 99% inhibition of *CAMK2D* gene transcript and/or CAMK2D protein expression in a cell or a tissue.

[0089] By "subject" or "individual" or "animal" or "patient" or "mammal," is meant any subject, particularly a mammalian subject, for whom diagnosis, prognosis, or therapy is desired. Mammalian subjects include humans, domestic animals, farm animals, sports animals, and zoo animals including, *e.g.*, humans, non-human primates, dogs, cats, guinea pigs, rabbits, rats, mice, horses, cattle, bears, and so on.

[0090] The term "pharmaceutical composition" refers to a preparation which is in such form as to permit the biological activity of the active ingredient to be effective, and which contains no additional components which are unacceptably toxic to a subject to which the composition would be administered. Such composition can be sterile.

[0091] An "effective amount" of an ASO as disclosed herein is an amount sufficient to carry out a specifically stated purpose. An "effective amount" can be determined empirically and in a routine manner, in relation to the stated purpose.

[0092] Terms such as "treating" or "treatment" or "to treat" or "alleviating" or "to alleviate" refer to both (1) therapeutic measures that cure, slow down, lessen symptoms of, and/or halt progression of a diagnosed pathologic condition or disorder and (2) prophylactic or preventative measures that prevent and/or slow the development of a targeted pathologic condition or disorder. Thus, those in need of treatment include those already with the disorder; those prone to have the disorder; and those in whom the disorder is to be prevented. In certain embodiments, a subject is successfully "treated" for a disease or condition disclosed elsewhere herein according to the methods provided herein if the patient shows, *e.g.*, total, partial, or transient alleviation or elimination of symptoms associated with the disease or disorder.

II. Antisense Oligonucleotides

[0093] The present disclosure employs antisense oligonucleotides (ASOs) for use in modulating the function of nucleic acid molecules encoding mammalian CAMK2D, such as the *CAMK2D* nucleic acid, *e.g.*, *CAMK2D* transcript, including *CAMK2D* pre-mRNA,

and *CAMK2D* mRNA, or naturally occurring variants of such nucleic acid molecules encoding mammalian *CAMK2D*. The term "ASO" in the context of the present disclosure, refers to a molecule formed by covalent linkage of two or more nucleotides (*i.e.*, an oligonucleotide).

[0094] The ASO comprises a contiguous nucleotide sequence of from about 10 to about 30, such as 10–20, 14–20, 16–20, or 15–25, nucleotides in length. The terms "antisense ASO," "antisense oligonucleotide," and "oligomer" as used herein are interchangeable with the term "ASO."

[0095] A reference to a SEQ ID number includes a particular nucleobase sequence, but does not include any design or full chemical structure. Furthermore, the ASOs disclosed in the figures herein show a representative design, but are not limited to the specific design shown in the Figures unless otherwise indicated. Herein, a single nucleotide (unit) can also be referred to as a monomer or unit. When this specification refers to a specific ASO number, the reference includes the sequence, the specific ASO design, and the chemical structure. When this specification refers to a specific DES number, the reference includes the sequence and the specific ASO design. For example, when a claim (or this specification) refers to SEQ ID NO: 158, it includes the nucleotide sequence of tacatattatattactctc only. When a claim (or the specification) refers to DES-0231, it includes the nucleotide sequence of tacatattatattactctc with the ASO design of TACatattatattactcCTC. Alternatively, the design of ASO-0231 can also be written as SEQ ID NO: 158, wherein each of the first nucleotide, the second nucleotide, the third nucleotide, the 18th nucleotide, the 19th nucleotide, and the 20th nucleotide from the 5' end is a modified nucleotide, *e.g.*, LNA, and each of the other nucleotides is a non-modified nucleotide (*e.g.*, DNA). The ASO number includes the sequence and the ASO design, as well as the specific details of the ASO. Therefore, for instance, ASO-0231 referred to in this application indicates OxyTs OxyAs OxyMCs DNAas DNAts DNAas DNAts DNAts DNAas DNAts DNAas DNAts DNAts DNAas DNAs DNAts DNAs OxyMCs OxyTs OxyMC, wherein "s" indicates phosphorothioate linkage.

[0096] In various embodiments, the ASO of the disclosure does not comprise RNA (units). In some embodiments, the ASO comprises one or more DNA units. In one embodiment, the ASO according to the disclosure is a linear molecule or is synthesized as a linear molecule. In some embodiments, the ASO is a single stranded molecule, and does not comprise short regions of, for example, at least 3, 4 or 5 contiguous nucleotides, which are complementary to equivalent regions within the same ASO (*i.e.* duplexes) - in this

regard, the ASO is not (essentially) double stranded. In some embodiments, the ASO is essentially not double stranded. In some embodiments, the ASO is not a siRNA. In various embodiments, the ASO of the disclosure can consist entirely of the contiguous nucleotide region. Thus, in some embodiments the ASO is not substantially self-complementary.

[0097] In other embodiments, the present disclosure includes fragments of ASOs. For example, the disclosure includes at least one nucleotide, at least two contiguous nucleotides, at least three contiguous nucleotides, at least four contiguous nucleotides, at least five contiguous nucleotides, at least six contiguous nucleotides, at least seven contiguous nucleotides, at least eight contiguous nucleotides, or at least nine contiguous nucleotides of the ASOs disclosed herein. Fragments of any of the sequences disclosed herein are contemplated as part of the disclosure.

II.A. The Target

[0098] Suitably the ASO of the disclosure is capable of down-regulating (*e.g.*, reducing or removing) expression of the *CAMK2D* mRNA or protein. In this regard, the ASO of the disclosure can affect indirect inhibition of CAMK2D protein through the reduction in *CAMK2D* mRNA levels, typically in a mammalian cell, such as a human cell, such as a cardiocyte. In particular, the present disclosure is directed to ASOs that target one or more regions of the *CAMK2D* pre-mRNA (*e.g.*, intron regions, exon regions, and/or exon-intron junction regions). Unless indicated otherwise, the term "CAMK2D," as used herein, can refer to CAMK2D from one or more species (*e.g.*, humans, non-human primates, dogs, cats, guinea pigs, rabbits, rats, mice, horses, cattle, and bears).

[0099] Calcium/calmodulin-dependent protein kinase type II delta (*CAMK2D*) is also known as CaM kinase II subunit delta and CamK-II subunit delta. Synonyms of *CAMK2D* are known and include CaMKII δ or CAMKD. The sequence for the human *CAMK2D* gene can be found under publicly available GenBank Accession Number NC_000004.12. The sequence for the human *CAMK2D* pre-mRNA transcript (SEQ ID NO: 1) corresponds to the reverse complement of residues 113,451,032 – 113,761,927 of NC_000004.12. The *CAMK2D* mRNA sequence (GenBank Accession No. NM_001221.3) is provided in SEQ ID NO: 2, except that the nucleotide "t" in SEQ ID NO: 2 is shown as "u" in the mRNA. The sequence for human CAMK2D protein can be found under publicly available Accession Numbers: Q13557 (canonical sequence, SEQ

ID NO: 3), A8MVS8, Q52PK4, Q59G21, Q8N553, Q9UGH6, Q9UQE9, each of which is incorporated by reference herein in its entirety.

[0100] Natural variants of the human *CAMK2D* gene product are known. For example, natural variants of human CAMK2D protein can contain one or more amino acid substitutions selected from: D167E, Q463E, and T493I, and any combinations thereof. Additional variants of human CAMK2D protein resulting from alternative splicing are also known in the art. CAMK2D Isoform Delta 3 (identifier: Q13557-3 at UniProt) differs from the canonical sequence (SEQ ID NO: 3) as follows: 328-328: K → KKRKSSSSVQMM. The sequence of CAMK2D Isoform Delta 4 (identifier: Q13557-4) differs from the canonical sequence (SEQ ID NO: 3) as follows: 328-328: K → KINNKANVVTSPKENIPTPAL. The sequence of CAMK2D Isoform Delta 6 (identifier: Q13557-8) differs from the canonical sequence (SEQ ID NO: 3) as follows: 479-499: Missing. The sequence of CAMK2D Isoform Delta 7 (identifier: Q13557-9) differs from the canonical sequence (SEQ ID NO: 3) as follows: 328-328: K → KKRKSSSSVQMM and 479-499: Missing. The sequence of CAMK2D Isoform Delta 8 (identifier: Q13557-5) differs from the canonical sequence (SEQ ID NO: 3) as follows: 328-328: K → KINNKANVVTSPKENIPTPAL and 479-499: Missing. The sequence of CAMK2D Isoform Delta 9 (identifier: Q13557-6) differs from the canonical sequence (SEQ ID NO: 3) as follows: 329-329: E → EPQTTVIHNP DGNKE. The sequence of CAMK2D Isoform Delta 10 (identifier: Q13557-10) differs from the canonical sequence (SEQ ID NO: 3) as follows: 329-329: E → EPQTTVIHNP DGNKE and 479-499: Missing. The sequence of CAMK2D Isoform Delta 11 (identifier: Q13557-11) differs from the canonical sequence (SEQ ID NO: 3) as follows: 328-328: K → KKRKSSSSVQMMEPQTTVIHNP DGNK. The sequence of CAMK2D Isoform Delta 12 (identifier: Q13557-12) differs from the canonical sequence (SEQ ID NO: 3) as follows: 478-478: K → N and 479-499: Missing. Therefore, the ASOs of the present disclosure can be designed to reduce or inhibit expression of the natural variants of the CAMK2D protein.

[0101] An example of a target nucleic acid sequence of the ASOs is *CAMK2D* pre-mRNA. SEQ ID NO: 1 represents a human *CAMK2D* genomic sequence (*i.e.*, reverse complement of nucleotides 113,451,032 to 113,761,927 of GenBank Accession No. NC_000004.12). SEQ ID NO: 1 is identical to a *CAMK2D* pre-mRNA sequence except that nucleotide "t" in SEQ ID NO: 1 is shown as "u" in pre-mRNA. In certain embodiments, the "target nucleic acid" comprises an intron of a CAMK2D protein-

encoding nucleic acids or naturally occurring variants thereof, and RNA nucleic acids derived therefrom, *e.g.*, pre-mRNA. In other embodiments, the target nucleic acid comprises an exon region of a CAMK2D protein-encoding nucleic acids or naturally occurring variants thereof, and RNA nucleic acids derived therefrom, *e.g.*, pre-mRNA. In yet other embodiments, the target nucleic acid comprises an exon-intron junction of a CAMK2D protein-encoding nucleic acids or naturally occurring variants thereof, and RNA nucleic acids derived therefrom, *e.g.*, pre-mRNA. In some embodiments, for example when used in research or diagnostics the "target nucleic acid" can be a cDNA or a synthetic oligonucleotide derived from the above DNA or RNA nucleic acid targets. The human CAMK2D protein sequence encoded by the *CAMK2D* pre-mRNA is shown as SEQ ID NO: 3. In other embodiments, the target nucleic acid comprises an untranslated region of a CAMK2D protein-encoding nucleic acids or naturally occurring variants thereof, *e.g.*, 5' UTR, 3' UTR, or both.

[0102] In some embodiments, an ASO of the disclosure hybridizes to a region within the introns of a *CAMK2D* transcript, *e.g.*, SEQ ID NO: 1. In certain embodiments, an ASO of the disclosure hybridizes to a region within the exons of a *CAMK2D* transcript, *e.g.*, SEQ ID NO: 1. In other embodiments, an ASO of the disclosure hybridizes to a region within the exon-intron junction of a *CAMK2D* transcript, *e.g.*, SEQ ID NO: 1. In some embodiments, an ASO of the disclosure hybridizes to a region within a *CAMK2D* transcript (*e.g.*, an intron, exon, or exon-intron junction), *e.g.*, SEQ ID NO: 1, wherein the ASO has a design according to formula: 5' A-B-C 3' as described elsewhere herein (*e.g.*, Section II.G).

[0103] In some embodiments, the ASO targets a mRNA encoding a particular isoform of CAMK2D protein (*e.g.*, Isoform Delta 3-12). In some embodiments, the ASO targets all isoforms of CAMK2D protein. In other embodiments, the ASO targets two isoforms (*e.g.*, Isoform Delta 3 and Isoform Delta 7, Isoform Delta 4 and Isoform Delta 8, and Isoform Delta 9 and Isoform Delta 10) of CAMK2D protein.

[0104] In some embodiments, the ASO comprises a contiguous nucleotide sequence (*e.g.*, 10 to 30 nucleotides in length) that are complementary to a nucleic acid sequence within a *CAMK2D* transcript, *e.g.*, a region corresponding to SEQ ID NO: 1. In some embodiments, the ASO comprises a contiguous nucleotide sequence that hybridizes to a nucleic acid sequence, or a region within the sequence, of a *CAMK2D* transcript ("target region"), wherein the nucleic acid sequence corresponds to nucleotides (i) nucleotides 625 – 842 of SEQ ID NO: 1; (ii) nucleotides 1,398 – 59,755 of SEQ ID NO: 1; (iii)

nucleotides 61,817 – 104,725 of SEQ ID NO: 1; (iv) nucleotides 112,162 – 118,021 of SEQ ID NO: 1; (v) nucleotides 119,440 – 135,219 of SEQ ID NO: 1; (vi) nucleotides 137,587 – 157,856 of SEQ ID NO: 1; (vii) nucleotides 159,191 – 266,174 of SEQ ID NO: 1; and (viii) nucleotides 272,788 – 310,949 of SEQ ID NO: 1, and wherein, optionally, the ASO has one of the designs described herein (*e.g.*, Section II.G) or a chemical structure shown elsewhere herein (*e.g.*, FIGs. 1A and 1B).

[0105] In some embodiments, the target region corresponds to nucleotides 725 – 742 of SEQ ID NO: 1. In other embodiments, the target region corresponds to nucleotides 1,498 – 59,655 of SEQ ID NO: 1. In certain embodiments, the target region corresponds to nucleotides 61,917 – 104,625 of SEQ ID NO: 1. In some embodiments, the target region corresponds to nucleotides 112,262 – 117,921 of SEQ ID NO: 1. In some embodiments, the target region corresponds to nucleotides 119,540 – 135,119 of SEQ ID NO: 1. In further embodiments, the target region corresponds to nucleotides 137,687 – 157,756 of SEQ ID NO: 1. In certain embodiments, the target region corresponds to nucleotides 159,291 – 266,074 of SEQ ID NO: 1. In some embodiments, the target region corresponds to nucleotides 272,888 – 310,849 of SEQ ID NO: 1.

[0106] In some embodiments, the target region corresponds to nucleotides 725 – 742 of SEQ ID NO: 1 ± 10 , ± 20 , ± 30 , ± 40 , ± 50 , ± 60 , ± 70 , ± 80 , or ± 90 nucleotides at the 3' end and/or the 5' end. In other embodiments, the target region corresponds to nucleotides 1,498 – 59,655 of SEQ ID NO: 1 ± 10 , ± 20 , ± 30 , ± 40 , ± 50 , ± 60 , ± 70 , ± 80 , or ± 90 nucleotides at the 3' end and/or the 5' end. In certain embodiments, the target region corresponds to nucleotides 61,917 – 104,625 of SEQ ID NO: 1 ± 10 , ± 20 , ± 30 , ± 40 , ± 50 , ± 60 , ± 70 , ± 80 , or ± 90 nucleotides at the 3' end and/or the 5' end. In some embodiments, the target region corresponds to nucleotides 112,262 – 117,921 of SEQ ID NO: 1 ± 10 , ± 20 , ± 30 , ± 40 , ± 50 , ± 60 , ± 70 , ± 80 , or ± 90 nucleotides at the 3' end and/or the 5' end. In some embodiments, the target region corresponds to nucleotides 119,540 – 135,119 of SEQ ID NO: 1 ± 10 , ± 20 , ± 30 , ± 40 , ± 50 , ± 60 , ± 70 , ± 80 , or ± 90 nucleotides at the 3' end and/or the 5' end. In further embodiments, the target region corresponds to nucleotides 137,687 – 157,756 of SEQ ID NO: 1 ± 10 , ± 20 , ± 30 , ± 40 , ± 50 , ± 60 , ± 70 , ± 80 , or ± 90 nucleotides at the 3' end and/or the 5' end. In certain embodiments, the target region corresponds to nucleotides 159,291 – 266,074 of SEQ ID NO: 1 ± 10 , ± 20 , ± 30 , ± 40 , ± 50 , ± 60 , ± 70 , ± 80 , or ± 90 nucleotides at the 3' end and/or the 5' end. In some embodiments, the target region corresponds to nucleotides

272,888 – 310,849 of SEQ ID NO: 1 $\pm$ 10, $\pm$ 20, $\pm$ 30, $\pm$ 40, $\pm$ 50, $\pm$ 60, $\pm$ 70, $\pm$ 80, or $\pm$ 90 nucleotides at the 3' end and/or the 5' end.

[0107] In some embodiments, the ASO of the present disclosure hybridizes to multiple target regions within the *CAMK2D* transcript (e.g., pre-mRNA, SEQ ID NO: 1). In some embodiments, the ASO hybridizes to two different target regions within the *CAMK2D* transcript. In some embodiments, the ASO hybridizes to three different target regions within the *CAMK2D* transcript. The sequences of exemplary ASOs that hybridizes to multiple target regions, and the start/end sites of the different target regions are provided in FIG. 1B. In some embodiments, the ASOs that hybridizes to multiple regions within the *CAMK2D* transcript (e.g., pre-mRNA, SEQ ID NO: 1) are more potent (e.g., having lower EC₅₀) at reducing *CAMK2D* expression compared to ASOs that hybridizes to a single region within the *CAMK2D* transcript (e.g., pre-mRNA, SEQ ID NO: 1).

[0108] In some embodiments, the ASO of the disclosure is capable of hybridizing to the target nucleic acid (e.g., *CAMK2D* transcript) under physiological condition, i.e., *in vivo* condition. In some embodiments, the ASO of the disclosure is capable of hybridizing to the target nucleic acid (e.g., *CAMK2D* transcript) *in vitro*. In some embodiments, the ASO of the disclosure is capable of hybridizing to the target nucleic acid (e.g., *CAMK2D* transcript) *in vitro* under stringent conditions. Stringency conditions for hybridization *in vitro* are dependent on, *inter alia*, productive cell uptake, RNA accessibility, temperature, free energy of association, salt concentration, and time (see, e.g., Stanley T Crooke, *Antisense Drug Technology: Principles, Strategies and Applications*, 2nd Edition, CRC Press (2007)). Generally, conditions of high to moderate stringency are used for *in vitro* hybridization to enable hybridization between substantially similar nucleic acids, but not between dissimilar nucleic acids. An example of stringent hybridization conditions includes hybridization in 5X saline-sodium citrate (SSC) buffer (0.75 M sodium chloride/0.075 M sodium citrate) for 1 hour at 40°C, followed by washing the sample 10 times in 1X SSC at 40°C and 5 times in 1X SSC buffer at room temperature. *In vivo* hybridization conditions consist of intracellular conditions (e.g., physiological pH and intracellular ionic conditions) that govern the hybridization of antisense oligonucleotides with target sequences. *In vivo* conditions can be mimicked *in vitro* by relatively low stringency conditions. For example, hybridization can be carried out *in vitro* in 2X SSC (0.3 M sodium chloride/0.03 M sodium citrate), 0.1% SDS at 37°C. A wash solution containing 4X SSC, 0.1% SDS can be used at 37°C, with a final wash in 1X SSC at 45°C.

[0109] In some embodiments, the ASO of the present disclosure is capable of targeting a *CAMK2D* transcript from one or more species (*e.g.*, humans, non-human primates, dogs, cats, guinea pigs, rabbits, rats, mice, horses, cattle, and bears). In certain embodiments, the ASO disclosed herein is capable of targeting both human and rodent (*e.g.*, mice or rats) *CAMK2D* transcript. Accordingly, in some embodiments, the ASO is capable of down-regulating (*e.g.*, reducing or removing) expression of the *CAMK2D* mRNA or protein both in humans and in rodents (*e.g.*, mice or rats).

[0110] Sequences of mouse *CAMK2D* transcript are known in the art. For instance, the sequence for the mouse *CAMK2D* gene can be found under publicly available GenBank Accession Number NC_000069.6. The sequence for the mouse *CAMK2D* pre-mRNA transcript corresponds to residues 126,596,354 – 126,846,326 of NC_000069.6. The sequences for mouse *CAMK2D* mRNA transcript (both canonical and variants) are known and available as Accession Numbers NM_001025438.2 (canonical sequence), NM_001025439.2, NM_001293663.1, NM_001293664.1, NM_023813.4, NM_001346635.1, NM_001346636.1, NM_001293665.1, XM_006500836.3, XM_006500833.3, XM_006500835.3, XM_017319415.1, XM_006500818.3, XM_017319417.1, XM_017319418.1, XM_017319420.1, NM_001293666.1, XM_006500819.3, XM_017319416.1, XM_006500820.3, XM_006500822.3, XM_006500823.3, XM_006500824.3, XM_017319419.1, XM_006500826.3, XM_006500825.3, XM_006500829.3, BC052894.1, XM_006500831.3, XM_006500832.3, XM_017319422.1, XM_006500834.3, XM_006500839.3, and XM_017319421.1. . The sequence of mouse CAMK2D protein can be found under publicly available Accession Numbers: Q6PHZ2 (canonical sequence), Q3UF87, Q3UQH9, Q5DTK4, Q8CAC5, and Q9CZE2, each of which is incorporated by reference herein in its entirety. Three isoforms of the mouse CAMK2D protein are known. The sequence of CAMK2D Isoform Delta 6 differs from the canonical sequence as follows: 478-478: K → N and 479-499: Missing. The sequence of CAMK2D Isoform Delta 10 differs from the canonical as follows: 329-329: E → EPQTTVIHNPdGNKE; 478-478: K → N; and 479-499: Missing. The sequence of CAMK2D Isoform Delta 5 differs from the canonical sequence (as follows: 328-328: K → KINNKANVVTSPKENIPTPALEPQTTVIHNPdGNK; 478-478: K → N; and 479-499: Missing.

[0111] Sequences of rat *CAMK2D* transcript are also known in the art. The rat *CAMK2D* gene can be found under publicly available GenBank Accession Number NC_005101.4.

The sequence for the rat *CAMK2D* pre-mRNA transcript corresponds to residues 230,900,907 – 231,132,207 of NC_005101.4. The sequences for rat *CAMK2D* mRNA transcript (both canonical and variants) are known and available as Accession Number NM_012519.2 (canonical sequence), BC107562.1, XM_017590621.1, XM_017590605.1, XM_008761452.1, XM_017590606.1, XM_017590607.1, XM_017590608.1, XM_017590610.1, XM_017590611.1, XM_017590612.1, XM_006233285.3, XM_017590614.1, XM_017590615.1, XM_017590616.1, XM_017590613.1, XM_017590617.1, XM_017590618.1, XM_017590604.1, XM_017590609.1, XM_017590624.1, XM_017590625.1, XM_017590619.1, XM_017590620.1, XM_017590622.1, and XM_017590623.1. The sequence of rat CAMK2D protein can be found under publicly available Accession Numbers: P15791 (canonical sequence), P97915, P97916, Q3B7L0, Q63904, Q63905, Q63906, Q63907, and Q63908, each of which is incorporated by reference herein in its entirety. Six isoforms of rat CAMK2D protein are known. The sequence of CAMK2D Isoform Delta 2 differs from the canonical sequence as follows: 329-362: Missing. The sequence of CAMK2D Isoform Delta 3 differs from the canonical sequence as follows: 329-335: INNKANV → KRKSSSV; 337-359: Missing; and 360-362: GNK → QMM. The sequence of CAMK2D Isoform Delta 4 differs from the canonical sequence as follows: 349-362: Missing. The sequence of CAMK2D Isoform Delta 5 differs from the canonical sequence as follows: 329-362: Missing and 512-533: KPPCIPNGKENFSGGTSLWQNI → N. The sequence of CAMK2D Isoform Delta 6 differs from the canonical sequence as follows: 512-533: KPPCIPNGKENFSGGTSLWQNI → N. The sequence of CAMK2D Isoform Delta 7 differs from the canonical sequence as follows: 349-362: Missing and 512-533: KPPCIPNGKENFSGGTSLWQNI → N.

II.B. ASO Sequences

- [0112] The ASOs of the disclosure comprise a contiguous nucleotide sequence which corresponds to the complement of a region of *CAMK2D* transcript, *e.g.*, a nucleotide sequence corresponding to SEQ ID NO: 1.
- [0113] In certain embodiments, the disclosure provides an ASO from 10 – 30, such as 10 – 15 nucleotides, 10 – 20 nucleotides, or 10 – 25 nucleotides in length, wherein the contiguous nucleotide sequence has at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to a region within the complement of a

CAMK2D transcript, such as SEQ ID NO: 1 or naturally occurring variant thereof. Thus, for example, the ASO hybridizes to a single stranded nucleic acid molecule having the sequence of SEQ ID NO: 1 or a portion thereof.

[0114] The ASO can comprise a contiguous nucleotide sequence which is fully complementary (perfectly complementary) to the equivalent region of a nucleic acid which encodes a mammalian CAMK2D protein (*e.g.*, SEQ ID NO: 1). The ASO can comprise a contiguous nucleotide sequence which is fully complementary (perfectly complementary) to a nucleic acid sequence, or a region within the sequence, corresponding to nucleotides X-Y of SEQ ID NO: 1, wherein X and Y are the start site and the end site, respectively, as shown in FIGs. 1A and 1B.

[0115] In some embodiments, the nucleotide sequence of the ASOs of the disclosure or the contiguous nucleotide sequence has at least about 80% sequence identity to a sequence selected from SEQ ID NOs: 4 to 1713 (*i.e.*, the sequences in FIGs. 1A and 1B), such as at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96% sequence identity, at least about 97% sequence identity, at least about 98% sequence identity, at least about 99% sequence identity, such as about 100% sequence identity (homologous). In some embodiments, the ASO has a design described elsewhere herein (*e.g.*, Section II.G) or a chemical structure shown elsewhere herein (*e.g.*, FIGs. 1A and 1B).

[0116] In some embodiments the ASO (or contiguous nucleotide portion thereof) is selected from, or comprises, one of the sequences selected from the group consisting of SEQ ID NOs: 4 to 1713 or a region of at least 10 contiguous nucleotides thereof, wherein the ASO (or contiguous nucleotide portion thereof) can optionally comprise one, two, three, or four mismatches when compared to the corresponding *CAMK2D* transcript.

[0117] In some embodiments, the ASO comprises a sequence selected from the group consisting of SEQ ID NO: 254, SEQ ID NO: 27, SEQ ID NO: 114, SEQ ID NO: 158, SEQ ID NO: 190, SEQ ID NO: 327, SEQ ID NO: 463, SEQ ID NO: 513, SEQ ID NO: 516, SEQ ID NO: 519, SEQ ID NO: 657, SEQ ID NO: 659, SEQ ID NO: 827, SEQ ID NO: 1249, SEQ ID NO: 1326, SEQ ID NO: 1409, SEQ ID NO: 1524, SEQ ID NO: 1530, SEQ ID NO: 1662, and SEQ ID NO: 1676.

[0118] In some embodiments, the ASO comprises a sequence selected from the group consisting of SEQ ID NO: 55, SEQ ID NO: 61, SEQ ID NO: 63, SEQ ID NO: 71, SEQ ID NO: 75, SEQ ID NO: 79, SEQ ID NO: 84, SEQ ID NO: 85, SEQ ID NO: 92, SEQ ID

NO: 102, SEQ ID NO: 105, SEQ ID NO: 128, SEQ ID NO: 130, SEQ ID NO: 133, SEQ ID NO: 138, SEQ ID NO: 161, SEQ ID NO: 178, SEQ ID NO: 180, SEQ ID NO: 186, SEQ ID NO: 195, SEQ ID NO: 200, SEQ ID NO: 202, SEQ ID NO: 234, SEQ ID NO: 264, SEQ ID NO: 387, SEQ ID NO: 390, SEQ ID NO: 396, SEQ ID NO: 441, SEQ ID NO: 446, SEQ ID NO: 457, SEQ ID NO: 467, SEQ ID NO: 523, SEQ ID NO: 524, SEQ ID NO: 636, SEQ ID NO: 640, SEQ ID NO: 700, SEQ ID NO: 740, SEQ ID NO: 832, SEQ ID NO: 965, SEQ ID NO: 1015, SEQ ID NO: 1065, SEQ ID NO: 1071, SEQ ID NO: 1155, SEQ ID NO: 1475, SEQ ID NO: 1508, SEQ ID NO: 1685, SEQ ID NO: 1686, SEQ ID NO: 1687, SEQ ID NO: 1688, and SEQ ID NO: 1690.

[0119] In some embodiments, the ASOs of the disclosure bind to the target nucleic acid sequence (*e.g.*, *CAMK2D* transcript) and are capable of inhibiting or reducing expression of the *CAMK2D* transcript by at least 10% or 20% compared to the normal (*i.e.*, control) expression level in the cell, *e.g.*, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% compared to the normal expression level (*e.g.*, expression level in cells that have not been exposed to the ASO).

[0120] In some embodiments, the ASOs of the disclosure are capable of reducing expression of *CAMK2D* mRNA *in vitro* by at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% in HEK293 cells when the cells are in contact with 25 μ M of the ASO compared to HEK293 cells that are not in contact with the ASO (*e.g.*, contact with saline).

[0121] In some embodiments, the ASOs of the disclosure are capable of reducing expression of *CAMK2D* mRNA *in vitro* by at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% in human inducible pluripotent stem cell-derived cardiomyocytes (hiPSC-CM) cells when the cells are in contact with 500 nM of the ASO compared to hiPSC-CM cells that are not in contact with the ASO (*e.g.*, contact with saline).

[0122] In certain embodiments, the ASO of the disclosure has at least one property selected from the group consisting of: (i) reducing an mRNA level encoding *CAMK2D* in

Inducible Pluripotent Stem Cell-Derived Cardiomyocytes (hiPSC-CM); (ii) reducing a protein level of CAMK2D in hiPSC-CM; (iii) reducing, ameliorating, or treating one or more symptoms of a cardiovascular disease or disorder, and (iv) any combination thereof.

[0123] In some embodiments, the ASO can tolerate 1, 2, 3, or 4 (or more) mismatches, when hybridizing to the target sequence and still sufficiently bind to the target to show the desired effect, *i.e.*, down-regulation of the target mRNA and/or protein. Mismatches can, for example, be compensated by increased length of the ASO nucleotide sequence and/or an increased number of nucleotide analogs, which are disclosed elsewhere herein.

[0124] In some embodiments, the ASO of the disclosure comprises no more than 3 mismatches when hybridizing to the target sequence. In other embodiments, the contiguous nucleotide sequence comprises no more than 2 mismatches when hybridizing to the target sequence. In other embodiments, the contiguous nucleotide sequence comprises no more than 1 mismatch when hybridizing to the target sequence.

II.C. ASO Length

[0125] The ASOs can comprise a contiguous nucleotide sequence of a total of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 contiguous nucleotides in length. It should be understood that when a range is given for an ASO, or contiguous nucleotide sequence length, the range includes the lower and upper lengths provided in the range, for example from (or between) 10–30, includes both 10 and 30.

[0126] In some embodiments, the ASOs comprise a contiguous nucleotide sequence of a total of about 14–20, 14, 15, 16, 17, 18, 19, or 20 contiguous nucleotides in length.

II.D. Nucleosides and Nucleoside analogs

[0127] In one aspect of the disclosure, the ASOs comprise one or more non-naturally occurring nucleoside analogs. "Nucleoside analogs" as used herein are variants of natural nucleosides, such as DNA or RNA nucleosides, by virtue of modifications in the sugar and/or base moieties. Analogs could in principle be merely "silent" or "equivalent" to the natural nucleosides in the context of the oligonucleotide, *i.e.* have no functional effect on the way the oligonucleotide works to inhibit target gene expression. Such "equivalent" analogs can nevertheless be useful if, for example, they are easier or cheaper to manufacture, or are more stable to storage or manufacturing conditions, or represent a tag or label. In some embodiments, however, the analogs will have a functional effect on the way in which the ASO works to inhibit expression; for example by producing increased

binding affinity to the target and/or increased resistance to intracellular nucleases and/or increased ease of transport into the cell. Specific examples of nucleoside analogs are described by *e.g.* Freier & Altmann; *Nucl. Acid Res.*, 1997, 25, 4429-4443 and Uhlmann; *Curr. Opinion in Drug Development*, 2000, 3(2), 293-213, and in Scheme 1. The ASOs of the present disclosure can contain more than one, more than two, more than three, more than four, more than five, more than six, more than seven, more than eight, more than nine, more than 10, more than 11, more than 12, more than 13, more than 14, more than 15, more than 16, more than 18, more than 19, or more than 20 nucleoside analogs. In some embodiments, the nucleoside analogs in the ASOs are the same. In other embodiments, the nucleoside analogs in the ASOs are different. The nucleotide analogs in the ASOs can be any one of or combination of the following nucleoside analogs.

II.D.1. Nucleobase

- [0128] The term nucleobase includes the purine (*e.g.*, adenine and guanine) and pyrimidine (*e.g.*, uracil, thymine and cytosine) moiety present in nucleosides and nucleotides which form hydrogen bonds in nucleic acid hybridization. In the context of the present disclosure, the term nucleobase also encompasses modified nucleobases which may differ from naturally occurring nucleobases, but are functional during nucleic acid hybridization. In some embodiments, the nucleobase moiety is modified by modifying or replacing the nucleobase. In this context, "nucleobase" refers to both naturally occurring nucleobases such as adenine, guanine, cytosine, thymidine, uracil, xanthine and hypoxanthine, as well as non-naturally occurring variants. Such variants are for example described in Hirao *et al.*, (2012) *Accounts of Chemical Research* vol 45 page 2055 and Bergstrom (2009) *Current Protocols in Nucleic Acid Chemistry Suppl.* 37 1.4.1.
- [0129] In some embodiments, the nucleobase moiety is modified by changing the purine or pyrimidine into a modified purine or pyrimidine, such as substituted purine or substituted pyrimidine, such as a nucleobase selected from isocytosine, pseudoisocytosine, 5-methyl-cytosine, 5-thiazolo-cytosine, 5-propynyl-cytosine, 5-propynyl-uracil, 5-bromouracil, 5-thiazolo-uracil, 2-thio-uracil, 2-thio-thymine, inosine, diaminopurine, 6-aminopurine, 2-aminopurine, 2,6-diaminopurine, and 2-chloro-6-aminopurine.
- [0130] The nucleobase moieties may be indicated by the letter code for each corresponding nucleobase, *e.g.*, A, T, G, C, or U, wherein each letter may optionally include modified nucleobases of equivalent function. For example, in the exemplified oligonucleotides, the

nucleobase moieties are selected from A, T, G, C, and 5-methyl-cytosine. Optionally, for LNA gapmers, 5-methyl-cytosine LNA nucleosides may be used.

II.D.2. Sugar Modification

[0131] The ASO of the disclosure can comprise one or more nucleosides which have a modified sugar moiety, *i.e.* a modification of the sugar moiety when compared to the ribose sugar moiety found in DNA and RNA. Numerous nucleosides with modification of the ribose sugar moiety have been made, primarily with the aim of improving certain properties of oligonucleotides, such as affinity and/or nuclease resistance.

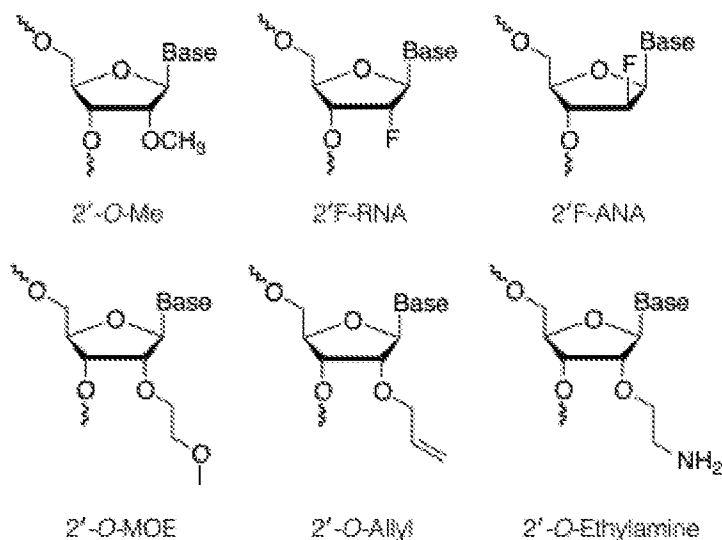
[0132] Such modifications include those where the ribose ring structure is modified, *e.g.* by replacement with a hexose ring (HNA), or a bicyclic ring, which typically have a biradical bridge between the C2' and C4' carbons on the ribose ring (LNA), or an unlinked ribose ring which typically lacks a bond between the C2' and C3' carbons (*e.g.*, UNA). Other sugar modified nucleosides include, for example, bicyclohexose nucleic acids (WO2011/017521) or tricyclic nucleic acids (WO2013/154798). Modified nucleosides also include nucleosides where the sugar moiety is replaced with a non-sugar moiety, for example in the case of peptide nucleic acids (PNA), or morpholino nucleic acids.

[0133] Sugar modifications also include modifications made via altering the substituent groups on the ribose ring to groups other than hydrogen, or the 2'-OH group naturally found in RNA nucleosides. Substituents may, for example be introduced at the 2', 3', 4', or 5' positions. Nucleosides with modified sugar moieties also include 2' modified nucleosides, such as 2' substituted nucleosides. Indeed, much focus has been spent on developing 2' substituted nucleosides, and numerous 2' substituted nucleosides have been found to have beneficial properties when incorporated into oligonucleotides, such as enhanced nucleoside resistance and enhanced affinity.

II.D.2.a 2' modified nucleosides

[0134] A 2' sugar modified nucleoside is a nucleoside which has a substituent other than H or -OH at the 2' position (2' substituted nucleoside) or comprises a 2' linked biradical, and includes 2' substituted nucleosides and LNA (2' - 4' biradical bridged) nucleosides. For example, the 2' modified sugar may provide enhanced binding affinity (*e.g.*, affinity enhancing 2' sugar modified nucleoside) and/or increased nuclease resistance to the oligonucleotide. Examples of 2' substituted modified nucleosides are 2'-O-alkyl-RNA, 2'-

O-methyl-RNA, 2'-alkoxy-RNA, 2'-O-methoxyethyl-RNA (MOE), 2'-amino-DNA, 2'-Fluoro-RNA, 2'-Fluoro-DNA, arabino nucleic acids (ANA), and 2'-Fluoro-ANA nucleoside. For further examples, please see, e.g., Freier & Altmann; *Nucl. Acid Res.*, 1997, 25, 4429-4443; Uhlmann, *Curr. Opinion in Drug Development*, 2000, 3(2), 293-213; and Deleavey and Damha, *Chemistry and Biology* 2012, 19, 937. Below are illustrations of some 2' substituted modified nucleosides.



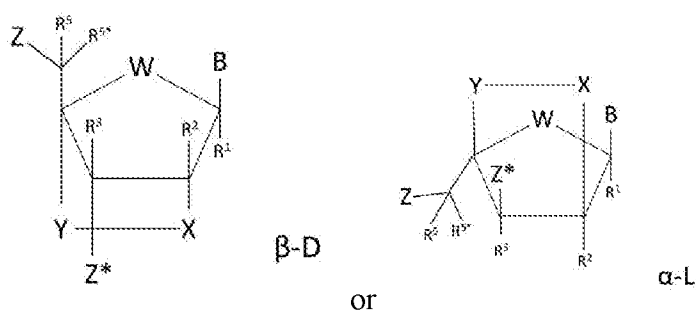
II.D.2.b Locked Nucleic Acid Nucleosides (LNA).

[0135] LNA nucleosides are 2'-sugar modified nucleosides which comprise a linker group (referred to as a biradical or a bridge) between C2' and C4' of the ribose sugar ring of a nucleoside (*i.e.*, 2'-4' bridge), which restricts or locks the conformation of the ribose ring. These nucleosides are also termed bridged nucleic acid or bicyclic nucleic acid (BNA) in the literature. The locking of the conformation of the ribose is associated with an enhanced affinity of hybridization (duplex stabilization) when the LNA is incorporated into an oligonucleotide for a complementary RNA or DNA molecule. This can be routinely determined by measuring the melting temperature of the oligonucleotide/complement duplex.

[0136] Non limiting, exemplary LNA nucleosides are disclosed in WO 99/014226, WO 00/66604, WO 98/039352, WO 2004/046160, WO 00/047599, WO 2007/134181, WO 2010/077578, WO 2010/036698, WO 2007/090071, WO 2009/006478, WO 2011/156202, WO 2008/154401, WO 2009/067647, WO 2008/150729, Morita *et al.*, *Bioorganic & Med.Chem. Lett.* 12, 73-76, Seth *et al.*, *J. Org. Chem.* 2010, Vol 75(5) pp. 1569-81, and Mitsuoka *et al.*, *Nucleic Acids Research* 2009, 37(4), 1225-1238.

- [0137] The 2'-4' bridge comprises 1 to 4 bridging atoms and is in particular of formula -X-Y- wherein
- [0138] X is oxygen, sulfur, $-\text{CR}^{\text{a}}\text{R}^{\text{b}}-$, $-\text{C}(\text{R}^{\text{a}})=\text{C}(\text{R}^{\text{b}})-$, $-\text{C}(=\text{CR}^{\text{a}}\text{R}^{\text{b}})-$, $-\text{C}(\text{R}^{\text{a}})=\text{N}-$, $-\text{Si}(\text{R}^{\text{a}})_2-$, $-\text{SO}_2-$, $-\text{NR}^{\text{a}}-$, $-\text{O}-\text{NR}^{\text{a}}-$, $-\text{NR}^{\text{a}}-\text{O}-$, $>\text{C}=\text{J}$, Se; $-\text{cPr}-$, $-\text{O}-\text{NR}^{\text{a}}-$, $\text{NR}^{\text{a}}-\text{CR}^{\text{a}}\text{R}^{\text{b}}-$, $-\text{N}(\text{R}^{\text{a}})-\text{O}-$, or $-\text{O}-\text{CR}^{\text{a}}\text{R}^{\text{b}}-$;
- [0139] Y is oxygen, sulfur, $-(\text{CR}^{\text{a}}\text{R}^{\text{b}})_n-$, $-\text{CR}^{\text{a}}\text{R}^{\text{b}}-\text{O}-\text{CR}^{\text{a}}\text{R}^{\text{b}}-$, $-\text{C}(\text{R}^{\text{a}})=\text{C}(\text{R}^{\text{b}})-$, $-\text{C}(\text{R}^{\text{a}})=\text{N}-$, $-\text{Si}(\text{R}^{\text{a}})_2-$, $-\text{SO}_2-$, $-\text{NR}^{\text{a}}-$, or $>\text{C}=\text{J}$ Se; $-\text{cPr}-$, $-\text{O}-\text{NR}^{\text{a}}-$, $-\text{O}-\text{CR}^{\text{a}}\text{R}^{\text{b}}-$, or $\text{NR}^{\text{a}}-\text{CR}^{\text{a}}\text{R}^{\text{b}}-$; wherein n is 1 or 2;
- [0140] with the proviso that -X-Y- is not $-\text{O}-\text{O}-$, $\text{Si}(\text{R}^{\text{a}})_2-\text{Si}(\text{R}^{\text{a}})_2-$, $-\text{SO}_2-\text{SO}_2-$, $-\text{C}(\text{R}^{\text{a}})=\text{C}(\text{R}^{\text{b}})-\text{C}(\text{R}^{\text{a}})=\text{C}(\text{R}^{\text{b}})-$, $-\text{C}(\text{R}^{\text{a}})=\text{N}-\text{C}(\text{R}^{\text{a}})=\text{N}-$, $-\text{C}(\text{R}^{\text{a}})=\text{N}-\text{C}(\text{R}^{\text{a}})=\text{C}(\text{R}^{\text{b}})-$, $-\text{C}(\text{R}^{\text{a}})=\text{C}(\text{R}^{\text{b}})-\text{C}(\text{R}^{\text{a}})=\text{N}-$, or $-\text{Se}-\text{Se}-$;
- [0141] J is oxygen, sulfur, CH_2 , or $=\text{N}(\text{R}^{\text{a}})$;
- [0142] R^{a} and R^{b} are independently selected from hydrogen, halogen, hydroxyl, cyano, thiohydroxyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, alkoxyalkyl, alkenyloxy, carboxyl, alkoxycarbonyl, alkylcarbonyl, formyl, aryl, heterocycle, amino, alkylamino, carbamoyl, alkylaminocarbonyl, aminoalkylaminocarbonyl, alkylaminoalkylaminocarbonyl, alkylcarbonylamino, carbamido, alkanoyloxy, sulfone alkylsulfonyloxy, nitro, azido, thiolsulfidealkylsulfanyl, aryloxy, arylcarbonyl, heteroaryl, heteroaryloxy, heteroarylcarbonyl, $-\text{OC}(=\text{X}^{\text{a}})\text{R}^{\text{c}}$, $-\text{OC}(=\text{X}^{\text{a}})\text{NR}^{\text{c}}\text{R}^{\text{d}}$ and $-\text{NR}^{\text{c}}\text{C}(=\text{X}^{\text{a}})\text{NR}^{\text{c}}\text{R}^{\text{d}}$; or two geminal R^{a} and R^{b} together form optionally substituted methylene; wherein substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkoxy and substituted methylene are alkyl, alkenyl, alkynyl and methylene substituted with 1 to 3 substituents independently selected from halogen, hydroxyl, alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, alkenyloxy, carboxyl, alkoxycarbonyl, alkylcarbonyl, formyl, heterocycle, aryl, and heteroaryl;
- X^{a} is oxygen, sulfur or $-\text{NRC}$;
- R^{c} , R^{d} , and R^{e} are independently hydrogen or alkyl; and
- n is 1, 2 or 3.
- [0143] In some embodiments, X is oxygen, sulfur, $-\text{NR}^{\text{a}}-$, $-\text{CR}^{\text{a}}\text{R}^{\text{b}}-$ or $-\text{C}(=\text{CR}^{\text{a}}\text{R}^{\text{b}})-$, particularly oxygen, sulfur, $-\text{NH}-$, $-\text{CH}_2-$ or $-\text{C}(=\text{CH}_2)-$, more particularly oxygen.
- [0144] In some embodiments, Y is $-\text{CR}^{\text{a}}\text{R}^{\text{b}}-$, $-\text{CR}^{\text{a}}\text{R}^{\text{b}}-\text{CR}^{\text{a}}\text{R}^{\text{b}}-$ or $-\text{CR}^{\text{a}}\text{R}^{\text{b}}-\text{CR}^{\text{a}}\text{R}^{\text{b}}-\text{CR}^{\text{a}}\text{R}^{\text{b}}-$, particularly $-\text{CH}_2-\text{CHCH}_3-$, $-\text{CHCH}_3-\text{CH}_2-$, CH_2-CH_2- or $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$.

- [0145] In some embodiments, -X-Y- is $-\text{O}-(\text{CR}^a\text{R}^b)_n-$, $-\text{S}-\text{CR}^a\text{R}^b-$, $-\text{N}(\text{R}^a)\text{CR}^a\text{R}^b-$, $-\text{CR}^a\text{R}^b-\text{CR}^a\text{R}^b-$, $-\text{O}-\text{CR}^a\text{R}^b-\text{O}-\text{CR}^a\text{R}^b-$, $-\text{CR}^a\text{R}^b-\text{O}-\text{CR}^a\text{R}^b-$, $-\text{C}(=\text{CR}^a\text{R}^b)-\text{CR}^a\text{R}^b-$, $-\text{N}(\text{R}^a)\text{CR}^a\text{R}^b-$, $-\text{O}-\text{N}(\text{R}^a)\text{CR}^a\text{R}^b-$, or $-\text{N}(\text{R}^a)-\text{O}-\text{CR}^a\text{R}^b-$.
- [0146] In some embodiments, R^a and R^b are independently selected from the group consisting of hydrogen, halogen, hydroxyl, alkyl and alkoxyalkyl, in particular, hydrogen, alkyl and alkoxyalkyl.
- [0147] In some embodiments, R^a and R^b are independently selected from the group consisting of hydrogen, halogen, such as fluoro, hydroxyl, methyl and $-\text{CH}_2-\text{O}-\text{CH}_3$, in particular, hydrogen, methyl and $-\text{CH}_2-\text{O}-\text{CH}_3$.
- [0148] In some embodiments, R^a is hydrogen or alkyl, in particular, hydrogen or methyl.
- [0149] In some embodiments, R^b is hydrogen or alkyl, in particular hydrogen or methyl. In some embodiments, one or both of R^a and R^b are hydrogen. In certain embodiments, only one of R^a and R^b is hydrogen. In some embodiments, one of R^a and R^b is methyl and the other one is hydrogen. In other embodiments, R^a and R^b are both methyl at the same time.
- [0150] In a particular embodiment of the invention, -X-Y- is $-\text{O}-\text{CH}_2-$, $-\text{S}-\text{CH}_2-$, $-\text{S}-\text{CH}(\text{CH}_3)-$, $-\text{NH}-\text{CH}_2-$, $-\text{O}-\text{CH}_2\text{CH}_2-$, $-\text{O}-\text{CH}(\text{CH}_2-\text{O}-\text{CH}_3)-$, $-\text{O}-\text{CH}(\text{CH}_2\text{CH}_3)-$, $-\text{O}-\text{CH}(\text{CH}_3)-$, $-\text{O}-\text{CH}_2-\text{O}-\text{CH}_2-$, $-\text{O}-\text{CH}_2-\text{O}-\text{CH}_2-$, $-\text{CH}_2-\text{O}-\text{CH}_2-$, $-\text{C}(=\text{CH}_2)\text{CH}_2-$, $-\text{C}(=\text{CH}_2)\text{CH}(\text{CH}_3)-$, $-\text{N}(-\text{O}-\text{CH}_3)-$ or $-\text{N}(\text{CH}_3)-$;
- [0151] In some embodiments, -X-Y- is $-\text{O}-\text{CR}^a\text{R}^b-$ wherein R^a and R^b are independently selected from the group consisting of hydrogen, alkyl and alkoxyalkyl, in particular, hydrogen, methyl and $-\text{CH}_2-\text{O}-\text{CH}_3$.
- [0152] In some embodiments, -X-Y- is $-\text{O}-\text{CH}_2-$ or $-\text{O}-\text{CH}(\text{CH}_3)-$, particularly $-\text{O}-\text{CH}_2-$.
- [0153] The 2'-4' bridge can be positioned either below the plane of the ribose ring (beta-D-configuration), or above the plane of the ring (alpha-L-configuration), as illustrated in formula (A) and formula (B) respectively.
- [0154] In some embodiments, the modified nucleoside or the LNA nucleosides of the ASO of the disclosure has a general structure of the formula II or III:



Formula II

Formula III

wherein

W is selected from -O-, -S-, -N(R^a)-, -C(R^aR^b)-, in particular -O-;

B is a nucleobase or a modified nucleobase moiety;

Z is an internucleoside linkage to an adjacent nucleoside or a 5'-terminal group;

Z* is an internucleoside linkage to an adjacent nucleoside or a 3'-terminal group;

R¹, R², R³, R⁵ and R^{5*} are independently selected from hydrogen, halogen, alkyl, alkenyl, alkynyl, hydroxy, alkoxy, alkoxyalkyl, alkenyloxy, carboxyl, alkoxy carbonyl, alkyl carbonyl, formyl, azide, heterocycle and aryl; and

X, Y, R^a and R^b are as defined herein.

[0155] In some embodiments, -X-Y-, R^a is hydrogen or alkyl, in particular hydrogen or methyl. In some embodiments of -X-Y-, R^b is hydrogen or alkyl, in particular hydrogen or methyl. In other embodiments of -X-Y-, one or both of R^a and R^b are hydrogen. In further embodiments of -X-Y-, only one of R^a and R^b is hydrogen. In some embodiments of -X-Y-, one of R^a and R^b is methyl and the other one is hydrogen. In certain embodiments of -X-Y-, R^a and R^b are both methyl at the same time.

[0156] In some embodiments, -X-, R^a is hydrogen or alkyl, in particular hydrogen or methyl. In some embodiments of -X-, R^b is hydrogen or alkyl, in particular hydrogen or methyl. In other embodiments of -X-, one or both of R^a and R^b are hydrogen. In certain embodiments of -X-, only one of R^a and R^b is hydrogen. In certain embodiments of -X-, one of R^a and R^b is methyl and the other one is hydrogen. In other embodiments of -X-, R^a and R^b are both methyl at the same time.

[0157] In some embodiments, -Y-, R^a is hydrogen or alkyl, in particular hydrogen or methyl. In certain embodiments of -Y-, R^b is hydrogen or alkyl, in particular hydrogen or methyl. In other embodiments of -Y-, one or both of R^a and R^b are hydrogen. In some embodiments of -Y-, only one of R^a and R^b is hydrogen. In other embodiments of -Y-, one of R^a and R^b is methyl and the other one is hydrogen. In some embodiments of -Y-, R^a and R^b are both methyl at the same time.

[0158] In some embodiments, R¹, R², R³, R⁵ and R^{5*} are independently selected from hydrogen and alkyl, in particular hydrogen and methyl.

[0159] In some embodiments, R¹, R², R³, R⁵ and R^{5*} are all hydrogen at the same time.

[0160] In some embodiments, R¹, R², R³, are all hydrogen at the same time, one of R⁵ and R^{5*} is hydrogen and the other one is as defined above, in particular alkyl, more particularly methyl.

- [0161] In some embodiments, R^1 , R^2 , R^3 , are all hydrogen at the same time, one of R^5 and R^{5*} is hydrogen and the other one is azide..
- [0162] In some embodiments, -X-Y- is -O-CH₂-, W is oxygen and R^1 , R^2 , R^3 , R^5 and R^{5*} are all hydrogen at the same time. Such LNA nucleosides are disclosed in WO 99/014226, WO 00/66604, WO 98/039352 and WO 2004/046160, which are all hereby incorporated by reference, and include what are commonly known in the art as beta-D-oxy LNA and alpha-L-oxy LNA nucleosides.
- [0163] In some embodiments, -X-Y- is -S-CH₂-, W is oxygen and R^1 , R^2 , R^3 , R^5 and R^{5*} are all hydrogen at the same time. Such thio LNA nucleosides are disclosed in WO 99/014226 and WO 2004/046160 which are hereby incorporated by reference.
- [0164] In some embodiments, -X-Y- is -NH-CH₂-, W is oxygen and R^1 , R^2 , R^3 , R^5 and R^{5*} are all hydrogen at the same time. Such amino LNA nucleosides are disclosed in WO 99/014226 and WO 2004/046160, which are hereby incorporated by reference.
- [0165] In some embodiments, -X-Y- is -O-CH₂CH₂- or -OCH₂CH₂CH₂-, W is oxygen, and R^1 , R^2 , R^3 , R^5 and R^{5*} are all hydrogen at the same time. Such LNA nucleosides are disclosed in WO 00/047599 and Morita *et al.*, *Bioorganic & Med.Chem. Lett.* 12, 73-76, which are hereby incorporated by reference, and include what are commonly known in the art as 2'-O-4'C-ethylene bridged nucleic acids (ENA).
- [0166] In some embodiments, -X-Y- is -O-CH₂-, W is oxygen, R^1 , R^2 , R^3 are all hydrogen at the same time, one of R^5 and R^{5*} is hydrogen and the other one is not hydrogen, such as alkyl, for example methyl. Such 5' substituted LNA nucleosides are disclosed in WO 2007/134181, which is hereby incorporated by reference.
- [0167] In some embodiments, -X-Y- is -O-CR^aR^b-, wherein one or both of R^a and R^b are not hydrogen, in particular alkyl such as methyl, W is oxygen, R^1 , R^2 , R^3 are all hydrogen at the same time, one of R^5 and R^{5*} is hydrogen and the other one is not hydrogen, in particular alkyl, for example methyl. Such bis modified LNA nucleosides are disclosed in WO 2010/077578, which is hereby incorporated by reference.
- [0168] In some embodiments, -X-Y- is -O-CH(CH₂-O-CH₃)- ("2' O-methoxyethyl bicyclic nucleic acid", Seth *et al.*, *J. Org. Chem.* 2010, Vol 75(5) pp. 1569-81).
- [0169] In some embodiments,, -X-Y- is -O-CHR^a-, W is oxygen and R^1 , R^2 , R^3 , R^5 and R^{5*} are all hydrogen at the same time. Such 6'-substituted LNA nucleosides are disclosed in WO 2010/036698 and WO 2007/090071, which are both hereby incorporated by reference. In such 6'-substituted LNA nucleosides, R^a is in particular C1-C6 alkyl, such as methyl.

- [0170] In some embodiments, -X-Y- is -O-CH(CH₂-O-CH₃)-, W is oxygen and R¹, R², R³, R⁵ and R^{5*} are all hydrogen at the same time. Such LNA nucleosides are also known in the art as cyclic MOEs (cMOE) and are disclosed in WO 2007/090071.
- [0171] In some embodiments, -X-Y- is -O-CH(CH₃)-.
- [0172] In some embodiments, -X-Y- is -O-CH₂-O-CH₂- (Seth *et al.*, *J. Org. Chem* 2010 op. cit.)
- [0173] In some embodiments, -X-Y- is -O-CH(CH₃)-, W is oxygen and R¹, R², R³, R⁵ and R^{5*} are all hydrogen at the same time. Such 6'-methyl LNA nucleosides are also known in the art as cET nucleosides, and may be either (S)-cET or (R)-cET diastereoisomers, as disclosed in WO 2007/090071 (beta-D) and WO 2010/036698 (alpha-L) which are both hereby incorporated by reference.
- [0174] In some embodiments, -X-Y- is -O-CR^aR^b-, wherein neither R^a nor R^b is hydrogen, W is oxygen, and R¹, R², R³, R⁵ and R^{5*} are all hydrogen at the same time. In certain embodiments, R^a and R^b are both alkyl at the same time, in particular both methyl at the same time. Such 6'-di-substituted LNA nucleosides are disclosed in WO 2009/006478 which is hereby incorporated by reference.
- [0175] In some embodiments, -X-Y- is -S-CHR^a-, W is oxygen, and R¹, R², R³, R⁵ and R^{5*} are all hydrogen at the same time. Such 6'-substituted thio LNA nucleosides are disclosed in WO 2011/156202, which is hereby incorporated by reference. In certain embodiments of such 6'-substituted thio LNA, R^a is alkyl, in particular methyl.
- [0176] In some embodiments, -X-Y- is -C(=CH₂)C(R^aR^b)-, such as, W is oxygen, and R¹, R², R³, R⁵ and R^{5*} are all hydrogen at the same time. Such vinyl carbo LNA nucleosides are disclosed in WO 2008/154401 and WO 2009/067647, which are both hereby incorporated by reference.
- [0177] In some embodiments, -X-Y- is -N(OR^a)-CH₂-, W is oxygen and R¹, R², R³, R⁵ and R^{5*} are all hydrogen at the same time. In some embodiments, R^a is alkyl such as methyl. Such LNA nucleosides are also known as N substituted LNAs and are disclosed in WO 2008/150729, which is hereby incorporated by reference.
- [0178] In some embodiments, -X-Y- is -O-NCH₃- (Seth *et al.*, *J. Org. Chem* 2010 op. cit.).
- [0179] In some embodiments, -X-Y- is ON(R^a)-N(R^a)-O-, -NR^a-CR^aR^b-CR^aR^b-, or -NR^a-CR^aR^b-, W is oxygen, and R¹, R², R³, R⁵ and R^{5*} are all hydrogen at the same time. In certain embodiments, R^a is alkyl, such as methyl. (Seth *et al.*, *J. Org. Chem* 2010 op. cit.).
- [0180] In some embodiments, R⁵ and R^{5*} are both hydrogen at the same time. In other embodiments, one of R⁵ and R^{5*} is hydrogen and the other one is alkyl, such as methyl. In

such embodiments, R^1 , R^2 and R^3 can be in particular hydrogen and -X-Y- can be in particular -O-CH₂- or -O-CHC(R^a)₃-, such as -O-CH(CH₃)-

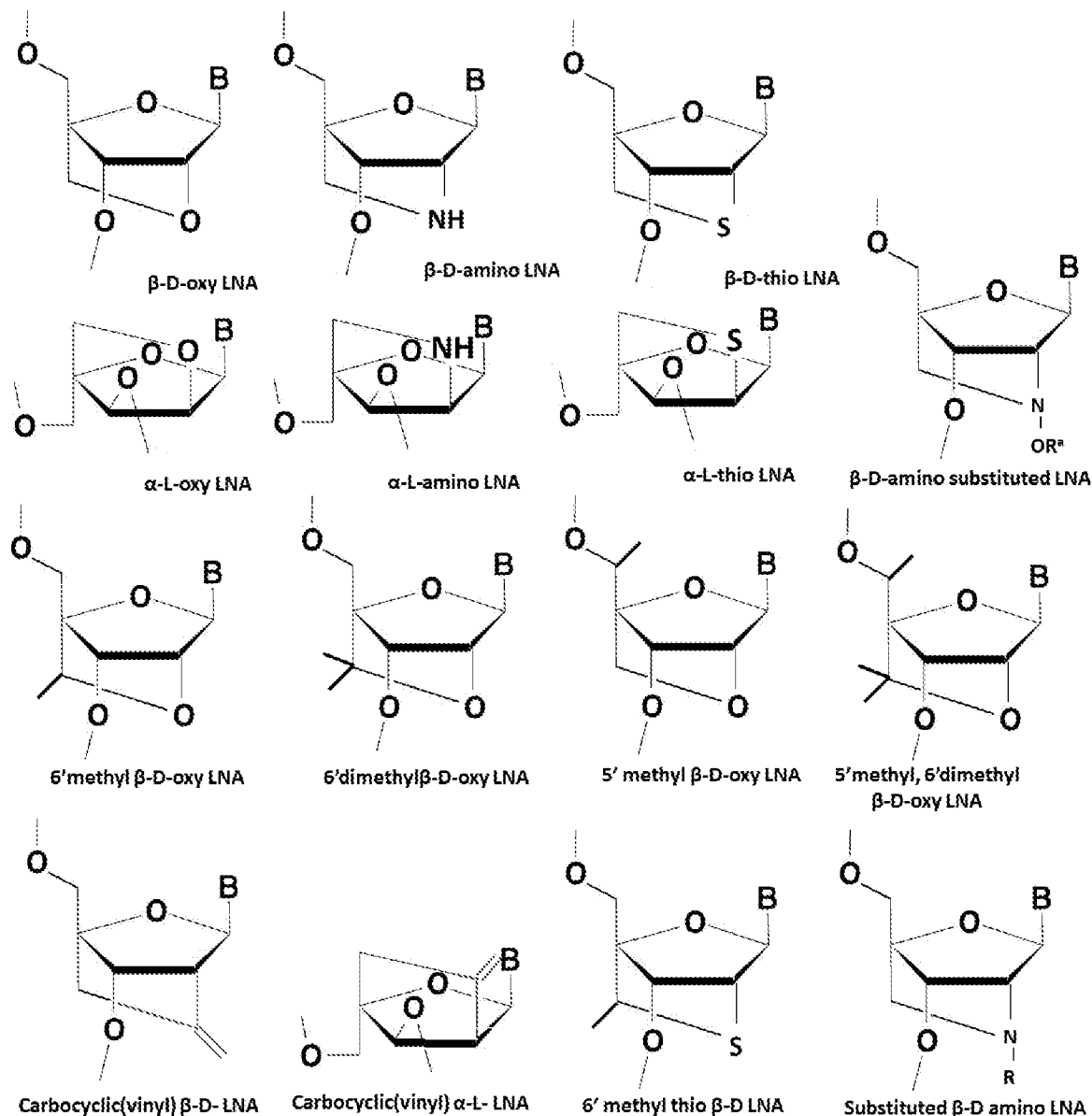
[0181] In some embodiments, -X-Y- is -CR^aR^b-O-CR^aR^b-, such as -CH₂-O-CH₂-, W is oxygen and R^1 , R^2 , R^3 , R^5 and R^{5*} are all hydrogen at the same time. In such embodiments, R^a can be in particular alkyl such as methyl. Such LNA nucleosides are also known as conformationally restricted nucleotides (CRNs) and are disclosed in WO 2013/036868, which is hereby incorporated by reference.

[0182] In some embodiments, -X-Y- is -O-CR^aR^b-O-CR^aR^b-, such as -O-CH₂-O-CH₂-, W is oxygen and R^1 , R^2 , R^3 , R^5 and R^{5*} are all hydrogen at the same time. In certain embodiments, R^a can be in particular alkyl such as methyl. Such LNA nucleosides are also known as COC nucleotides and are disclosed in Mitsuoka *et al.*, *Nucleic Acids Research* 2009, 37(4), 1225-1238, which is hereby incorporated by reference.

[0183] It will be recognized that, unless specified, the LNA nucleosides may be in the beta-D or alpha-L stereoisomer.

[0184] Certain examples of LNA nucleosides are presented in Scheme 1.

Scheme 1



[0185] As illustrated elsewhere, in some embodiments of the disclosure the LNA nucleosides in the oligonucleotides are beta-D-oxy-LNA nucleosides.

II.E. Nuclease mediated degradation

[0186] Nuclease mediated degradation refers to an oligonucleotide capable of mediating degradation of a complementary nucleotide sequence when forming a duplex with such a sequence.

[0187] In some embodiments, the oligonucleotide may function via nuclease mediated degradation of the target nucleic acid, where the oligonucleotides of the disclosure are capable of recruiting a nuclease, particularly an endonuclease, preferably endoribonuclease (RNase), such as RNase H. Examples of oligonucleotide designs which

operate via nuclease mediated mechanisms are oligonucleotides which typically comprise a region of at least 5 or 6 DNA nucleosides and are flanked on one side or both sides by affinity enhancing nucleosides, for example gapmers, headmers and tailmers.

II.F. RNase H Activity and Recruitment

[0188] The RNase H activity of an antisense oligonucleotide refers to its ability to recruit RNase H when in a duplex with a complementary RNA molecule and induce degradation of the complementary RNA molecule. WO01/23613 provides *in vitro* methods for determining RNaseH activity, which may be used to determine the ability to recruit RNaseH. Typically, an oligonucleotide is deemed capable of recruiting RNase H if, when provided with a complementary target nucleic acid sequence, it has an initial rate, as measured in pmol/l/min, of at least 5%, such as at least 10% or more than 20% of the of the initial rate determined when using a oligonucleotide having the same base sequence as the modified oligonucleotide being tested, but containing only DNA monomers, with phosphorothioate linkages between all monomers in the oligonucleotide, and using the methodology provided by Example 91 - 95 of WO01/23613.

[0189] In some embodiments, an oligonucleotide is deemed essentially incapable of recruiting RNaseH if, when provided with the complementary target nucleic acid, the RNaseH initial rate, as measured in pmol/l/min, is less than 20%, such as less than 10%, such as less than 5% of the initial rate determined when using a oligonucleotide having the same base sequence as the oligonucleotide being tested, but containing only DNA monomers, with no 2' substitutions, with phosphorothioate linkages between all monomers in the oligonucleotide, and using the methodology provided by Example 91 - 95 of WO01/23613.

II.G. ASO Design

[0190] The ASO of the disclosure can comprise a nucleotide sequence which comprises both nucleosides and nucleoside analogs, and can be in the form of a gapmer, blockmer, mixmer, headmer, tailmer, or totalmer. Examples of configurations of a gapmer, blockmer, mixmer, headmer, tailmer, or totalmer that can be used with the ASO of the disclosure are described in U.S. Patent Appl. Publ. No. 2012/0322851.

[0191] The term "gapmer" as used herein refers to an antisense oligonucleotide which comprises a region of RNase H recruiting oligonucleotides (gap) which is flanked 5' and 3' by one or more affinity enhancing modified nucleosides (flanks). The terms

"headmers" and "tailmers" are oligonucleotides capable of recruiting RNase H where one of the flanks is missing, *i.e.*, only one of the ends of the oligonucleotide comprises affinity enhancing modified nucleosides. For headmers, the 3' flank is missing (*i.e.*, the 5' flank comprise affinity enhancing modified nucleosides) and for tailmers, the 5' flank is missing (*i.e.*, the 3' flank comprises affinity enhancing modified nucleosides). The term "LNA gapmer" is a gapmer oligonucleotide wherein at least one of the affinity enhancing modified nucleosides is an LNA nucleoside. The term "mixed wing gapmer" refers to an LNA gapmer wherein the flank regions comprise at least one LNA nucleoside and at least one DNA nucleoside or non-LNA modified nucleoside, such as at least one 2' substituted modified nucleoside, such as, for example, 2'-O-alkyl-RNA, 2'-O-methyl-RNA, 2'-alkoxy-RNA, 2'-O-methoxyethyl-RNA (MOE), 2'-amino-DNA, 2'-Fluoro-RNA, 2'-Fluoro-DNA, arabino nucleic acid (ANA), and 2'-Fluoro-ANA nucleoside(s).

[0192] Other "chimeric" ASOs, called "mixmers", consist of an alternating composition of (i) DNA monomers or nucleoside analog monomers recognizable and cleavable by RNase, and (ii) non-RNase recruiting nucleoside analog monomers.

[0193] A "totalmer" is a single stranded ASO which only comprises non-naturally occurring nucleotides or nucleotide analogs.

[0194] In some embodiments, in addition to enhancing affinity of the ASO for the target region, some nucleoside analogs also mediate RNase (*e.g.*, RNaseH) binding and cleavage. Since α -L-LNA monomers recruit RNaseH activity to a certain extent, in some embodiments, gap regions (*e.g.*, region B as referred to herein) of ASOs containing α -L-LNA monomers consist of fewer monomers recognizable and cleavable by the RNaseH, and more flexibility in the mixmer construction is introduced.

II.G.1. Gapmer Design

[0195] In some embodiments, the ASO of the disclosure is a gapmer and comprises a contiguous stretch of nucleotides (*e.g.*, one or more DNA) which is capable of recruiting an RNase, such as RNaseH, referred to herein as region B (B), wherein region B is flanked at both 5' and 3' by regions of nucleoside analogs 5' and 3' to the contiguous stretch of nucleotides of region B— these regions are referred to as regions A (A) and C (C), respectively. In some embodiments, the nucleoside analogs are sugar modified nucleosides (*e.g.*, high affinity sugar modified nucleosides). In certain embodiments, the sugar modified nucleosides of regions A and C enhance the affinity of the ASO for the target nucleic acid (*i.e.*, affinity enhancing 2' sugar modified nucleosides). In some

embodiments, the sugar modified nucleosides are 2' sugar modified nucleosides, such as high affinity 2' sugar modifications, such as LNA or 2'-MOE.

[0196] In a gapmer, the 5' and 3' most nucleosides of region B are DNA nucleosides, and are positioned adjacent to nucleoside analogs (*e.g.*, high affinity sugar modified nucleosides) of regions A and C, respectively. In some embodiments, regions A and C can be further defined by having nucleoside analogs at the end most distant from region B (*i.e.*, at the 5' end of region A and at the 3' end of region C).

[0197] In some embodiments, the ASOs of the present disclosure comprise a nucleotide sequence of formula (5' to 3') A-B-C, wherein: (A) (5' region or a first wing sequence) comprises at least one nucleoside analog (*e.g.*, 3-5 LNA units); (B) comprises at least four consecutive nucleosides (*e.g.*, 4-24 DNA units), which are capable of recruiting RNase (when formed in a duplex with a complementary RNA molecule, such as the pre-mRNA or mRNA target); and (C) (3' region or a second wing sequence) comprises at least one nucleoside analog (*e.g.*, 3-5 LNA units).

[0198] In some embodiments, region A comprises 3-5 nucleotide analogs, such as LNA, region B consists of 6-24 (*e.g.*, 6, 7, 8, 9, 10, 11, 12, 13, or 14) DNA units, and region C consists of 3 or 4 nucleotide analogs, such as LNA. Such designs include (A-B-C) 3-14-3, 3-11-3, 3-12-3, 3-13-3, 4-9-4, 4-10-4, 4-11-4, 4-12-4, and 5-10-5. In some embodiments, the ASO has a design of LLLD_nLLL, LLLLD_nLLLL, or LLLLLD_nLLLLL, wherein the L is a nucleoside analog, the D is DNA, and n can be any integer between 4 and 24. In some embodiments, n can be any integer between 6 and 14. In some embodiments, n can be any integer between 8 and 12.

[0199] Further gapmer designs are disclosed in WO2004/046160, WO 2007/146511, and WO2008/113832, each of which is hereby incorporated by reference in its entirety.

II.H. Internucleotide Linkages

[0200] The monomers of the ASOs described herein are coupled together via linkage groups. Suitably, each monomer is linked to the 3' adjacent monomer via a linkage group.

[0201] The person having ordinary skill in the art would understand that, in the context of the present disclosure, the 5' monomer at the end of an ASO does not comprise a 5' linkage group, although it may or may not comprise a 5' terminal group.

[0202] The terms "linkage group" or "internucleoside linkage" are intended to mean a group capable of covalently coupling together two nucleosides. Specific and preferred examples include phosphate groups and phosphorothioate groups.

[0203] The nucleosides of the ASO of the disclosure or contiguous nucleosides sequence thereof are coupled together via linkage groups. Suitably each nucleoside is linked to the 3' adjacent nucleoside via a linkage group.

[0204] In some embodiments, the internucleoside linkage is modified from its normal phosphodiester to one that is more resistant to nuclease attack, such as phosphorothioate, which is cleavable by RNaseH, also allows that route of antisense inhibition in reducing the expression of the target gene. In some embodiments, at least 75%, at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% of internucleoside linkages are modified.

II.I. Conjugates

[0205] The term conjugate as used herein refers to an ASO which is covalently linked to a non-nucleotide moiety (conjugate moiety or region C or third region).

[0206] Conjugation of the ASO of the disclosure to one or more non-nucleotide moieties may improve the pharmacology of the ASO, *e.g.*, by affecting the activity, cellular distribution, cellular uptake, or stability of the ASO. In some embodiments, the non-nucleotide moieties modify or enhance the pharmacokinetic properties of the ASO by improving cellular distribution, bioavailability, metabolism, excretion, permeability, and/or cellular uptake of the ASO. In certain embodiments, the non-nucleotide moieties may target the ASO to a specific organ, tissue, or cell type and thereby enhance the effectiveness of the ASO in that organ, tissue, or cell type. In other embodiments, the non-nucleotide moieties reduce the activity of the ASO in non-target cell types, tissues, or organs, *e.g.*, off target activity or activity in non-target cell types, tissues, or organs. WO 93/07883 and WO2013/033230 provides suitable conjugate moieties. Further suitable conjugate moieties are those capable of binding to the asialoglycoprotein receptor (ASGPr). In particular, tri-valent N-acetylgalactosamine conjugate moieties are suitable for binding to the ASGPr, *see, e.g.*, WO 2014/076196, WO 2014/207232, and WO 2014/179620, each of which are hereby incorporated by reference.

[0207] In some embodiments, the non-nucleotide moiety (conjugate moiety) is selected from the group consisting of carbohydrates, cell surface receptor ligands, drug substances, hormones, lipophilic substances, polymers, proteins, peptides, toxins (*e.g.*, bacterial toxins), vitamins, viral proteins (*e.g.*, capsids), and combinations thereof.

II.J. Activated ASOs

[0208] The term "activated ASO," as used herein, refers to an ASO that is covalently linked (*i.e.*, functionalized) to at least one functional moiety that permits covalent linkage of the ASO to one or more conjugated moieties, *i.e.*, moieties that are not themselves nucleic acids or monomers, to form the conjugates herein described. Typically, a functional moiety will comprise a chemical group that is capable of covalently bonding to the ASO via, *e.g.*, a 3'-hydroxyl group or the exocyclic NH₂ group of the adenine base, a spacer that can be hydrophilic and a terminal group that is capable of binding to a conjugated moiety (*e.g.*, an amino, sulfhydryl or hydroxyl group). In some embodiments, this terminal group is not protected, *e.g.*, is an NH₂ group. In other embodiments, the terminal group is protected, for example, by any suitable protecting group such as those described in "Protective Groups in Organic Synthesis" by Theodora W Greene and Peter G M Wuts, 3rd edition (John Wiley & Sons, 1999), which is hereby incorporated by reference.

[0209] In some embodiments, ASOs of the disclosure are functionalized at the 5' end in order to allow covalent attachment of the conjugated moiety to the 5' end of the ASO. In other embodiments, ASOs of the disclosure can be functionalized at the 3' end. In still other embodiments, ASOs of the disclosure can be functionalized along the backbone or on the heterocyclic base moiety. In yet other embodiments, ASOs of the disclosure can be functionalized at more than one position independently selected from the 5' end, the 3' end, the backbone and the base.

[0210] In some embodiments, activated ASOs of the disclosure are synthesized by incorporating during the synthesis one or more monomers that is covalently attached to a functional moiety. In other embodiments, activated ASOs of the disclosure are synthesized with monomers that have not been functionalized, and the ASO is functionalized upon completion of synthesis.

III. Pharmaceutical Compositions and Administration Routes

[0211] The ASO of the disclosure can be used in pharmaceutical formulations and compositions. In some embodiments, such compositions comprise a pharmaceutically acceptable diluent, carrier, salt, or adjuvant. In certain embodiments, a pharmaceutically acceptable salt comprises a sodium salt, a potassium salt, or an ammonium salt

- [0212] The ASO of the disclosure can be included in a unit formulation such as in a pharmaceutically acceptable carrier or diluent in an amount sufficient to deliver to a patient a therapeutically effective amount without causing serious side effects in the treated patient. However, in some forms of therapy, serious side effects may be acceptable in terms of ensuring a positive outcome to the therapeutic treatment.
- [0213] The formulated drug may comprise pharmaceutically acceptable binding agents and adjuvants. Capsules, tablets, or pills can contain for example the following compounds: microcrystalline cellulose, gum or gelatin as binders; starch or lactose as excipients; stearates as lubricants; various sweetening or flavoring agents. For capsules, the dosage unit can contain a liquid carrier like fatty oils. Likewise, coatings of sugar or enteric agents can be part of the dosage unit. The ASO formulations can also be emulsions of the active pharmaceutical ingredients and a lipid forming a micellular emulsion.
- [0214] The pharmaceutical compositions of the present disclosure can be administered in a number of ways depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration can be (a) oral; (b) pulmonary, *e.g.*, by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal, intranasal, (c) topical including epidermal, transdermal, ophthalmic and to mucous membranes including vaginal and rectal delivery; or (d) parenteral including intravenous, intraarterial, subcutaneous, intraperitoneal or intramuscular injection or infusion; or intracranial, *e.g.*, intrathecal, intra-cerebroventricular, or intraventricular, administration. In some embodiments, the ASO is administered intravenously, intraperitoneally, orally, topically, or as a bolus injection or administered directly in to the target organ. In some embodiments, the ASO is administered intracardially or intraventricularly as a bolus injection. In some embodiments, the ASO is administered subcutaneously. In some embodiments, the ASO is administered orally.
- [0215] Pharmaceutical compositions and formulations for topical administration can include transdermal patches, ointments, lotions, creams, gels, drops, sprays, suppositories, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable. Examples of topical formulations include those in which the ASO of the disclosure are in admixture with a topical delivery agent such as lipids, liposomes, fatty acids, fatty acid esters, steroids, chelating agents and surfactants. Compositions and formulations for oral administration include but are not limited to powders or granules, microparticulates, nanoparticulates, suspensions or solutions in water or non-aqueous media, capsules, gel capsules, sachets,

tablets or minitables. Compositions and formulations for parenteral, intrathecal, intracerebroventricular, or intraventricular administration can include sterile aqueous solutions which can also contain buffers, diluents and other suitable additives such as, but not limited to, penetration enhancers, carrier compounds and other pharmaceutically acceptable carriers or excipients.

[0216] Pharmaceutical compositions of the present disclosure include, but are not limited to, solutions, emulsions, and liposome-containing formulations. These compositions may be generated from a variety of components that include, but are not limited to, preformed liquids, self-emulsifying solids and self-emulsifying semisolids. Delivery of drug to the target tissue can be enhanced by carrier-mediated delivery including, but not limited to, cationic liposomes, cyclodextrins, porphyrin derivatives, branched chain dendrimers, polyethylenimine polymers, nanoparticles and microspheres (Dass CR. *J Pharm Pharmacol* 2002; 54(1):3-27).

[0217] The pharmaceutical formulations of the present disclosure, which can conveniently be presented in unit dosage form, can 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 or finely divided solid carriers or both, and then, if necessary, shaping the product.

[0218] For parenteral, subcutaneous, intradermal, or topical administration the formulation can include a sterile diluent, buffers, regulators of tonicity and antibacterials. The active ASOs can be prepared with carriers that protect against degradation or immediate elimination from the body, including implants or microcapsules with controlled release properties. For intravenous administration the carriers can be physiological saline or phosphate buffered saline. International Publication No. WO2007/031091 (A2), published March 22, 2007, further provides suitable pharmaceutically acceptable diluent, carrier and adjuvants - which are hereby incorporated by reference.

IV. Diagnostics

[0219] This disclosure further provides a diagnostic method useful during diagnosis of cardiovascular diseases, *e.g.*, a heart failure. Non-limiting examples of cardiovascular diseases that can be diagnosed with the present ASOs include, but are not limited to, coronary artery disease, stroke, heart failure, hypertensive heart disease, rheumatic heart

disease, cardiomyopathy, heart arrhythmia, congenital heart disease, valvular heart disease, aortic aneurysms, peripheral artery disease, thromboembolic disease, and venous thrombosis. In some embodiments, heart failure comprises a left-sided heart failure, a right-sided heart failure, a congestive heart failure, a heart failure with reduced ejection fraction (HFrEF), a heart failure with preserved ejection fraction (HFpEF), a heart failure with mid-range ejection fraction (HFmrEF), a hypertrophic cardiomyopathy (HCM), a hypertensive heart disease (HHD), or hypertensive hypertrophic cardiomyopathy.

[0220] The ASOs of the disclosure can be used to measure expression of *CAMK2D* transcript in a tissue or body fluid from an individual and comparing the measured expression level with a standard *CAMK2D* transcript expression level in normal tissue or body fluid, whereby an increase in the expression level compared to the standard is indicative of a disorder treatable by an ASO of the disclosure.

[0221] The ASOs of the disclosure can be used to assay *CAMK2D* transcript levels in a biological sample using any methods known to those of skill in the art. (Touboul *et. al.*, *Anticancer Res.* (2002) 22 (6A): 3349-56; Verjout *et. al.*, *Mutat. Res.* (2000) 640: 127-38); Stowe *et. al.*, *J. Virol. Methods* (1998) 75 (1): 93-91).

[0222] The term "biological sample" refers to any biological sample obtained from an individual, cell line, tissue culture, or other source of cells potentially expressing *CAMK2D* transcript. Methods for obtaining such a biological sample from mammals are well known in the art.

V. Kits comprising ASOs

[0223] This disclosure further provides kits that comprise an ASO of the disclosure described herein and that can be used to perform the methods described herein. In certain embodiments, a kit comprises at least one ASO in one or more containers. In some embodiments, the kits contain all of the components necessary and/or sufficient to perform a detection assay, including all controls, directions for performing assays, and any necessary software for analysis and presentation of results. One skilled in the art will readily recognize that the disclosed ASO can be readily incorporated into one of the established kit formats which are well known in the art.

VI. Methods of Using

- [0224] The ASOs of the disclosure can be utilized as research reagents for, for example, diagnostics, therapeutics, and prophylaxis.
- [0225] In research, such ASOs can be used to specifically inhibit the synthesis of CAMK2D protein (typically by degrading or inhibiting the mRNA and thereby prevent protein formation) in cells and experimental animals thereby facilitating functional analysis of the target or an appraisal of its usefulness as a target for therapeutic intervention. Further provided are methods of down-regulating the expression of *CAMK2D* mRNA and/or CAMK2D protein in cells or tissues comprising contacting the cells or tissues, *in vitro* or *in vivo*, with an effective amount of one or more of the ASOs, conjugates or compositions of the disclosure.
- [0226] In diagnostics, the ASOs can be used to detect and quantitate *CAMK2D* transcript expression in cell and tissues by northern blotting, *in-situ* hybridization, or similar techniques.
- [0227] For therapeutics, an animal or a human, suspected of having a disease or disorder, which can be treated by modulating the expression of *CAMK2D* transcript and/or CAMK2D protein is treated by administering ASOs in accordance with this disclosure. Further provided are methods of treating a mammal, such as treating a human, suspected of having or being prone to a disease or condition, associated with increased expression of *CAMK2D* transcript and/or CAMK2D protein by administering a therapeutically or prophylactically effective amount of one or more of the ASOs or compositions of the disclosure. The ASO, a conjugate, or a pharmaceutical composition according to the disclosure is typically administered in an effective amount. In some embodiments, the ASO or conjugate of the disclosure is used in therapy.
- [0228] The disclosure further provides for an ASO according to the disclosure, for use for the treatment of one or more of the cardiovascular diseases referred to herein, such as a disease selected from a coronary artery disease, stroke, heart failure, hypertensive heart disease, rheumatic heart disease, cardiomyopathy, heart arrhythmia, congenital heart disease, valvular heart disease, carditis, aortic aneurysms, peripheral artery disease, thromboembolic disease, and venous thrombosis.
- [0229] In certain embodiments, the disease, disorder, or condition is associated with overexpression of *CAMK2D* gene transcript and/or CAMK2D protein.

- [0230] The disclosure also provides for methods of inhibiting (*e.g.*, by reducing) the expression of *CAMK2D* gene transcript and/or CAMK2D protein in a cell or a tissue, the method comprising contacting the cell or tissue, *in vitro* or *in vivo*, with an effective amount of one or more ASOs, conjugates, or pharmaceutical compositions thereof, of the disclosure to affect degradation of expression of *CAMK2D* gene transcript thereby reducing CAMK2D protein.
- [0231] The disclosure also provides for the use of the ASO or conjugate of the disclosure as described for the manufacture of a medicament for the treatment of a disorder as referred to herein, or for a method of the treatment of as a disorder as referred to herein.
- [0232] The disclosure further provides for a method for inhibiting or reducing CAMK2D protein in a cell which is expressing CAMK2D comprising administering an ASO or a conjugate according to the disclosure to the cell so as to affect the inhibition or reduction of CAMK2D protein in the cell.
- [0233] The disclosure includes a method of reducing, ameliorating, preventing, or treating hyperexcitability of motor neurons (*e.g.*, such as those found in cardiomyocytes) in a subject in need thereof comprising administering an ASO or a conjugate according to the disclosure.
- [0234] The disclosure also provides for a method for treating a disorder as referred to herein the method comprising administering an ASO or a conjugate according to the disclosure as herein described and/or a pharmaceutical composition according to the disclosure to a patient in need thereof.
- [0235] The ASOs and other compositions according to the disclosure can be used for the treatment of conditions associated with over expression of CAMK2D protein.
- [0236] Generally stated, one aspect of the disclosure is directed to a method of treating a mammal suffering from or susceptible to conditions associated with abnormal levels of CAMK2D, comprising administering to the mammal and therapeutically effective amount of an ASO targeted to *CAMK2D* transcript that comprises one or more LNA units. The ASO, a conjugate, or a pharmaceutical composition according to the disclosure is typically administered in an effective amount.
- [0237] An interesting aspect of the disclosure is directed to the use of an ASO (compound) as defined herein or a conjugate as defined herein for the preparation of a medicament for the treatment of a disease, disorder or condition as referred to herein.
- [0238] The methods of the disclosure can be employed for treatment or prophylaxis against diseases caused by abnormal levels of CAMK2D protein. In some embodiments, diseases

caused by abnormal levels of CAMK2D protein are cardiovascular diseases. In certain embodiments, cardiovascular diseases can include a coronary artery disease, stroke, heart failure, hypertensive heart disease, rheumatic heart disease, cardiomyopathy, heart arrhythmia, congenital heart disease, valvular heart disease, aortic aneurysms, peripheral artery disease, thromboembolic disease, and venous thrombosis.

[0239] In certain embodiments, the cardiovascular disease is a heart failure, which can include a left-sided heart failure, a right-sided heart failure, congestive heart failure, a heart failure with reduced ejection fraction (HFrEF), a heart failure with preserved ejection fraction (HFpEF), a heart failure with mid-range ejection fraction (HFmrEF), a hypertrophic cardiomyopathy (HCM), a hypertensive heart disease (HHD), or hypertensive hypertrophic cardiomyopathy.

[0240] Alternatively stated, in some embodiments, the disclosure is furthermore directed to a method for treating abnormal levels of CAMK2D protein, the method comprising administering a ASO of the disclosure, or a conjugate of the disclosure or a pharmaceutical composition of the disclosure to a patient in need thereof.

[0241] The disclosure also relates to an ASO, a composition or a conjugate as defined herein for use as a medicament.

[0242] The disclosure further relates to use of a compound, composition, or a conjugate as defined herein for the manufacture of a medicament for the treatment of abnormal levels of CAMK2D protein or expression of mutant forms of CAMK2D protein (such as allelic variants, wherein the allelic variants are associated with one of the diseases referred to herein).

[0243] A patient who is in need of treatment is a patient suffering from or likely to suffer from the disease or disorder.

[0244] The practice of the present disclosure will employ, unless otherwise indicated, conventional techniques of cell biology, cell culture, molecular biology, transgenic biology, microbiology, recombinant DNA, and immunology, which are within the skill of the art. Such techniques are explained fully in the literature. *See*, for example, Sambrook *et al.*, ed. (1989) *Molecular Cloning A Laboratory Manual* (2nd ed.; Cold Spring Harbor Laboratory Press); Sambrook *et al.*, ed. (1992) *Molecular Cloning: A Laboratory Manual*, (Cold Springs Harbor Laboratory, NY); D. N. Glover ed., (1985) *DNA Cloning*, Volumes I and II; Gait, ed. (1984) *Oligonucleotide Synthesis*; Mullis *et al.* U.S. Pat. No. 4,683,195; Hames and Higgins, eds. (1984) *Nucleic Acid Hybridization*; Hames and Higgins, eds. (1984) *Transcription And Translation*; Freshney (1987) *Culture Of Animal Cells* (Alan R.

Liss, Inc.); Immobilized Cells And Enzymes (IRL Press) (1986); Perbal (1984) A Practical Guide To Molecular Cloning; the treatise, Methods In Enzymology (Academic Press, Inc., N.Y.); Miller and Calos eds. (1987) Gene Transfer Vectors For Mammalian Cells, (Cold Spring Harbor Laboratory); Wu *et al.*, eds., Methods In Enzymology, Vols. 154 and 155; Mayer and Walker, eds. (1987) Immunochemical Methods In Cell And Molecular Biology (Academic Press, London); Weir and Blackwell, eds., (1986) Handbook Of Experimental Immunology, Volumes I-IV; Manipulating the Mouse Embryo, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., (1986);); Crooke, Antisense drug Technology: Principles, Strategies and Applications, 2nd Ed. CRC Press (2007) and in Ausubel *et al.* (1989) Current Protocols in Molecular Biology (John Wiley and Sons, Baltimore, Md.).

- [0245] All of the references cited above, as well as all references cited herein, are incorporated herein by reference in their entirety.
- [0246] The following examples are offered by way of illustration and not by way of limitation.

EXAMPLES

Example 1: Construction of ASOs

- [0247] Antisense oligonucleotides described herein were designed to target various regions in the *CAMK2D* pre-mRNA (SEQ ID NO: 1). SEQ ID NO: 1 shows the genomic *CAMK2D* sequence, which corresponds to the reverse complement of residues 113,451,032 to 113,761,927 of GenBank Accession No. NC_000004.12. For example, the ASOs were constructed to target the regions denoted using the start and end sites of SEQ ID NO: 1, as shown in FIGs. 1A and 1B. The exemplary sequences of the ASOs of the present disclosure are provided in FIGs. 1A and 1B. In some embodiments, the ASOs were designed to be gapmers as shown in FIG. 3. The disclosed gapmers were constructed to contain locked nucleic acids – LNAs (upper case letters). For example, a gapmer can have beta-deoxy LNA at the 5' end and the 3' end and have a phosphorothioate backbone. But the LNA can also be substituted with any other nucleoside analogs and the backbone can be other types of backbones (*e.g.*, phosphodiester linkage, a phosphotriester linkage, a methylphosphonate linkage, a phosphoramidate linkage, or any combinations thereof).

[0248] The ASOs were synthesized using methods well known in the art. Exemplary methods of preparing such ASOs are described in Barciszewski *et al.*, Chapter 10 – "Locked Nucleic Acid Aptamers" in *Nucleic Acid and Peptide Aptamers: Methods and Protocols*, vol. 535, Gunter Mayer (ed.) (2009), the entire contents of which is hereby expressly incorporated by reference herein.

Example 2: qPCR assay to measure reduction of *CAMK2D* mRNA in HEK293 cells

[0249] The ASOs of the present disclosure were tested for their ability to reduce *CAMK2D* mRNA expression in human embryonic kidney cells (HEK293) (European Collection of Authenticated Cell Cultures (ECACC), catalog no. 85120602). The HEK293 cells were grown in cell culture media (DMEM AQ D0819, 10% FBS, and Pen/Strep). Every 5 days, cells were trypsinized by washing with Phosphate Buffered Saline (PBS), followed by addition of 0.25% Trypsin-EDTA solution, 2-3 minutes incubation at 37°C, and trituration before cell seeding. Cells were maintained in culture for up to 15 passages.

[0250] For experimental use, 3,500 cells per well were seeded in 96 well plates in 100 µL growth media. ASOs were prepared from a 750 µM stock and dissolved in PBS. Approximately 24 hours after seeding the cells, ASOs were added to the cells at a final concentration of 25 µM. Cells were then incubated for 3 days without any media change. After incubation, cells were harvested by removal of media followed by addition of 125 µL PURELINK[®] Pro 96 Lysis buffer and 125 µL 70% ethanol. Then, RNA was purified according to the manufacture's instruction and eluted in a final volume of 50 µL water, resulting in an RNA concentration of 10-20 ng/µL. Next, RNA was diluted 10 fold in water prior to the one-step qPCR reaction.

[0251] For the one-step qPCR reaction, qPCR-mix (qScriptTMXLE 1-step RT-qPCR TOUGHMIX[®] Low ROX from QauntaBio) was mixed with two Taqman probes at a ratio 10:1:1 (qPCR mix: probe1:probe2) to generate the mastermix. Taqman probes were acquired from LifeTechnologies: *CAMK2D*_Hs009943538_m1; *GAPDH* 4325792. The mastermix (6 µL) and RNA (4µL, 1-2 ng/µL) were then mixed in a qPCR plate (MICROAMP[®] optical 384 well, catalog no. 4309849). After sealing the plate, the plate was given a quick spin, 1000g for 1 minute at RT, and transferred to a ViiaTM 7 system (Applied Biosystems, Thermo). The following PCR conditions were used: 50°C for 15 minutes; 95°C for 3 minutes; 40 cycles of: 95°C for 5 sec, followed by a temperature decrease of 1.6 °C/sec, followed by 60 °C for 45 sec. The data was analyzed using the

QuantStudio™ Real_time PCR Software. The percent inhibition for the ASO treated samples was calculated relative to the control treated samples. Results are shown in FIGs. 2 and 4.

Example 3: QUANTIGENE® Analysis (96-well assay) to Measure *CAMK2D* mRNA Reduction in Human Inducible Pluripotent Stem Cell-Derived Cardiomyocytes (hiPSC-CM)

- [0252] The ability of ASOs to reduce human *CAMK2D* mRNA was measured *in vitro* by QUANTIGENE® analysis. Human inducible pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) from Cellular Dynamics International ("iCell²") cells were thawed, plated, and cultured per the manufacturer's instructions. These cardiomyocytes are derived from human induced pluripotent stem cells, which were first successfully differentiated into functional cardiomyocytes back in 2009. Zhang *et al.*, *Circ Res* 104(4):230-41 (2009). Since then, hiPSC-CMs have been used to study various aspects of the human heart and related diseases. Because these cells bear the genetic traits of the human donors from whom they are obtained, they are often to be better predictors of human physiology or pathophysiology compared to existing animal models. Blazeski *et al.*, *Prog Biophys Mol Biol* 110:166-177 (2012).
- [0253] Workflow: Prior to cell seeding, pre-collagen-coated 96-well plates were coated with fibronectin as follows. Fibronectin (1 mg/mL) was diluted 1:100 in PBS (-Ca²⁺, -Mg²⁺) and 50 µL of dilute fibronectin solution was added to each well of the 96-well plate. The plate was gently shaken horizontally to ensure an even coating of fibronectin on the bottom of each well. Then the plates were incubated at 37°C for 90 minutes. Cells were added to the plates immediately following aspiration of the fibronectin solution as per the manufacturer's instructions. Cells were seeded at 30,000 cells/well in 100 µL of the manufacturer's Plating Media and then incubated at 37°C and 5% CO₂ for 4 hours. Then the Plating Media was aspirated and replaced with 100 µL of the manufacturer's Maintenance Media. Cells were incubated at 37°C and 5% CO₂ with media exchange every other day. The ASOs were diluted in water and added to cells at DIV08 (*i.e.*, 8 days post plating). The cells were then incubated at 37°C and 5% CO₂ for 3 days following ASO addition to achieve steady state reduction of mRNA.
- [0254] After the incubation, the media was removed and cells were lysed as follows. Working cell lysis buffer was made by adding 1 part proteinase K to 99 parts of QUANTIGENE® 3x lysis buffer and then diluting 1:3 in dH₂O. The working lysis buffer

was added to the plates at 220 uL/well. After adding lysis buffer, the plate was shaken on a plate shaker for 10 minutes at medium speed (*i.e.*, speed 5-6 out of 10). The plates were then incubated at 55°C for 30 minutes. Following this incubation, the lysates were either frozen at -80°C or assayed immediately. Measurement of lysate mRNA was performed using the QUANTIGENE[®] 2.0 Reagent System (AFFYMETRIX[®]), which quantifies RNA using a branched DNA signal amplification method reliant on the specifically-designed target RNA capture probe set.

[0255] Assay: Each well of the capture plate (96-well polystyrene plate coated with capture probes) was loaded with 20 uL of working probe set. Working probe set reagents were generated by combining nuclease-free water (12.05 µL), lysis mixture (6.65 µL), blocking reagent (1 µL), and specific 2.0 probe set (0.3 µL) (human CAMK2D catalogue #SA-3000428 or human POLR2A catalogue #SA-10004) per manufacturer's instructions (QUANTIGENE[®] 2.0 AFFYMETRIX[®]). The cell lysates (or 1x lysis buffer for use in background control blank wells) were then added to the capture plates at a volume of 80 µL/well, giving 100 uL of total fluid per well. The plates were sealed using the QUANTIGENE[®] foil seal in combination with a hand crank sealer. Plates were centrifuged at 240g for 60 seconds and then incubated for 16-20 hours at 55°C to hybridize (target RNA capture).

[0256] Signal amplification and detection of target RNA began by washing plates with wash buffer 3 times (200, 300, and 300 µL/well in series, with buffer removal between each step) to remove any unbound material, followed by an upside-down centrifugation step for 1 min at 240g to dry the wells. Next, the 2.0 Pre-Amplifier hybridization reagent (100 µL/well) was added, incubated at 55°C for 1 hour, then aspirated, and wash buffer was added and aspirated 3 times (200, 300, and 300 uL/well in series, with buffer removal between each step), followed by an upside-down centrifugation step for 1 min at 240g to dry the wells. The 2.0 Amplifier hybridization reagent was then added (100 µL/well), incubated for 1 hour at 55°C, and then the wash, aspiration, and drying steps were repeated as described above. The 2.0 Label Probe hybridization reagent was added next (100 µL/well), incubated for 1 hour at 50°C, and then the wash, aspiration, and drying steps were repeated as described previously. Then the 2.0 Substrate was added (100 µL/well) to the plates. Plates were incubated for 5 minutes at room temperature and then imaged on a PerkinElmer Envision multilabel plate reader in luminometer mode within 15 minutes.

[0257] Data determination: For the gene of interest, the average assay background signal was subtracted from the average signal of each technical replicate. The background-subtracted, average signals for the gene of interest were then normalized to the background-subtracted average signal for the housekeeping POLR2A mRNA. The percent inhibition for the treated sample was calculated relative to the control treated sample lysate. Results of QUANTIGENE[®] assays for cells treated with the ASOs at a concentration of 500 nM are provided in FIG. 4.

Example 4: Analysis of *CAMK2D* mRNA Reduction *In Vivo*

[0258] To evaluate the potency of the ASOs in reducing *CAMK2D* mRNA level *in vivo*, female C57BL/6JBom mice were subcutaneously administered with one of the ASOs shown in FIG. 5. The ASOs were administered at a dose of 30 mg/kg/day for three consecutive days (day 1, 2, and 3). The mice were observed with regards to behavioral and body weight changes. Mice were sacrificed on day 8 and cardiac tissue was harvested for RNA isolation and analysis as described below.

[0259] MagNA Pure tissue lysis buffer (Roche) was added to the cardiac tissue section and homogenized using stainless steel beads until a uniform lysate was obtained. Incubation for 30 minutes at room temperature completed lysis. RNA was isolated using the MagNA Pure96 (Roche) with the Cellular RNA Large Volume Kit.

[0260] The RNA concentration was normalized to 5 ng/μl and one-step qPCR was performed using 20 ng RNA, qPCR Taqman Mastermix, and the following Taqman probes: *CAMK2D* (Thermo Mm00499266_m1) and *GAPDH* (Thermo 4352339E).

[0261] PCR conditions were as follows: 50°C for 15 minutes; 95°C for 3 minutes; 40 cycles of: 95°C for 5 sec. The data was analyzed using the QUANTSTUDIO[™] Real-time PCR Software. The percent inhibition for the ASO treated samples was calculated relative to saline treated samples.

[0262] As shown in FIG. 5, all the ASOs tested were able to decrease *CAMK2D* mRNA level when administered to the C57BL/6JBom mice. Collectively, the results provided herein demonstrate the potency of the ASOs both *in vitro* and *in vivo*, and support that *CAMK2D*-specific ASOs are disease-modifying therapeutics for the treatment of various medical disorders, such as cardiovascular-related diseases or disorders.

[0263] This PCT application claims priority benefit of U.S. Provisional Application Nos. 62/633,502, filed February 21, 2018; 62/635,954, filed February 27, 2018; 62/665,998

filed May 2, 2018; and 62/778,679, filed December 12, 2018, each of which is incorporated herein by reference in its entirety.

What is Claimed

1. An antisense oligonucleotide (ASO) comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that is complementary, such as fully complementary, to a nucleic acid sequence within a calcium/calmodulin-dependent protein kinase type II delta (*CAMK2D*) transcript.
2. The ASO of claim 1, or contiguous nucleotide sequence thereof, which is at least about 80%, at least about 85%, at least about 90%, at least about 95%, or about 100% complementary to the nucleic acid sequence within the *CAMK2D* transcript.
3. The ASO of claim 1 or 2, wherein the *CAMK2D* transcript is selected from the group consisting of SEQ ID NO: 1 and SEQ ID NO: 2.
4. The ASO of any one of claims 1 to 3, wherein the ASO is capable of reducing *CAMK2D* protein expression in a human cell (*e.g.*, HEK293 cell) which is expressing the *CAMK2D* protein.
5. The ASO of claim 4, wherein the *CAMK2D* protein expression is reduced by at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or about 100% compared to *CAMK2D* protein expression in a human cell that is not exposed to the ASO.
6. The ASO of any one of claims 1 to 5, which is capable of reducing *CAMK2D* transcript (*e.g.*, mRNA) expression in a human cell (*e.g.*, HEK293 cell), which is expressing the *CAMK2D* transcript.
7. The ASO of claim 6, wherein the *CAMK2D* transcript expression is reduced by at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or about 100% compared to *CAMK2D* transcript expression in a human cell that is not exposed to the ASO.
8. The ASO of any one of claims 1 to 7, wherein the ASO is a gapmer.
9. The ASO of any one of claims 1 to 8, wherein the ASO has a design of $LLLD_nLLL$, $LLLLD_nLLLL$, or $LLLLLD_nLLLLL$, wherein the L is a nucleoside analog, the D is DNA, and n can be any integer between 4 and 24.
10. The ASO of claim 9, wherein the n can be any integer between 6 and 14.
11. The ASO of claim 9, wherein the n can be any integer between 8 and 12.

12. The ASO of any one of claims 9 to 11, wherein the nucleoside analog comprises a 2'-O-alkyl-RNA; 2'-O-methyl RNA (2'-OMe); 2'-alkoxy-RNA; 2'-O-methoxyethyl-RNA (2'-MOE); 2'-amino-DNA; 2'-fluoro-RNA; 2'-fluoro-DNA; arabino nucleic acid (ANA); 2'-fluoro-ANA; or bicyclic nucleoside analog (LNA).

13. The ASO of any one of claims 9 to 12, wherein one or more of the nucleoside analog is a sugar modified nucleoside.

14. The ASO of claim 13, wherein the sugar modified nucleoside is an affinity enhancing 2' sugar modified nucleoside.

15. The ASO of any one of claims 9 to 12, wherein one or more of the nucleoside analog comprises a nucleoside comprising a bicyclic sugar.

16. The ASO of claim 14, wherein the affinity enhancing 2' sugar modified nucleoside is an LNA.

17. The ASO of claim 16, wherein the LNA is selected from the group consisting of constrained ethyl nucleoside (cEt), 2',4'-constrained 2'-O-methoxyethyl (cMOE), α -L-LNA, β -D-LNA, 2'-O,4'-C-ethylene-bridged nucleic acids (ENA), amino-LNA, oxy-LNA, thio-LNA, or any combination thereof.

18. The ASO of any one of claims 1 to 17, wherein the ASO comprises one or more 5'-methyl-cytosine nucleobases.

19. The ASO of any one of claims 1 to 18, wherein the ASO is capable of (i) reducing an mRNA level encoding CAMK2D in Inducible Pluripotent Stem Cell-Derived Cardiomyocytes (hiPSC-CM); (ii) reducing a protein level of CAMK2D in hiPSC-CM; (iii) reducing, ameliorating, or treating one or more symptoms of a cardiovascular disease or disorder, and (iv) any combination thereof.

20. The ASO of any one of claims 1 to 19, wherein the contiguous nucleotide sequence is complementary to a nucleic acid sequence comprising (i) nucleotides 625 – 842 of SEQ ID NO: 1; (ii) nucleotides 1,398 – 59,755 of SEQ ID NO: 1; (iii) nucleotides 61,817 – 104,725 of SEQ ID NO: 1; (iv) nucleotides 112,162 – 118,021 of SEQ ID NO: 1; (v) nucleotides 119,440 – 135,219 of SEQ ID NO: 1; (vi) nucleotides 137,587 – 157,856 of SEQ ID NO: 1; (vii) nucleotides 159,191 – 266,174 of SEQ ID NO: 1; or (viii) nucleotides 272,788 – 310,949 of SEQ ID NO: 1.

21. The ASO of any one of claims 1 to 19, wherein the contiguous nucleotide sequence is complementary to a nucleic acid sequence comprising (i) nucleotides 675 – 792 of SEQ ID NO: 1; (ii) nucleotides 1,448 – 59,705 of SEQ ID NO: 1; (iii) nucleotides 61,867 – 104,675 of SEQ ID NO: 1; (iv) nucleotides 112,212 – 117,971 of SEQ ID NO: 1; (v) nucleotides 119,490 –

135,169 of SEQ ID NO: 1; (vi) nucleotides 137,637 – 157,806 of SEQ ID NO: 1; (vii) nucleotides 159,241 – 266,124 of SEQ ID NO: 1; or (viii) nucleotides 272,838 – 310,899 of SEQ ID NO: 1.

22. The ASO of any one of claims 1 to 19, wherein the contiguous nucleotide sequence is complementary to a nucleic acid sequence comprising (i) nucleotides 725 – 742 of SEQ ID NO: 1; (ii) nucleotides 1,498 – 59,655 of SEQ ID NO: 1; (iii) nucleotides 61,917 – 104,625 of SEQ ID NO: 1; (iv) nucleotides 112,262 – 117,921 of SEQ ID NO: 1; (v) nucleotides 119,540 – 135,119 of SEQ ID NO: 1; (vi) nucleotides 137,687 – 157,756 of SEQ ID NO: 1; (vii) 159,291 – 266,074 of SEQ ID NO: 1; or (viii) nucleotides 272,888 – 310,849 of SEQ ID NO: 1.

23. The ASO of any one of claims 1 to 22, wherein the contiguous nucleotide sequence comprises SEQ ID NO: 4 to SEQ ID NO: 1713 with one or two mismatches.

24. The ASO of any one of claims 1 to 23, wherein the contiguous nucleotide sequence comprises the nucleotide sequence selected from the sequences in FIGs. 1A and 1B (SEQ ID NO: 4 to SEQ ID NO: 1713).

25. The ASO of any one of claims 1 to 24, wherein the contiguous nucleotide sequence comprises SEQ ID NO: 25, SEQ ID NO: 27, SEQ ID NO: 114, SEQ ID NO: 158, SEQ ID NO: 190, SEQ ID NO: 327, SEQ ID NO: 463, SEQ ID NO: 513, SEQ ID NO: 516, SEQ ID NO: 519, SEQ ID NO: 657, SEQ ID NO: 659, SEQ ID NO: 827, SEQ ID NO: 1249, SEQ ID NO: 1326, SEQ ID NO: 1409, SEQ ID NO: 1524, SEQ ID NO: 1530, SEQ ID NO: 1662, or SEQ ID NO: 1676.

26. The ASO of any one of claims 1 to 24, wherein the contiguous nucleotide sequence comprises SEQ ID NO: 55, SEQ ID NO: 61, SEQ ID NO: 63, SEQ ID NO: 71, SEQ ID NO: 75, SEQ ID NO: 79, SEQ ID NO: 84, SEQ ID NO: 85, SEQ ID NO: 92, SEQ ID NO: 102, SEQ ID NO: 105, SEQ ID NO: 128, SEQ ID NO: 130, SEQ ID NO: 133, SEQ ID NO: 138, SEQ ID NO: 161, SEQ ID NO: 178, SEQ ID NO: 180, SEQ ID NO: 186, SEQ ID NO: 195, SEQ ID NO: 200, SEQ ID NO: 202, SEQ ID NO: 234, SEQ ID NO: 264, SEQ ID NO: 387, SEQ ID NO: 390, SEQ ID NO: 396, SEQ ID NO: 441, SEQ ID NO: 446, SEQ ID NO: 457, SEQ ID NO: 467, SEQ ID NO: 523, SEQ ID NO: 524, SEQ ID NO: 636, SEQ ID NO: 640, SEQ ID NO: 700, SEQ ID NO: 740, SEQ ID NO: 832, SEQ ID NO: 965, SEQ ID NO: 1015, SEQ ID NO: 1065, SEQ ID NO: 1071, SEQ ID NO: 1155, SEQ ID NO: 1475, SEQ ID NO: 1508, SEQ ID NO: 1685, SEQ ID NO: 1686, SEQ ID NO: 1687, SEQ ID NO: 1688, or SEQ ID NO: 1690.

27. The ASO of claim 1 or 26, which has a design selected from the group consisting of the designs in Fig. 3, wherein the upper letter is a sugar modified nucleoside and the lower case letter is DNA.

28. The ASO of any one of claims 1 to 27, which is capable of reducing expression of CAMK2D protein in a hiPSC-CM cell which is expressing the CAMK2D protein.

29. The ASO of claim 28, wherein the expression of CAMK2D protein is reduced by at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100% compared to a cell not exposed to the ASO.

30. The ASO of any one of claims 1 to 29, which is capable of reducing expression of *CAMK2D* transcript (e.g., mRNA) in a hiPSC-CM cell which is expressing the *CAMK2D* transcript.

31. The ASO of claim 30, wherein the expression of *CAMK2D* transcript is reduced by at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100% compared to a cell not exposed to the ASO.

32. The ASO of any one of claims 1 to 31, which has from 14 to 20 nucleotides in length.

33. The ASO of any one of claims 1 to 32, wherein the nucleotide sequence comprises one or more modified internucleoside linkages.

34. The ASO of any one of claims 1 to 33, wherein the one or more modified internucleoside linkages is a phosphorothioate linkage.

35. The ASO of claim 33 or 34, wherein at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or 100% of internucleoside linkages are modified.

36. The ASO of claim 35, wherein each of the internucleoside linkages in the ASO is a phosphorothioate linkage.

37. A conjugate comprising the ASO of any one of claims 1 to 36, wherein the ASO is covalently attached to at least one non-nucleotide or non-polynucleotide moiety.

38. The conjugate of claim 37, wherein the non-nucleotide or non-polynucleotide moiety comprises a protein, a fatty acid chain, a sugar residue, a glycoprotein, a polymer, or any combinations thereof.

39. A pharmaceutical composition comprising the ASO of any one of claims 1 to 36 or the conjugate of claim 37 or 38, and a pharmaceutically acceptable diluent, carrier, salt, or adjuvant.

40. The pharmaceutical composition of claim 39, wherein the pharmaceutically acceptable salt comprises a sodium salt, a potassium salt, an ammonium salt, or any combination thereof.

41. The pharmaceutical composition of claim 39 or 40, which further comprises at least one further therapeutic agent.

42. The pharmaceutical composition of claim 41, wherein the further therapeutic agent is a CAMK2D antagonist.

43. The pharmaceutical composition of claim 42, wherein the CAMK2D antagonist is an anti-CAMK2d antibody or fragment thereof.

44. A kit comprising the ASO of any one of claims 1 to 36, the conjugate of claim 37 or 38, or the pharmaceutical composition of any one of claims 39 to 43, and instructions for use.

45. A diagnostic kit comprising the ASO of any one of claims 1 to 36, the conjugate of claim 37 or 38, or the pharmaceutical composition of any one of claims 39 to 43, and instructions for use.

46. A method of inhibiting or reducing CAMK2D protein expression in a cell, comprising administering the ASO of any one of claims 1 to 36, the conjugate of claim 37 or 38, or the pharmaceutical composition of any one of claims 39 to 43 to the cell expressing CAMK2D protein, wherein the CAMK2D protein expression in the cell is inhibited or reduced after the administration.

47. An *in vitro* method of inhibiting or reducing CAMK2D protein expression in a cell, comprising contacting the ASO of any one of claims 1 to 36, the conjugate of claim 37 or 38, or the pharmaceutical composition of any one of claims 39 to 43 to the cell expressing CAMK2D protein, wherein the CAMK2D protein expression in the cell is inhibited or reduced after the contacting.

48. The method of claim 46 or 47, wherein the ASO inhibits or reduces expression of *CAMK2D* transcript (*e.g.*, mRNA) in the cell after the administration.

49. The method of claim 48, wherein the expression of *CAMK2D* transcript (*e.g.*, mRNA) is reduced by at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100% after the administration compared to a cell not exposed to the ASO.

50. The method of any one of claims 46 to 49, wherein the expression of CAMK2D protein is reduced by at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% after the administration compared to a cell not exposed to the ASO.

51. The method of any one of claims 46 to 50, wherein the cell is a cardiac cell, *e.g.*, hiPSC-CM.

52. A method of reducing, ameliorating, or treating one or more symptoms of a cardiovascular disease or disorder in a subject in need thereof, comprising administering an effective amount of the ASO of any one of claims 1 to 36, the conjugate of claim 37 or 38, or the pharmaceutical composition of any one of claims 39 to 43 to the subject.

53. Use of the ASO of any one of claims 1 to 36, the conjugate of claim 37 or 38, or the pharmaceutical composition of any one of claims 39 to 43 for the manufacture of a medicament.

54. Use of the ASO of any one of claims 1 to 36, the conjugate of claim 37 or 38, or the pharmaceutical composition of any one of claims 39 to 43 for the manufacture of a medicament for the treatment of a cardiovascular disease or disorder in a subject in need thereof.

55. The ASO of any one of claims 1 to 36, the conjugate of claim 37 or 38, or the pharmaceutical composition of any one of claims 39 to 43 for use in therapy.

56. The ASO of any one of claims 1 to 36, the conjugate of claim 37 or 38, or the pharmaceutical composition of any one of claims 39 to 43 for use in therapy of a cardiovascular disease or disorder in a subject in need thereof.

57. The ASO of claim 19, the method of claim 52, the use of claim 54, or the ASO for use of claim 56, wherein the cardiovascular disease or disorder comprises a coronary artery disease, stroke, heart failure, hypertensive heart disease, rheumatic heart disease, cardiomyopathy, heart arrhythmia, congenital heart disease, valvular heart disease, aortic aneurysms, peripheral artery disease, thromboembolic disease, venous thrombosis, or any combination thereof.

58. The method, use, or ASO of claim 57, wherein the cardiovascular disease or disorder is heart failure.

59. The method, use, or ASO of claim 58, wherein the heart failure comprises a left-sided heart failure, a right-sided heart failure, a congestive heart failure, a heart failure with reduced ejection fraction (HFrEF), a heart failure with preserved ejection fraction (HFpEF), a heart failure with mid-range ejection fraction (HFmrEF), a hypertrophic cardiomyopathy (HCM), a hypertensive heart disease (HHD), or hypertensive hypertrophic cardiomyopathy.

60. The method of any one of claims 52 and 57 to 59, , the use of any one of claims 54 and 57 to 59, or the ASO for use of any one of claims 56 to 59, wherein the subject is a human.

61. The method of any one of claims 52 and 57 to 60, the use of any one of claims 54 and 57 to 60, or the ASO for use of any one of claims 56 to 60, wherein the ASO, the conjugate, or the pharmaceutical composition is administered intracardially, orally, parenterally, intrathecally, intra-cerebroventricularly, pulmorarily, topically, or intraventricularly.

FIG. 1A (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
			TGATAAT	0120	DNAts DNAGs DNAAs OxyTs OxyAs OxyAs OxyT
41	2578	2596	GCTTTTGGTG TTGATAAT	ASO-0121	OxyGs OxyMCs OxyTs DNAts DNAts DNAts DNAGs DNAGs DNAts DNAGs
42	2578	2597	AGCTTTTGGT GTTGATAAT	ASO-0122	OxyAs DNAGs DNAGs DNAts DNAts DNAts DNAts DNAts DNAGs DNAGs DNAts
43	2579	2596	GCTTTTGGTG TTGATAA	ASO-0123	OxyGs OxyMCs DNAts DNAts DNAts DNAts DNAts DNAts DNAGs DNAGs DNAts
44	2579	2597	AGCTTTTGGT GTTGATAA	ASO-0124	OxyAs OxyGs OxyMCs DNAts DNAts DNAts DNAts DNAts DNAts DNAGs DNAGs DNAts
45	2579	2598	AAGCTTTTGG TGTTGATAA	ASO-0125	OxyAs OxyAs OxyGs OxyMCs DNAts DNAts DNAts DNAts DNAts DNAts DNAGs DNAGs
46	2580	2596	GCTTTTGGTG TTGATA	ASO-0126	OxyGs OxyMCs DNAts DNAts DNAts DNAts DNAts DNAts DNAGs DNAGs DNAts
47	2580	2597	AGCTTTTGGT GTTGATA	ASO-0127	OxyAs OxyGs DNAGs DNAts DNAts DNAts DNAts DNAts DNAts DNAGs DNAGs DNAts
48	2580	2598	AAGCTTTTGG TGTTGATA	ASO-0128	OxyAs DNAAs DNAGs DNAGs DNAts DNAts DNAts DNAts DNAts DNAts DNAGs DNAGs
49	2581	2597	AGCTTTTGGT GTTGAT	ASO-0129	OxyAs OxyGs OxyMCs DNAts DNAts DNAts DNAts DNAts DNAts DNAGs DNAGs DNAts
50	2581	2598	AAGCTTTTGG TGTTGAT	ASO-0130	OxyAs OxyAs OxyGs OxyMCs DNAts DNAts DNAts DNAts DNAts DNAts DNAGs DNAGs
51	2582	2598	AAGCTTTTGG TGTTGA	ASO-0131	OxyAs OxyAs OxyGs OxyMCs DNAts DNAts DNAts DNAts DNAts DNAts DNAGs DNAGs
52	2607	2623	GTTGAAAATAC CCACCC	ASO-0132	OxyGs DNAts DNAts DNAGs DNAGs DNAGs DNAGs DNAGs DNAGs DNAts DNAGs DNAGs
53	2851	2870	TTTAAATATAG TTATTCAT	ASO-0133	OxyTs OxyTs OxyTs OxyAs DNAGs DNAGs DNAGs DNAGs DNAGs DNAGs DNAts DNAGs
54	3239	3256	TTATGTCAACA GCTATTT	ASO-0134	OxyTs OxyTs OxyAs OxyTs DNAGs DNAts DNAts DNAts DNAts DNAts DNAGs DNAGs
55	3576	3593	ATTGCAATAA ATATGGA	ASO-0135	OxyAs OxyTs OxyTs DNAGs DNAGs DNAGs DNAGs DNAGs DNAGs DNAts DNAGs
56	3778	3794	CTGTGGAGTAG AGACTA	ASO-0136	OxyMCs OxyTs DNAGs DNAts DNAGs DNAGs DNAGs DNAGs DNAGs DNAts DNAGs
57	4221	4240	TAGGTAGTCT TTGAAGCAG	ASO-0137	OxyTs DNAGs DNAGs DNAGs DNAts DNAGs DNAGs DNAGs DNAGs DNAts DNAGs
58	4225	4241	GTAGGTAGTTC TTTGAA	ASO-0138	OxyGs OxyTs OxyAs OxyGs DNAGs DNAts DNAts DNAts DNAts DNAts DNAGs DNAGs
59	4926	4945	GTAAATTTGAC	ASO-	OxyGs OxyTs OxyAs OxyAs DNAGs DNAGs DNAts DNAts DNAts DNAts DNAGs DNAGs

[illegible]

FIG. 1A (cont.)

[illegible]

FIG. 1A (cont.)

[illegible]

FIG. 1A (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
			TGTTTC	0192	DNAts DNAGs OxyTs OxyTs OxyTs OxyMC
117	22342	22358	GCCAAATTCCTTCTAGT	ASO-0193	OxyGs OxyMCs DNAs DNAs DNAs DNAs DNAts DNAts DNAts DNAts
118	22992	23011	AAAATAAATAACACATCCCA	ASO-0194	OxyAs OxyAs OxyAs DNAts DNAs DNAs DNAs DNAs DNAts DNAts DNAts DNAts
119	23373	23392	TTTTAAATGTGTTATTATCCT	ASO-0195	DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
120	23595	23614	GACCTAAATATATATACAAGA	ASO-0196	OxyGs OxyAs OxyMCs OxyMCs DNAts DNAs DNAs DNAs DNAts DNAts DNAts DNAts
121	23727	23744	TGAAGAAATCTAATATGT	ASO-0197	DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
122	24150	24166	ATCATCTGGTTGTGAAT	ASO-0198	OxyAs OxyTs OxyMCs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
123	24404	24423	CTTAATGAATATAGAGTTCT	ASO-0016	OxyMCs OxyTs OxyTs OxyAs DNAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts
124	24407	24424	ACTTAATGAATATAGAGT	ASO-0199	OxyAs OxyMCs OxyTs OxyTs DNAs DNAs DNAts DNAts DNAts DNAts DNAts DNAts
125	24747	24764	TTAATAATCATATATACC	ASO-0200	OxyTs OxyTs OxyAs OxyAs DNAts DNAs DNAts DNAts DNAts DNAts DNAts DNAts
126	24874	24891	CATAATAATAGTATTTGG	ASO-0201	OxyMCs OxyAs OxyTs OxyAs DNAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts
127	26041	26060	AATAAGAAATTTCCATAACTT	ASO-0202	OxyAs OxyAs OxyTs OxyAs DNAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts
128	26381	26397	GAGATCAATAAAGTATA	ASO-0203	OxyGs OxyAs OxyGs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
129	27197	27215	ATTTGAAAGGCGTGATGGGA	ASO-0204	OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
130	27363	27380	ATGTAAATCAATAGTTTC	ASO-0205	OxyAs OxyTs OxyGs OxyTs DNAs DNAs DNAts DNAts DNAts DNAts DNAts DNAts
131	27712	27731	GAAGAGTAATTTAAAGGCTT	ASO-0206	OxyGs OxyAs OxyAs OxyGs DNAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts
132	28063	28080	TTGACATCTGACTTTTAA	ASO-0207	OxyTs OxyTs OxyGs DNAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts
133	28249	28265	AGATATAGTTACTTTAAC	ASO-0208	OxyAs OxyGs OxyAs OxyTs DNAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts
134	28369	28385	GTCAGTTATCAGGTAT	ASO-0209	OxyGs OxyTs OxyMCs OxyAs DNAs DNAts DNAts DNAts DNAts DNAts DNAts
135	28782	28801	GACAGAGACTG	ASO-	OxyGs OxyAs OxyMCs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts

FIG. 1A (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
			AAATGATAA	0017	DNAs DNAs DNAs DNAs DNAs DNAs OxyTs OxyAs OxyA
136	28857	28873	CTGGAGAAGTT TTGAAG	ASO-0210	OxyMCs OxyTs OxyGs DNAs DNAs DNAs DNAs DNAs DNAs
137	28897	28915	TAAAAGAGTTT GCATAGGA	ASO-0211	OxyTs OxyAs OxyAs DNAs DNAs DNAs DNAs DNAs DNAs
138	29430	29446	AATATTATTGGT TGAGC	ASO-0212	DNAs DNAs DNAs DNAs DNAs DNAs OxyGs OxyA
139	30003	30020	TCTCATAAACTT CATTCC	ASO-0213	OxyTs OxyMCs DNAs DNAs DNAs DNAs DNAs DNAs
140	30007	30024	CCTCTCTCATA AACTTCA	ASO-0214	DNAs DNAs DNAs DNAs DNAs DNAs OxyTs OxyMCs OxyA
141	30420	30439	ACATTATCTTCA TTAAACAA	ASO-0215	OxyAs OxyMCs OxyAs OxyTs DNAs DNAs DNAs DNAs DNAs
142	30634	30653	ATAACTCTGTG TATTAGCAT	ASO-0216	DNAs DNAs DNAs DNAs DNAs DNAs DNAs DNAs DNAs
143	30870	30888	CAGATTTTATTT GTCATTC	ASO-0217	OxyMCs OxyAs OxyGs DNAs DNAs DNAs DNAs DNAs DNAs
144	31207	31225	AGAAAAGAAATG AAACTGTT	ASO-0218	DNAs DNAs DNAs DNAs DNAs DNAs DNAs DNAs DNAs
145	31565	31582	TGAATTAAAT GAGAGTA	ASO-0219	OxyTs OxyGs OxyAs OxyAs DNAs DNAs DNAs DNAs DNAs
146	31711	31728	TAACCTTTTCAG ATGGCAT	ASO-0220	DNAs DNAs DNAs DNAs DNAs DNAs DNAs DNAs DNAs
147	32776	32793	TAAGTCATCAT CATCGTC	ASO-0221	OxyTs OxyAs OxyAs OxyGs DNAs DNAs DNAs DNAs DNAs
148	33003	33022	AAAGAACAGTC CTAATACAA	ASO-0222	DNAs DNAs DNAs DNAs DNAs DNAs DNAs DNAs DNAs
149	33008	33024	CCAAAGAACAG TCCTAA	ASO-0223	OxyMCs OxyAs DNAs DNAs DNAs DNAs DNAs DNAs
150	33577	33596	ATAAGTAACAA CACAGATGA	ASO-0224	DNAs DNAs DNAs DNAs DNAs DNAs DNAs DNAs DNAs
151	33580	33598	CAATAAGTAAC AACACAGA	ASO-0018	OxyMCs OxyAs OxyTs DNAs DNAs DNAs DNAs DNAs DNAs
152	34058	34077	GCAAAAGTCTT AAATACTTC	ASO-0225	OxyGs OxyMCs OxyAs OxyAs DNAs DNAs DNAs DNAs DNAs
153	34060	34077	GCAAAAGTCTT AAATACT	ASO-0226	DNAs DNAs DNAs DNAs DNAs DNAs DNAs DNAs DNAs
154	34238	34256	ATCAATATTAAA	ASO-	OxyAs OxyTs OxyMCs OxyAs DNAs DNAs DNAs DNAs DNAs

FIG. 1A (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
			TATTTCT	0227	DNAas DNAas DNAts DNAas DNAts OxyTs OxyTs OxyMCs OxyT
155	34716	34732	ATCAGGACAGG TTATTT	ASO- 0228	OxyAs OxyTs OxyMCs OxyAs DNags DNags DNAas DNacs DNacs DNags
156	35091	35110	TATATTACTAGT CAAAGGGC	ASO- 0229	OxyTs OxyAs OxyTs DNAas DNAts DNAts DNAas DNacs DNats DNAas DNags
157	35150	35166	CTTATTAGGTA ATTGAA	ASO- 0230	DNAas DNAts OxyTs OxyTs OxyGs OxyAs OxyA
158	35743	35762	TACATATTATAT TACTCCTC	ASO- 0231	OxyTs OxyAs OxyMCs DNAas DNAts DNAts DNAts DNAts DNAts DNAts
159	35839	35856	ATTTAAGTTTAT TGAGAT	ASO- 0232	OxyAs OxyTs OxyTs DNAas DNAas DNags DNats DNats DNats DNats
160	36133	36149	AATAGTTTCAA GTCCAG	ASO- 0233	OxyAs OxyTs DNAas DNags DNats DNats DNats DNats DNats DNats
161	37100	37119	ATTTAGCACAT ACATTTAAC	ASO- 0234	OxyAs OxyTs OxyTs DNAas DNags DNacs DNacs DNacs DNacs DNacs
162	37299	37317	CCTTTGGTTAT TTGTTTAT	ASO- 0235	OxyMCs OxyMCs DNats DNats DNats DNats DNags DNags DNats DNats
163	37666	37683	GTTAATTATTG TTATTG	ASO- 0236	OxyGs OxyTs OxyTs OxyAs DNAas DNats DNats DNats DNats DNats
164	37987	38006	ATAAATTTTATT AATTGCCT	ASO- 0237	OxyAs OxyTs OxyAs DNAas DNAas DNats DNats DNats DNats DNats
165	38072	38090	TTTACAGGATT GTTATCAA	ASO- 0019	OxyTs OxyTs OxyTs OxyAs DNacs DNacs DNags DNags DNats DNats
166	38079	38095	CTAAATTTTACA GGATTG	ASO- 0238	OxyMCs OxyTs OxyAs OxyAs DNAas DNats DNats DNats DNats DNacs
167	38833	38851	TTTTGAGGATT AAAGAGAA	ASO- 0239	OxyTs OxyTs OxyTs OxyTs DNags DNags DNags DNags DNats DNats
168	38835	38854	TTGTTTTGAGG ATTAAGAG	ASO- 0240	OxyTs OxyTs OxyGs OxyTs DNats DNats DNats DNats DNags DNags
169	39616	39635	ATTGCTTAAATT GACCTCTA	ASO- 0241	OxyAs DNats DNats DNags DNacs DNats DNats DNats DNats DNats
170	39622	39640	ATTAATTGCTT AAATTGA	ASO- 0242	OxyAs OxyTs OxyTs OxyAs DNAas DNats DNats DNats DNats DNats
171	40300	40319	TTTATTTTAAGC TGAAGACA	ASO- 0243	OxyTs OxyTs OxyTs OxyAs DNats DNats DNats DNats DNats DNags
172	40317	40333	TGGTTGGTATA AATTTT	ASO- 0244	OxyTs OxyGs OxyGs OxyTs DNats DNags DNags DNats DNats DNats
173	40624	40643	GTGATATTCAA	ASO-	OxyGs OxyTs DNags DNAas DNats DNats DNats DNats DNats DNats

FIG. 1A (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
			GAAATAGCA	0245	DNAGs DNAas DNAas DNAts DNAts OxyAs OxyGs OxyMCs OxyA
174	40947	40963	TGTTAAGATGT AATTGG	ASO-0246	OxyTs OxyGs OxyTs OxyTs DNAas DNAas DNAGs DNAas DNAts DNAts DNAGs DNAts
175	40998	41017	AACATATTAAAG TACAAGTGA	ASO-0020	OxyAs OxyAs OxyMCs OxyAs DNAts DNAts DNAas DNAts DNAts DNAas DNAas DNAGs DNAts DNAas DNAGs DNAts
176	40999	41016	ACATATTAAAGT ACAAGTG	ASO-0247	OxyAs OxyMCs OxyAs OxyTs DNAas DNAts DNAts DNAts DNAas DNAas DNAGs DNAts DNAas DNAGs DNAts
177	41740	41757	ACAAATCAATTA GTCATAT	ASO-0248	OxyAs OxyMCs OxyAs OxyAs DNAas DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
178	41742	41758	CACAAATCATTT AGTCTA	ASO-0249	OxyMCs OxyAs OxyMCs OxyAs DNAas DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
179	42527	42546	CATATTATGCT GTTTTCCTG	ASO-0250	OxyMCs OxyAs DNAts DNAas DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
180	42531	42548	TTCATATTATGC TGTTTT	ASO-0251	OxyTs OxyTs OxyMCs OxyAs DNAts DNAas DNAts DNAts DNAts DNAts DNAts DNAts DNAts
181	42952	42969	CAGTGAAAAATC TAAATTA	ASO-0252	OxyMCs OxyAs OxyGs OxyTs DNAGs DNAas DNAts DNAts DNAts DNAts DNAts DNAts DNAts
182	43391	43408	AATTGGGAAG GTTTAGA	ASO-0253	OxyAs OxyAs OxyTs OxyTs DNAts DNAts DNAGs DNAts DNAts DNAts DNAts DNAts DNAts
183	43393	43410	GCAATTTGGGA AGGTTTA	ASO-0254	OxyGs OxyMCs DNAas DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
184	43931	43949	AGGAGAAAGACT TAAATTTT	ASO-0255	OxyAs OxyGs OxyGs OxyAs DNAGs DNAas DNAts DNAts DNAts DNAts DNAts DNAts DNAts
185	44247	44264	GTGGAGAGAGT TGAATTT	ASO-0256	OxyGs OxyTs OxyGs DNAGs DNAas DNAts DNAts DNAts DNAts DNAts DNAts DNAts
186	44345	44361	AAAGTGAGTGT TAAAGT	ASO-0257	OxyAs OxyAs OxyGs DNAts DNAGs DNAas DNAts DNAts DNAts DNAts DNAts DNAts
187	44714	44731	ATTTTAATTTGT GAGTAG	ASO-0258	OxyAs OxyTs OxyTs OxyTs DNAts DNAts DNAas DNAts DNAts DNAts DNAts DNAts DNAts
188	44982	45001	AAATTGAACAA GTGAATAGT	ASO-0259	OxyAs OxyAs OxyTs DNAts DNAts DNAGs DNAas DNAts DNAts DNAts DNAts DNAts DNAts
189	45144	45160	AGTGAACCTTAG TGATAT	ASO-0260	OxyAs OxyGs OxyTs OxyGs DNAas DNAts DNAts DNAts DNAts DNAts DNAts DNAts
190	46568	46586	TGTTTCTAGGT TTCATTTT	ASO-0261	OxyTs OxyGs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
191	46816	46835	TACTTTACATTC TTTTATGT	ASO-0262	OxyTs OxyAs OxyMCs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
192	46826	46845	TCCTCTCAATTA	ASO-	OxyTs OxyMCs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts

FIG. 1A (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
			CTTTACAT	0021	DNAas DNAcs DNAts DNAts DNAts OxyAs OxyMCs OxyAs OxyT
193	47165	47183	CTAGTCATTTC TTTGGGTC	ASO- 0263	OxyMCs DNAts DNAas DNAGs DNAts DNAts DNAcs DNAts DNAts DNAts
194	47167	47183	CTAGTCATTTC TTTGGG	ASO- 0264	OxyMCs DNAts DNAas DNAGs DNAts DNAts DNAcs DNAts DNAts DNAts
195	47770	47788	TAATTTATCATG TATTTCAG	ASO- 0265	OxyTs OxyAs OxyAs OxyTs DNAts DNAts DNAts DNAas DNAts DNAcs DNAts
196	47915	47931	CATTACCACTA TATCAT	ASO- 0266	DNAGs DNAts DNAas DNAts OxyTs OxyMCs OxyAs OxyG
197	48166	48183	TTTTCTTATCAA TATGCA	ASO- 0267	OxyMCs OxyAs OxyTs DNAts DNAts DNAts DNAcs DNAts DNAas DNAts
198	48838	48855	TGAATAATGTTT TACTAA	ASO- 0268	DNAas DNAts DNAas OxyTs OxyGs OxyMCs OxyAs OxyA
199	49269	49286	ATCTGTGAATA CTTTGAA	ASO- 0269	DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
200	49272	49289	GAAATCTGTGA ATACTTT	ASO- 0270	OxyGs OxyAs OxyAs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts
201	50015	50034	TATACTTGTCT CTCACCTT	ASO- 0271	DNAas DNAts DNAas OxyMCs OxyTs OxyTs OxyT
202	50024	50041	CATTAAATATAC TTGTTC	ASO- 0272	OxyTs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
203	50265	50283	ATGAAAATAAA TGATCTAG	ASO- 0273	DNAas DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
204	50610	50628	TCATTCTTAAAA TACTAAC	ASO- 0274	DNAts DNAGs DNAas DNAts OxyMCs OxyTs OxyAs OxyG
205	50889	50907	CTTGTTTTAAAT TCTAATA	ASO- 0275	OxyTs OxyMCs OxyAs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts
206	51319	51337	TGATATAGCAA AGCAATGT	ASO- 0276	DNAas DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
207	51570	51588	TTATGACTGGA AGAACAAA	ASO- 0277	DNAas DNAGs DNAas DNAts DNAts DNAts DNAts DNAts DNAts DNAts
208	51576	51594	TGTTTATTATGA CTGGAAG	ASO- 0022	OxyTs OxyGs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts
209	51789	51807	ATTTGACAAG ACTTACAT	ASO- 0278	DNAas DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
210	51976	51993	TGCACCTTTAT CTTTAAC	ASO- 0279	DNAas DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
211	52383	52401	ATGATTTAAATA	ASO-	OxyAs OxyTs OxyGs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts

FIG. 1A (cont.)

[illegible]

FIG. 1A (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
			CAATGCA	0302	DNAs DNAs DNAs DNAs OxyGs OxyMCs OxyA
233	58617	58633	AAATAGGTTA GGTCTG	ASO-0303	OxyAs OxyAs OxyAs DNats DNats DNAs DNAs DNats DNats DNats DNAs
234	58780	58796	GTTGAGAAATAC AGATTG	ASO-0304	OxyGs OxyTs OxyTs OxyGs DNAs DNAs DNAs DNAs DNats DNats DNats DNAs
235	58919	58937	AGACACATTTTC ATTTTAAG	ASO-0305	OxyAs OxyGs OxyAs OxyMCs DNAs DNAs DNats DNats DNats DNats DNats
236	59562	59581	TTTATTTACAAT CCTTTAAA	ASO-0306	OxyTs OxyTs OxyTs OxyAs DNats DNats DNats DNats DNats DNats DNats DNats
237	59636	59654	TTTATATTAAGG ACCAGAC	ASO-0024	OxyTs OxyTs OxyTs OxyAs DNats DNats DNats DNats DNats DNats DNats DNats
238	59638	59655	TTTATATTAAG GACCAG	ASO-0307	OxyTs OxyTs OxyTs DNAs DNats DNats DNats DNats DNats DNats DNats DNats
239	61917	61935	TGTCATAATAT CTCCATC	ASO-0308	OxyTs DNags DNats DNats DNats DNats DNats DNats DNats DNats DNats
240	62140	62158	CATTATGATATA AACATGT	ASO-0309	OxyMCs OxyAs OxyTs OxyTs DNAs DNats DNats DNats DNats DNats DNats DNats
241	62487	62506	TAATCTAAGGT TTACTAAGA	ASO-0310	OxyTs OxyAs OxyTs DNats DNats DNats DNats DNats DNats DNats DNats
242	62667	62683	ATGGCTACTTT GGTTTT	ASO-0311	OxyAs OxyTs OxyGs DNags DNats DNats DNats DNats DNats DNats DNats
243	62877	62894	ATTGCCTAGAA GAAATGA	ASO-0312	OxyAs OxyTs OxyTs OxyGs DNats DNats DNats DNats DNats DNats DNats DNats
244	63189	63205	TTTGTGATAGG TATATG	ASO-0313	OxyTs OxyTs OxyTs OxyGs DNats DNags DNAs DNats DNats DNats DNats DNags
245	63479	63496	GTTTCTGTGAT AATTTAA	ASO-0314	OxyGs OxyTs OxyTs OxyTs DNats DNats DNats DNats DNats DNats DNats DNats
246	63973	63991	TATAAATGGCA GTACAGAT	ASO-0315	OxyTs OxyAs OxyTs DNAs DNAs DNats DNats DNats DNats DNats DNats DNats
247	63976	63994	ATTATAAATG GCAGTACA	ASO-0316	OxyAs OxyTs OxyTs OxyTs DNAs DNats DNats DNats DNats DNats DNats DNats
248	64358	64377	TATTTTCTTCTT TCTGTACT	ASO-0317	OxyTs OxyAs DNats DNats DNats DNats DNats DNats DNats DNats DNats
249	64756	64775	AGGGAAGGCA AAATCTACAT	ASO-0318	OxyAs OxyGs OxyGs DNags DNAs DNAs DNats DNats DNats DNats DNats DNats
250	64986	65003	ACAGAGAAGGT AATGCAT	ASO-0319	OxyAs OxyMCs OxyAs OxyGs DNAs DNags DNats DNats DNats DNats DNats
251	65329	65348	TAAGTGATTTT	ASO-	OxyTs DNAs DNAs DNags DNats DNats DNats DNats DNats DNats DNats DNats

FIG. 1A (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
			GTAGGGGCC	0320	DNAGs DNAts DNAAs DNAGs DNAGs DNAGs DNAGs OxyMCs OxyMC
252	65338	65357	GCTATTAGGTA AGTGATTTT	ASO-0025	OxyGs OxyMCs OxyTs DNAAs DNAts DNAts DNAAs DNAGs DNAGs DNAts DNAts
253	65831	65849	CCTTTACCTCA TTCAAAAC	ASO-0321	OxyMCs OxyMCs DNAts DNAts DNAts DNAAs DNAGs DNAGs DNAts DNAts DNAts DNAts
254	65833	65849	CCTTTACCTCA TTCAAA	ASO-0322	OxyMCs OxyMCs DNAts DNAts DNAts DNAAs DNAGs DNAGs DNAts DNAts DNAts DNAts
255	66693	66712	AAGAGTAAAGTA AAATAAAGA	ASO-0323	OxyAs OxyAs OxyGs OxyAs DNAGs DNAts DNAts DNAAs DNAGs DNAGs DNAts DNAts DNAts DNAts
256	66728	66744	CTTGGAATTTG TGGGAT	ASO-0324	OxyMCs OxyTs OxyTs OxyGs DNAGs DNAGs DNAts DNAts DNAts DNAts DNAts DNAts
257	66984	67001	GTTTATAGATT GATTCAAT	ASO-0325	OxyGs OxyTs OxyTs DNAts DNAts DNAts DNAAs DNAGs DNAGs DNAts DNAts DNAts DNAts
258	67218	67236	AGTAATTTTATAA GAACATT	ASO-0326	OxyAs OxyGs OxyTs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
259	67545	67563	CAATGTGTTTA TGTTTTGA	ASO-0327	OxyMCs OxyAs OxyAs OxyTs DNAGs DNAts DNAts DNAts DNAts DNAts DNAts DNAts
260	68059	68078	TTTCTAATTTTC ATGCTCTAT	ASO-0328	OxyTs OxyTs OxyTs OxyMCs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
261	68336	68353	ATTGTTTCTCAT ATTCCC	ASO-0329	OxyAs DNAts DNAts DNAGs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
262	68408	68425	AAACATCAAGT AAAGGCA	ASO-0330	OxyAs OxyAs OxyAs OxyMCs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
263	68767	68783	ATTCTGAGTAA GGGGTC	ASO-0331	OxyAs OxyTs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
264	69068	69086	ATACATTTTACA TTATTCT	ASO-0332	OxyAs OxyTs OxyAs OxyMCs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
266	69608	69625	CTACATTAAAAT ATGGCC	ASO-0335	OxyMCs OxyTs OxyAs OxyMCs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
267	69781	69798	TTCATAAATTCC AGGTGC	ASO-0336	OxyTs OxyTs OxyMCs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
268	69942	69960	TAGCAATACAT GAGAAGAA	ASO-0026	OxyTs OxyAs OxyGs OxyMCs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
269	70003	70020	ATTCTGTGTTG TGCTTTA	ASO-0337	OxyAs OxyTs OxyTs OxyMCs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
270	70130	70147	GAGTAAATGTT TCTGAAT	ASO-0338	OxyGs OxyAs OxyGs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
271	70606	70623	TATATACTTTAG	ASO-	OxyTs OxyAs OxyTs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts

FIG. 1A (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
			ATCTGTAA	0391	DNAas DNAts DNACs DNAts DNAGs OxyTs OxyAs OxyA
308	77709	77726	AAGCTAATGAA AATTGTA	ASO-0392	OxyAs OxyAs OxyGs OxyMCs DNAts DNAas DNAts DNAGs DNAas DNAas DNAas DNAas DNAts OxyTs OxyGs OxyTs OxyA
309	78259	78278	AAGGAATAGCA TGATTAACA	ASO-0393	OxyAs OxyAs OxyGs OxyGs DNAas DNAas DNAts DNAGs DNAGs DNAas DNAts DNAGs DNAas DNAts DNAts OxyAs OxyAs OxyMCs OxyA
310	78542	78558	TGGCTGAGAG GTGAATC	ASO-0394	OxyTs OxyGs OxyGs DNACs DNAts DNAGs DNAas DNAGs DNAGs DNAGs DNAts DNAGs DNAas DNAas OxyTs OxyMC
311	78838	78855	TCTAAATTAAA GTGAAGA	ASO-0395	OxyTs OxyMCs OxyTs OxyAs DNAas DNAts DNAts DNAts DNAas DNAas DNAas DNAGs DNAts DNAGs OxyAs OxyAs OxyGs OxyA
312	79088	79107	TGAAGTCAAAA TTAGTCATC	ASO-0028	OxyTs OxyGs OxyAs DNAas DNAGs DNAts DNACs DNAas DNAas DNAts DNAts DNAts DNAas DNAGs DNAts OxyMCs OxyAs OxyTs OxyMC
313	79090	79107	TGAAGTCAAAA TTAGTCA	ASO-0396	OxyTs OxyGs OxyAs OxyAs DNAGs DNAts DNACs DNAas DNAas DNAas DNAts DNAts DNAas OxyGs OxyTs OxyMCs OxyA
314	79400	79417	ATTACTTCAGT ACCAT	ASO-0397	OxyAs OxyTs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAas DNACs OxyMCs OxyAs OxyTs OxyT
315	81257	81273	GCTGCTTTGAT AGATGA	ASO-0398	OxyGs DNACs DNAts DNAGs DNACs DNAts DNAts DNAts DNAts DNAts DNAas DNAGs OxyAs OxyTs OxyGs OxyA
316	81553	81570	GTGCTGGGGT CTTAACCT	ASO-0399	OxyGs DNAts DNAGs DNACs DNAts DNAGs DNAGs DNAGs DNAts DNAts DNAts DNAts DNAas DNAas DNACs OxyTs OxyT
317	81771	81787	TATTTAAGTTCT TGTC	ASO-0400	OxyTs OxyAs OxyTs OxyTs DNAts DNAts DNAas DNAts DNAts DNAts DNAts DNAts OxyGs OxyTs OxyMCs OxyA
318	82146	82165	ACTTCATAGTA GGTGTCAGA	ASO-0401	OxyAs DNACs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAGs DNAGs DNAts DNAGs DNAts DNAts DNAts DNAts DNAts DNAts DNAas DNAGs OxyGs OxyA
319	82479	82498	TTAATTCCTCCC TAGATGTC	ASO-0402	OxyTs DNAts DNAas DNAas DNAts DNAts DNAts DNAts DNAts DNAts DNACs DNAts DNAas DNAGs DNAas DNAts DNAts DNAts OxyTs OxyMC
320	82701	82720	AAGGTTGTTAA TGCTAAAGA	ASO-0403	OxyAs OxyAs OxyGs DNAGs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAGs DNAts DNAts DNAas OxyAs OxyAs OxyGs OxyA
321	82880	82897	TAATACTTTATG TAATAG	ASO-0404	OxyTs OxyAs OxyAs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAGs DNAts DNAas OxyAs OxyTs OxyAs OxyG
322	83174	83190	ATTCCTAAAGG TCTAAG	ASO-0405	OxyAs OxyTs OxyTs OxyMCs DNAts DNAts DNAts DNAas DNAas DNAts DNAGs DNAts DNACs OxyTs OxyAs OxyAs OxyG
323	83423	83441	TAGTTGACACA TATTATA	ASO-0029	OxyTs OxyAs OxyGs OxyTs DNAts DNAts DNAGs DNAas DNAts DNAts DNAts DNAas DNAts DNAts OxyAs OxyTs OxyAs OxyA
324	83475	83491	GTGATTTTATA GTTGGT	ASO-0406	OxyGs OxyTs OxyGs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAGs DNAts DNAts DNAGs OxyGs OxyT
325	83877	83895	GAATATTTTATA ATTGTAT	ASO-0407	OxyGs OxyAs OxyAs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAas DNAas DNAts DNAts OxyTs OxyGs OxyAs OxyT
326	84066	84083	TACATATAAATC	ASO-	OxyTs OxyAs OxyMCs OxyAs DNAts DNAts DNAas DNAts DNAas DNAas

FIG. 1A (cont.)

[illegible]

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
			TCCTTA	0426	DNAas DNAts DNACs OxyTs OxyTs OxyTs OxyA
346	91524	91540	TATAAGGATAT TAGTTG	ASO-0427	OxyTs OxyAs OxyTs OxyAs DNAas DNAGs DNAts DNAas DNAts DNAas DNAts
347	92407	92424	TGGTGGA CTGT AGATTTTC	ASO-0428	OxyTs OxyGs DNAGs DNAts DNAGs DNAGs DNAas DNACs DNAts DNAGs DNAts
348	92646	92663	GTTTATTTAATG TCTGAT	ASO-0429	OxyGs OxyTs OxyTs DNAas DNAts DNAts DNAts DNAts DNAas DNAts DNAts
349	92967	92984	GCTGCTGTATA ATATATT	ASO-0430	OxyGs OxyMCs OxyTs OxyGs DNACs DNAts DNAGs DNAts DNAas DNAts
350	92982	93000	AATTGTTTAAG AGGGAGCT	ASO-0031	DNAas DNAas DNAts DNAGs DNAGs DNAts DNAts DNAts DNAas DNAts DNAGs
351	93112	93128	TTATTTGCTCTGA GTGTA	ASO-0431	OxyTs OxyTs OxyAs OxyTs DNAts DNAts DNAts DNAGs DNAts DNAts DNAts
352	93636	93655	ACACACTGTAA GAGACAAGC	ASO-0432	OxyAs DNACs DNAas DNACs DNAas DNACs DNAts DNAts DNAGs DNAts DNAas
353	93638	93655	ACACACTGTAA GAGACAA	ASO-0433	OxyAs OxyMCs OxyAs OxyMCs DNAas DNACs DNAts DNAts DNAGs DNAts DNAas
354	94310	94328	TTAAGTAGGTC ACATTTAA	ASO-0434	OxyTs OxyTs OxyAs OxyAs DNAGs DNAts DNAts DNAas DNAGs DNAts DNAts
355	94313	94330	ATTTAAGTAGG TCACATT	ASO-0435	OxyAs OxyTs OxyTs DNAas DNAas DNAGs DNAts DNAts DNAas DNAGs DNAts
356	95510	95529	ATTAGCATTAAT TATTACTC	ASO-0436	OxyAs OxyTs OxyAs DNAGs DNACs DNAas DNAts DNAts DNAts DNAas
357	95516	95535	CTCATTATTAG CATTAAATTA	ASO-0437	OxyMCs OxyTs OxyMCs OxyAs DNAts DNAts DNAts DNAas DNAts DNAts DNAas
358	95891	95908	ATGAGGTGGAA AATGTGA	ASO-0438	OxyAs OxyTs OxyGs DNAas DNAGs DNAGs DNAts DNAGs DNAGs DNAts
359	96245	96264	TTATCATTTAAT ATTTATTA	ASO-0439	OxyTs OxyTs OxyAs OxyTs DNACs DNAas DNAts DNAts DNAts DNAts DNAas
360	96525	96544	GTGAGGAGTGA TTAAATACC	ASO-0440	OxyGs OxyTs OxyGs DNAas DNAGs DNAGs DNAts DNAts DNAts DNAts DNAGs
361	96798	96817	GACTTTATAAC AATAGTACT	ASO-0441	OxyGs OxyAs OxyMCs DNAts DNAts DNAts DNAts DNAas DNAts DNAts DNAas
362	97132	97151	GCATCTTAGAA TTTGCTCTGC	ASO-0442	OxyGs DNACs DNAas DNAts DNACs DNAts DNAts DNAts DNAts DNAts DNAas
363	97133	97151	GCATCTTAGAA TTTGCTCTG	ASO-0032	OxyGs OxyMCs OxyAs DNAts DNACs DNAts DNAts DNAts DNAts DNAts DNAas
364	97147	97163	AGGATTATTAG	ASO-	OxyAs OxyGs DNAGs DNAas DNAts DNAts DNAas DNAts DNAts DNAts DNAts

FIG. 1A (cont.)

[illegible]

FIG. 1A (cont.)

[illegible]

FIG. 1A (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
			ATTGTAA	0580	DNAas DNAts DNAts OxyGs OxyTs OxyAs OxyA
454	114111	114127	GACCAGAAAGAT GTAATT	ASO- 0581	OxyGs OxyAs OxyMCs OxyMCs DNAas DNAGs DNAas DNAGs DNAas
455	114576	114594	AAGCAGTTTAT TTTTCTTTA	ASO- 0582	OxyAs OxyAs OxyGs OxyMCs DNAas DNAGs DNAts DNAts DNAts DNAts
456	114692	114710	TAGATTTATAA GGATTGTA	ASO- 0036	OxyTs OxyAs OxyGs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts
457	114694	114710	TAGATTTATAA GGATTG	ASO- 0583	OxyTs OxyAs OxyGs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts
458	115587	115606	AGGTACAATAA TAAACAAGA	ASO- 0584	OxyAs OxyGs OxyGs OxyTs DNAas DNACs DNACs DNAas DNAts DNAts
459	115589	115606	AGGTACAATAA TAAACAA	ASO- 0585	OxyAs OxyGs OxyGs OxyTs DNAas DNACs DNACs DNAas DNAts DNAts
460	115944	115960	AGATGTTAAGG AAGGTC	ASO- 0586	OxyAs OxyGs OxyAs OxyTs DNAGs DNAts DNAts DNAts DNAts DNAts
461	116188	116206	AATCCATGACA TTTTATTGA	ASO- 0587	OxyAs OxyAs OxyTs OxyMCs DNACs DNACs DNAas DNAts DNAts DNAts
462	116499	116516	ATGAAGTTTCT GTGGCTG	ASO- 0588	OxyAs OxyTs DNAGs DNAas DNAts DNAts DNAts DNAts DNAts DNAts
463	116502	116519	TTTATGAAGTTT CTGTGG	ASO- 0589	OxyTs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
464	117064	117079	GCATTAGGGAG TTCAG	ASO- 0590	OxyGs OxyMCs OxyAs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts
465	117269	117285	CATTAGACCTA GAATTG	ASO- 0591	OxyMCs OxyAs OxyTs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts
466	117601	117618	AAGTTTAAAAG TAAGAGC	ASO- 0592	OxyAs OxyAs OxyGs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts
467	117904	117921	GTC TTATATTAC ATCAAA	ASO- 0593	OxyGs OxyTs OxyMCs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts
468	119540	119556	AATTGAGGGAC AGGTAG	ASO- 0594	OxyAs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
469	119776	119795	AATCTGCCATT TTATCAAGG	ASO- 0595	OxyAs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
470	119780	119799	CAAGAATCTGC CATTTTATC	ASO- 0037	OxyMCs OxyAs OxyAs DNAGs DNAas DNAts DNAts DNAts DNAts DNAts
471	119782	119799	CAAGAATCTGC CATTTTA	ASO- 0596	OxyMCs OxyAs OxyAs DNAGs DNAas DNAts DNAts DNAts DNAts DNAts
472	120301	120317	TTACTGGGAAT	ASO-	OxyTs OxyTs OxyAs OxyMCs DNAts DNAts DNAts DNAts DNAts DNAts

FIG. 1A (cont.)

[illegible]

FIG. 1A (cont.)

[illegible]

[illegible]

FIG. 1A (cont.)

[illegible]

[illegible]

FIG. 1A (cont.)

[illegible]

FIG. 1A (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
			CTAGAAA	0736	DNAas DNAcs DNAts DNAas OxyGs OxyAs OxyA
603	152715	152733	CATGAAGTCGC ACTAGAAA	ASO-0737	OxyMCs OxyAs OxyTs DNAGs DNAas DNAas DNAGs DNAts DNAmcs DNAGs DNAcs DNAas DNAcs DNAts DNAas OxyGs OxyAs OxyA
604	152716	152731	TGAAGTCGCAC TAGAA	ASO-0738	OxyTs OxyGs OxyAs OxyAs DNAGs DNAts DNAmcs DNAGs DNAas DNAcs DNAts DNAas OxyGs OxyAs OxyA
605	152716	152732	ATGAAGTCGCA CTAGAA	ASO-0739	OxyAs OxyTs OxyGs OxyAs DNAas DNAGs DNAts DNAmcs DNAGs DNAcs DNAas DNAcs DNAts DNAas OxyGs OxyAs OxyA
606	152716	152733	CATGAAGTCGC ACTAGAA	ASO-0740	OxyMCs OxyAs OxyTs DNAGs DNAas DNAas DNAGs DNAts DNAmcs DNAGs DNAcs DNAas DNAcs DNAts DNAas OxyGs OxyAs OxyA
607	152760	152777	CAAA TCAAA CA CCAAGTA	ASO-0741	OxyMCs OxyAs OxyAs DNAts DNAcs DNAas DNAas DNAGs DNAts DNAas DNAcs DNAcs DNAas OxyAs OxyGs OxyTs OxyA
608	152760	152778	ACAAATCAAA C ACCAAGTA	ASO-0742	OxyAs OxyMCs OxyAs OxyAs DNAas DNAts DNAcs DNAas DNAas DNAGs DNAcs DNAas DNAcs DNAcs DNAas OxyGs OxyTs OxyA
609	152761	152779	TACAAATCAAA CACCAAGT	ASO-0743	OxyTs OxyAs OxyMCs OxyAs DNAas DNAts DNAcs DNAas DNAas DNAGs DNAas DNAcs DNAcs DNAcs OxyAs OxyAs OxyGs OxyT
610	152761	152780	TTACAAATCAA ACACCAAGT	ASO-0744	OxyTs OxyTs OxyAs OxyMCs DNAas DNAas DNAts DNAcs DNAts DNAGs DNAas DNAas DNAcs DNAas DNAGs OxyAs OxyAs OxyGs OxyT
611	152763	152782	ACTTACAAATC AAACACCAA	ASO-0745	OxyAs OxyMCs DNAts DNAts DNAas DNAGs DNAts DNAGs DNAts DNAGs DNAcs DNAas DNAas DNAcs DNAas OxyMCs OxyMCs OxyAs OxyA
612	152764	152782	ACTTACAAATC AAACACCA	ASO-0746	OxyAs OxyMCs DNAts DNAts DNAas DNAGs DNAts DNAGs DNAts DNAGs DNAcs DNAas DNAas DNAcs DNAGs OxyAs OxyMCs OxyMCs OxyA
613	152764	152783	TACTTACAAAT CAAACACCA	ASO-0747	OxyTs OxyAs OxyMCs DNAts DNAts DNAas DNAGs DNAts DNAGs DNAts DNAts DNAcs DNAas DNAas DNAGs DNAGs OxyAs OxyMCs OxyA
614	152765	152782	ACTTACAAATC AAACACCA	ASO-0748	OxyAs OxyMCs OxyTs OxyTs DNAas DNAGs DNAts DNAGs DNAts DNAGs DNAcs DNAas DNAas DNAcs OxyAs OxyMCs OxyMC
615	152765	152783	TACTTACAAAT CAAACACC	ASO-0749	OxyTs OxyAs OxyMCs DNAts DNAts DNAas DNAGs DNAts DNAGs DNAts DNAts DNAcs DNAas DNAas DNAGs OxyMCs OxyAs OxyMCs OxyMC
616	152765	152784	ATACTTACAAAT CAAACACC	ASO-0750	OxyAs OxyTs OxyAs OxyMCs DNAts DNAts DNAas DNAGs DNAts DNAGs DNAas DNAts DNAcs DNAas DNAGs DNAGs OxyAs OxyMCs OxyMC
617	152766	152783	TACTTACAAAT CAAACAC	ASO-0751	OxyTs OxyAs OxyMCs OxyTs DNAts DNAas DNAGs DNAts DNAGs DNAts DNAts DNAcs DNAas DNAas OxyAs OxyMCs OxyAs OxyMC
618	152766	152784	ATACTTACAAAT CAAACAC	ASO-0752	OxyAs OxyTs OxyAs OxyMCs DNAts DNAts DNAas DNAGs DNAts DNAGs DNAas DNAts DNAcs DNAas DNAGs OxyAs OxyMCs OxyAs OxyMC
619	152766	152785	TATACTTACAAA TCAAACAC	ASO-0753	OxyTs OxyAs OxyTs OxyAs DNAGs DNAts DNAts DNAGs DNAts DNAGs DNAas DNAts DNAcs DNAas DNAGs OxyAs OxyMCs OxyAs OxyMC
620	152767	152785	TATACTTACAAA TCAAACA	ASO-0754	OxyTs OxyAs OxyTs OxyAs DNAGs DNAts DNAts DNAGs DNAts DNAGs DNAas DNAts DNAcs DNAas OxyAs OxyAs OxyMCs OxyA
621	152767	152786	ATATACTTACAA	ASO-	OxyAs OxyTs OxyAs OxyTs DNAas DNAGs DNAts DNAts DNAGs DNAts DNAas DNAGs DNAGs

FIG. 1A (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
			ATCAACA	0755	DNAas DNAas DNAts DNacs DNAas OxyAs OxyAs OxyMCs OxyA
622	153220	153238	CATTATTTCCC TTCATTC	ASO-0756	OxyMCs OxyAs DNAts DNAts DNAas DNAts DNAts DNAts DNAts DNacs DNacs
623	153520	153536	TTCTCTATAATT GGATC	ASO-0757	OxyTs OxyTs OxyMCs OxyTs DNacs DNAts DNAas DNAts DNAas DNAts DNAts
624	153964	153983	AGTTGTAATTT CATTCCTT	ASO-0758	OxyAs DNags DNAts DNAts DNags DNAts DNAas DNAas DNAts DNAts DNAts
625	153969	153985	CCAGTTGTAAT TTCATT	ASO-0759	OxyMCs OxyMCs OxyAs OxyGs DNAts DNAts DNags DNAts DNAas DNAas
626	154743	154761	TCAACATTGG AAAGGAAG	ASO-0760	OxyTs OxyMCs OxyAs OxyAs DNAas DNacs DNacs DNAas DNAts DNAts DNags
627	154745	154761	TCAACATTGG AAAGGA	ASO-0761	OxyTs OxyMCs OxyAs OxyAs DNAas DNacs DNacs DNAas DNAts DNAts DNags
628	155365	155384	GACGAACAAT AATAAATTA	ASO-0762	OxyGs OxyAs OxyMCs OxyAs DNags DNags DNAas DNAas DNacs DNacs DNAts
629	155396	155415	CAGAGAAAGA ATTAGACAA	ASO-0763	OxyMCs OxyAs OxyGs OxyAs DNags DNags DNags DNAas DNAas DNags DNags
630	155941	155959	AGATAATCAAC AGGCAGCA	ASO-0764	OxyAs DNags DNAas DNAts DNAas DNAts DNAts DNAts DNAts DNAts DNAts
631	155942	155960	AAGATAATCAA CAGGCAGC	ASO-0044	OxyAs DNacs DNags DNags DNags DNags DNags OxyAs OxyGs OxyMCs OxyA
632	155943	155959	AGATAATCAAC AGGCAG	ASO-0765	OxyAs OxyGs DNAas DNAts DNAas DNAas DNAts DNAts DNAts DNAts DNAts
633	156515	156532	GTTAATCTCTC TCTTGTT	ASO-0766	OxyGs OxyTs DNAts DNAas DNAas DNAts DNAts DNAts DNAts DNAts DNAts
634	156666	156682	TTTCCATAAGT CAATTC	ASO-0767	OxyTs OxyTs OxyMCs DNacs DNAas DNAts DNAts DNAts DNAts DNAts DNags
635	157021	157039	ATGACTGTGGA AAACTGGC	ASO-0768	OxyAs DNAts DNags DNAas DNacs DNAts DNAts DNags DNAts DNags DNags
636	157447	157465	TTTATTAACTCTC ATTACT	ASO-0769	OxyTs OxyTs OxyAs DNAts DNAts DNAts DNAas DNAas DNAts DNAts DNAts
637	157735	157753	CAAGTAGTTAT TTTATCTC	ASO-0770	OxyMCs OxyAs OxyGs DNAts DNAts DNAas DNags DNAts DNAts DNAts DNAts
638	157739	157756	ATTCAAGTAGT TATTTTA	ASO-0771	OxyAs OxyTs OxyTs OxyMCs DNAas DNAas DNags DNags DNAts DNAts DNags
639	159291	159308	CAATTTGCTGT TCCTATA	ASO-0772	OxyMCs OxyAs DNAas DNAts DNAts DNAts DNags DNacs DNAts DNAts DNAts
640	159834	159851	ACACTATTTTA	ASO-	OxyAs OxyMCs OxyAs OxyMCs DNAts DNAas DNAts DNAts DNAts DNAts DNAts

FIG. 1A (cont.)

[illegible]

FIG. 1A (cont.)

[illegible]

FIG. 1A (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
			AGAACTCTTA	0808	DNAas DNAGs DNAas DNAas DNATs DNATs OxyTs OxyTs OxyA
679	172117	172136	AGATGGAATAA TTTAAAGCC	ASO- 0809	OxyAs OxyGs DNAas DNATs DNAGs DNAGs DNAas DNAas DNATs DNAas DNAas DNATs DNATs DNATs DNAas DNAas OxyAs OxyGs OxyMCs OxyMC
680	172259	172275	GAAGTGTCTTA GATATC	ASO- 0810	OxyGs OxyAs OxyAs OxyMCs DNATs DNAGs DNATs DNATs DNATs DNAas DNAGs DNAas OxyTs OxyAs OxyTs OxyMC
681	172675	172691	AGACTATATGA AGGTGA	ASO- 0811	OxyAs OxyGs OxyAs DNACs DNATs DNAas DNATs DNAas DNATs DNAGs DNAas DNAas DNAGs OxyGs OxyTs OxyGs OxyA
682	173063	173080	ATAAATTAATTC ATGGTA	ASO- 0812	OxyAs OxyTs OxyAs OxyAs DNAas DNATs DNATs DNATs DNAas DNATs DNATs DNACs DNAas DNATs OxyGs OxyGs OxyTs OxyA
683	173092	173108	ATAGTTGGTAA TATAGA	ASO- 0813	OxyAs OxyTs OxyAs OxyGs DNATs DNATs DNAGs DNAGs DNATs DNAas DNAas DNATs DNAas OxyTs OxyAs OxyGs OxyA
684	173465	173482	TTTCATTTCTTA AAACGT	ASO- 0814	OxyTs OxyTs OxyTs OxyMCs DNAas DNATs DNATs DNATs DNATs DNATs DNATs DNAas DNAas DNAas OxyAs OxyMCs OxyGs OxyT
685	173893	173911	AGGGTTGAATA GTTTTTCAG	ASO- 0815	OxyAs OxyGs OxyGs DNAGs DNATs DNATs DNAGs DNAas DNAas DNATs DNAas DNAGs DNATs DNATs DNATs DNATs DNATs DNATs OxyAs OxyG
686	173986	174004	CAGATCAGTAG GTTTCTTT	ASO- 0048	OxyMCs OxyAs DNAGs DNAas DNATs DNATs DNATs DNATs DNATs DNATs DNAas DNAGs DNATs DNATs DNATs DNATs DNATs DNATs OxyTs OxyTs OxyT
687	173988	174004	CAGATCAGTAG GTTTCT	ASO- 0816	OxyMCs OxyAs OxyGs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNAas DNAGs DNATs DNATs DNATs DNATs DNATs OxyMCs OxyT
688	174336	174352	CTGAAGGATTG AGGTTG	ASO- 0817	OxyMCs OxyTs OxyGs OxyAs DNAas DNAGs DNAGs DNATs DNATs DNATs DNAGs DNAas DNAGs DNAGs DNATs OxyTs OxyG
689	174679	174695	TATATGCTTGT CAGTTT	ASO- 0818	OxyTs OxyAs OxyTs OxyAs DNATs DNAGs DNATs DNATs DNATs DNATs DNATs DNACs DNAas DNAGs OxyTs OxyTs OxyT
690	174862	174879	TATTTTACAGTT GTTTCAT	ASO- 0819	OxyTs OxyAs OxyTs OxyTs DNATs DNATs DNATs DNAas DNATs DNATs DNATs DNATs DNAGs DNATs OxyTs OxyMCs OxyAs OxyT
691	175112	175128	GCTGGTTATAG TAATAA	ASO- 0820	OxyGs OxyMCs OxyTs OxyGs DNAGs DNATs DNATs DNAas DNATs DNATs DNAGs DNATs DNAas OxyAs OxyTs OxyAs OxyA
692	175638	175656	TGATGTAAGCC TGGAACGTG	ASO- 0821	OxyTs OxyGs OxyAs DNATs DNAGs DNATs DNAas DNATs DNATs DNATs DNATs DNATs DNAGs DNAGs DNAas DNATs DNATs DNATs OxyTs OxyG
693	175647	175663	GTAAGAAATGAT GTAAGC	ASO- 0822	OxyGs OxyTs OxyAs OxyAs DNAGs DNAas DNATs DNATs DNATs DNATs DNATs DNAGs DNATs OxyAs OxyAs OxyGs OxyMC
703	176315	176332	ATGACTGAATT AAATATG	ASO- 0842	OxyAs OxyTs OxyGs OxyAs DNATs DNATs DNATs DNATs DNAas DNATs DNATs DNAas DNAas DNATs OxyTs OxyAs OxyTs OxyG
704	176730	176747	GTGCATTAAAT TATCTAT	ASO- 0843	OxyGs OxyTs OxyGs OxyMCs DNATs DNATs DNATs DNATs DNATs DNAas DNATs DNATs DNATs DNATs DNATs DNATs OxyTs OxyAs OxyT
705	177165	177183	GCTACATATAA TGAGGAAA	ASO- 0844	OxyGs OxyMCs OxyTs OxyAs DNATs DNATs DNATs DNATs DNATs DNATs DNAas DNATs DNAGs DNAas DNATs OxyGs OxyAs OxyAs OxyA
706	177458	177477	TGGTTTATGCA	ASO-	OxyTs OxyGs DNAGs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNATs

FIG. 1A (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
			GGAAGAAGA	0845	DNags DNags DNAas DNAas DNags DNAas DNAas OxyGs OxyA
707	177608	177625	AAAGGGATAAT TAAGTGA	ASO- 0846	OxyAs OxyAs OxyGs DNags DNags DNAas DNats DNAas DNAas DNats
708	177919	177935	TTAATCATTGG CTGGGG	ASO- 0847	OxyTs DNats DNAas DNAas DNats DNacs DNAas DNats DNats DNags DNags
709	178222	178238	GTTTAAC TTATA TACAG	ASO- 0848	OxyGs OxyTs OxyTs DNAas DNAas DNacs DNats DNats DNats DNAas DNats
710	178648	178665	GAATTTGAATA AAAGCCT	ASO- 0849	OxyGs OxyAs OxyAs OxyTs DNats DNats DNags DNAas DNAas DNats DNAas
711	178649	178667	AAGAA TTTGAA TAAAAGCC	ASO- 0049	OxyAs OxyAs OxyGs OxyAs DNAas DNats DNats DNats DNags DNAas DNAas
712	178802	178820	ATGTAAATTTT ATCTTGA	ASO- 0850	OxyAs OxyTs OxyGs OxyMCs DNats DNAas DNAas DNats DNats DNats DNats
713	178822	178839	CTAATTTTAAAT TGCTGC	ASO- 0050	OxyMCs OxyTs OxyAs DNAas DNats DNats DNats DNats DNats DNAas DNAas
714	178822	178840	TCTAA TTTTAAA TTGTGTC	ASO- 0051	OxyTs OxyMCs DNats DNAas DNAas DNats DNats DNats DNats DNats DNAas
715	178822	178841	TTCTAA TTTTAA ATTGCTGC	ASO- 0851	OxyTs OxyTs DNacs DNats DNAas DNAas DNats DNats DNats DNats DNats
716	178823	178841	TTCTAA TTTTAA ATTGCTG	ASO- 0052	OxyTs OxyTs OxyMCs OxyTs DNAas DNAas DNats DNats DNats DNats DNats
717	178823	178842	CTTCTAA TTTTA AATTGCTG	ASO- 0852	OxyMCs OxyTs OxyTs OxyMCs DNats DNats DNAas DNAas DNats DNats DNats
718	178824	178842	CTTCTAA TTTTA AATTGCT	ASO- 0853	OxyMCs OxyTs OxyTs DNacs DNats DNAas DNAas DNats DNats DNats DNats
719	178824	178843	GCTTCTAA TTTT AAATTGCT	ASO- 0854	OxyGs OxyMCs DNats DNats DNacs DNats DNats DNats DNAas DNats DNats
720	178825	178843	GCTTCTAA TTTT AAATTGC	ASO- 0855	OxyGs OxyMCs DNats DNats DNacs DNats DNats DNats DNAas DNats DNats
721	179111	179127	TTATAAGCTTTA GACAG	ASO- 0856	OxyTs OxyTs OxyAs OxyTs DNAas DNAas DNags DNacs DNats DNats DNats
722	179547	179565	TTAACCTGAAT TTATTGAG	ASO- 0857	OxyTs OxyTs OxyAs OxyAs DNacs DNacs DNats DNats DNags DNAas DNats
723	179651	179667	ATGAATAGGAT AGGGGT	ASO- 0858	OxyAs OxyTs DNags DNAas DNAas DNats DNats DNAas DNags DNags DNats
724	180041	180058	AGTCAGATAAT TCAATTA	ASO- 0859	OxyAs OxyGs OxyTs OxyMCs DNas DNags DNAas DNats DNats DNats DNAas
725	180075	180092	AGCTATATTAA	ASO-	OxyAs OxyGs OxyMCs OxyTs DNAas DNats DNats DNAas DNats DNats DNAas

FIG. 1A (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
			GTAAGAAG	0860	DNAas DNAgs DNAts DNAas OxyAs OxyAs OxyG
726	180769	180785	TTAATATAAGG AGGTAG	ASO- 0861	OxyTs OxyTs OxyAs OxyAs DNAts DNAas DNAts DNAas DNAgs DNAts DNAas DNAgs OxyGs OxyTs OxyAs OxyG
727	180774	180793	TAATTTTATTAA TATAAGGA	ASO- 0862	OxyTs OxyAs OxyAs OxyTs DNAts DNAts DNAts DNAas DNAts DNAts DNAas DNAas DNAts DNAas DNAts DNAas OxyAs OxyGs OxyGs OxyA
728	181169	181188	AGATTATCAGG ATTAAATGA	ASO- 0863	OxyAs OxyGs OxyAs OxyTs DNAts DNAas DNAts DNAts DNAts DNAas DNAgs DNAts DNAas DNAts DNAts DNAas DNAas DNAts OxyTs OxyGs OxyA
729	181170	181188	AGATTATCAGG ATTAAATG	ASO- 0864	OxyAs OxyGs OxyAs OxyTs DNAts DNAas DNAts DNAts DNAts DNAas DNAts DNAts DNAas DNAts DNAts DNAas OxyAs OxyAs OxyTs OxyG
730	181774	181791	CCATGACCTTA TTAATGA	ASO- 0865	OxyMCs OxyMCs OxyAs DNAts DNAts DNAas DNAts DNAts DNAts DNAts DNAas DNAts DNAts DNAas DNAts OxyTs OxyGs OxyA
731	181775	181791	CCATGACCTTA TTAATG	ASO- 0866	OxyMCs OxyMCs OxyAs OxyTs DNAts DNAas DNAts DNAts DNAts DNAts DNAas DNAts DNAts DNAas DNAts OxyTs OxyG
732	182679	182696	AAATTGTTGCT TCTCATC	ASO- 0867	OxyAs OxyAs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts OxyMCs OxyAs OxyTs OxyMC
733	182764	182780	TTTTGGAGACT AAGCTA	ASO- 0868	OxyTs OxyTs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAas DNAas DNAts OxyMCs OxyTs OxyA
734	183386	183405	TTCATATCAGTT CAAAATGA	ASO- 0053	OxyTs OxyTs OxyMCs OxyAs DNAts DNAas DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAas DNAas DNAts DNAts OxyAs OxyTs OxyGs OxyA
735	183560	183576	ATTGTCAGGAT TGGGTC	ASO- 0869	OxyAs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts OxyTs OxyMC
736	183578	183595	TATTTGGTTATT TGTGAG	ASO- 0870	OxyTs OxyAs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts OxyTs OxyGs OxyAs OxyG
737	184119	184136	ATTGTCATAAAT GTTGTG	ASO- 0871	OxyAs OxyTs OxyTs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAas DNAts DNAts DNAts OxyTs OxyGs OxyTs OxyG
738	184370	184387	CCTTGATTATT GTCTGTT	ASO- 0872	OxyMCs OxyMCs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts OxyTs OxyT
739	184697	184714	TTAAAGTTTAT CAGCTT	ASO- 0873	OxyTs OxyTs OxyAs OxyAs DNAts DNAas DNAts DNAts DNAts DNAts DNAas DNAts DNAts DNAts OxyGs OxyMCs OxyTs OxyT
740	184958	184975	TTGTTTAGTATT CATTTTC	ASO- 0874	OxyTs OxyTs OxyGs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts OxyTs OxyTs OxyTs OxyMC
741	185161	185177	GAGGCTAGAAT AATTTTG	ASO- 0875	OxyGs OxyAs OxyGs OxyGs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAas DNAas OxyTs OxyTs OxyTs OxyG
742	185516	185533	ACAATGAAGAA TAGTATA	ASO- 0876	OxyAs OxyMCs OxyAs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAas DNAts DNAas DNAts OxyTs OxyAs OxyTs OxyA
743	186088	186104	TGTGGAATAAA GTGCAT	ASO- 0877	OxyTs OxyGs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts OxyGs OxyMCs OxyAs OxyT
744	186089	186105	TTGTGGAATAA	ASO-	OxyTs OxyTs OxyGs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAas DNAts DNAts DNAts DNAts

FIG. 1A (cont.)

[illegible]

FIG. 1A (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
			TTTGAGC	0895	DNats DNats DNats OxyGs OxyAs OxyGs OxyMC
764	192452	192471	GTTTTGGTTCTAA TAATTCTG	ASO-0896	OxyGs OxyTs OxyTs DNats DNats DNags DNats DNats DNacs DNats DNAs DNAs
765	192638	192656	CTTGTCCTTTT GTGTCATA	ASO-0897	DNAas DNats DNAas DNats OxyTs OxyMCs OxyTs OxyG OxyMCs DNats DNags DNats DNags DNacs DNats DNats DNats DNats DNats
766	192963	192980	GTTGTTAAAGTT ACAGAAG	ASO-0898	DNags DNats DNags DNats DNacs DNats DNats DNats DNats DNats DNats DNats
767	193072	193091	AATGATGAGTA ATGTTGAGT	ASO-0899	OxyAs OxyAs OxyTs OxyGs DNAas DNats DNats DNags DNags DNags DNats DNAs
768	193590	193607	ATTCAATATTTG TGCTTT	ASO-0900	DNAas DNats DNags DNats DNats DNats DNats DNats DNats DNats DNats DNats
769	193594	193610	ACCATTCAAATA TTTGTG	ASO-0901	OxyAs OxyMCs OxyMCs OxyAs DNats DNats DNats DNats DNats DNats DNats
770	194118	194136	TGTAAATTTAAA GAGCTAA	ASO-0902	DNAas DNats DNats DNats DNats DNats DNats DNats DNats DNats DNats DNats
771	194302	194320	GCAAAATATGGA TGAAATTT	ASO-0903	OxyGs OxyMCs OxyAs OxyAs DNAas DNats DNats DNats DNats DNats DNags
772	195006	195024	CATTACTCATT ATCCATC	ASO-0904	DNAas DNats DNats DNats DNats DNats DNats DNats DNats DNats DNats DNats
773	195355	195373	ATATCTAAATTC CTCTTTC	ASO-0905	OxyAs OxyTs OxyAs DNats DNacs DNats DNats DNats DNats DNats DNats DNats
774	195619	195636	GTAGAGTTCAG TCATTTT	ASO-0906	DNacs DNacs DNats DNags DNags DNags DNats DNats DNats DNats DNats DNags
775	195865	195883	TTCTTTTCAATA TTATCTT	ASO-0907	OxyTs OxyTs OxyMCs OxyTs DNats DNats DNats DNats DNats DNats DNats DNats
776	196021	196037	GTAGAGGCTAT TAATGA	ASO-0908	OxyGs OxyTs OxyAs DNags DNags DNags DNags DNags DNats DNats DNats DNats
777	196644	196662	TACAACAAATT AAAGAGGG	ASO-0909	DNats DNats DNats DNats DNats DNats DNats DNats DNats DNats DNats DNats
778	196726	196743	TTTGTGAAAGA GAACAGG	ASO-0910	OxyTs OxyTs OxyTs OxyGs DNats DNats DNats DNats DNats DNats DNats DNats
779	197052	197069	AGATGAGGAAT ATGATGG	ASO-0911	DNags DNats DNats DNats DNats DNats DNats DNats DNats DNats DNats DNats
780	197054	197073	TATTAGATGAG GAATATGAT	ASO-0056	OxyTs OxyAs OxyTs OxyTs DNats DNats DNats DNats DNats DNats DNats DNats
781	197415	197434	TTGTTTGATTTA AATTTTAC	ASO-0912	DNags DNats DNats DNats DNats DNats DNats DNats DNats DNats DNats DNats
782	197528	197546	CAATCTTGATTT	ASO-	OxyMCs OxyAs OxyAs OxyTs DNacs DNats DNats DNats DNats DNats DNats DNats

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
			AATTTTC	0913	DNats DNAAas DNAts OxyTs OxyTs OxyTs OxyMC
783	197899	197915	TGATGGAGATA ACTAGT	ASO-0914	OxyTs OxyGs OxyAs DNats DNAGs DNAAas DNAAas DNAAas DNAAas DNAAas
784	198307	198324	TAGTTTGGTGG ATGGTGC	ASO-0915	OxyTs DNAAas DNAGs DNAts DNAts DNAts DNAGs DNAts DNAGs DNAGs DNAGs
785	198518	198537	AATGTGTGGGT TTTCTTTCA	ASO-0916	DNAAas DNAts DNAGs DNAts DNAts DNAts DNAts DNAts DNAts DNAts
786	199058	199077	TATTTAAATTTAA TGAATGCC	ASO-0917	OxyTs OxyAs OxyTs DNats DNats DNAAas DNAAas DNAts DNats DNats DNAAas
787	199070	199088	ATATATGGCTT TATTTAAT	ASO-0918	DNAAas DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
788	199524	199540	ATTGAGGTAAG TCTAGA	ASO-0919	OxyAs OxyTs OxyTs DNAGs DNAAas DNAGs DNAGs DNAts DNAAas DNAAas DNAGs
789	199581	199599	TTATCTAAAAATC TTATTTA	ASO-0920	OxyTs OxyTs OxyAs OxyTs DNats DNAAas DNAAas DNAAas DNAAas DNAAas DNAAas
790	199958	199975	AATGTTTTATT GTATGTG	ASO-0921	OxyAs OxyAs OxyTs OxyGs DNAGs DNAts DNAts DNAts DNAts DNAts DNAts
791	200729	200745	CTACAGGGACT TACAAG	ASO-0922	OxyMCs OxyTs OxyAs OxyMCs DNAAas DNAGs DNAGs DNAGs DNAAas DNAAas
792	200739	200756	ATATTTTATTAC TACAGG	ASO-0923	OxyAs OxyTs OxyAs OxyTs DNats DNats DNats DNats DNAAas DNats DNats DNAAas
793	200989	201007	GAGAGGAGAG AATAATGAA	ASO-0924	OxyGs OxyAs OxyGs OxyAs DNAGs DNAGs DNAAas DNAGs DNAAas DNAAas DNAGs
794	201838	201855	TACTGTTACTG TTGATCC	ASO-0925	OxyTs DNAAas DNAAas DNAts DNAGs DNAts DNAts DNAAas DNAAas DNAts DNAGs
795	201843	201862	GAGGAGATACT GTTACTGTT	ASO-0057	OxyGs OxyAs DNAGs DNAGs DNAAas DNAGs DNAAas DNats DNats DNAAas DNats
796	202054	202073	TTCTAACATATT TCTAATCA	ASO-0926	OxyTs OxyTs OxyMCs OxyTs DNAAas DNAAas DNAAas DNAAas DNAAas DNAAas
797	202186	202204	TAATTCATCTAA AAGTTAG	ASO-0927	OxyTs OxyAs OxyAs OxyTs DNats DNAAas DNAAas DNAAas DNAAas DNAAas
798	202670	202687	TATTAACATATTG GAATTC	ASO-0928	OxyTs OxyAs OxyTs OxyTs DNAAas DNAAas DNAAas DNAAas DNAAas DNAAas
799	202673	202690	ATGTATTAACTA TTGGAA	ASO-0929	OxyAs OxyTs OxyGs OxyTs DNAAas DNats DNats DNats DNAAas DNAAas DNAAas
800	203349	203368	ATATCAGGGAC TTCAGTATC	ASO-0930	OxyAs OxyTs OxyAs DNats DNAAas DNAAas DNAAas DNAAas DNAAas DNAAas
801	203606	203623	TTTTAAATTCCTG	ASO-	OxyTs OxyTs OxyTs OxyTs DNAAas DNAAas DNAAas DNAAas DNAAas DNAAas

FIG. 1A (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
			AAGTCA	0931	DNAGs DNAas DNAas OxyGs OxyTs OxyMCs OxyA
802	203712	203728	CAGTTTTTCATA ATCACC	ASO-0932	OxyMCs OxyAs OxyGs OxyTs DNats DNats DNats DNacs DNAas DNats DNAas
803	204117	204133	CGTATATTATG AGCATG	ASO-0933	DNAas DNats DNacs OxyAs OxyMCs OxyA
804	204562	204579	ATTGTATCCC ACCTATC	ASO-0934	OxyAs DNats DNats DNats DNags DNats DNats DNats DNats DNacs DNacs DNacs
805	204568	204584	GCTTAATTTGT ATCCCA	ASO-0935	OxyGs OxyMCs DNats DNats DNats DNats DNats DNats DNats DNats DNats DNats
806	204987	205005	GTGAATAAGTG ATTAAATA	ASO-0936	OxyGs OxyTs OxyGs OxyAs DNAas DNats DNats DNats DNats DNats DNats DNats
807	205172	205188	TATGGGGATAC AATGAA	ASO-0937	OxyTs OxyAs OxyTs OxyGs DNags DNags DNags DNags DNats DNats DNats
808	205690	205706	AGTAATGGAGA TTAAGG	ASO-0938	OxyAs OxyGs OxyTs OxyAs DNAas DNats DNats DNats DNats DNats DNats DNats
809	205860	205879	GAGAAATGTCT GTGTTCAA	ASO-0939	OxyGs OxyAs DNags DNAas DNats DNats DNats DNats DNats DNats DNats
810	206273	206291	AGGCAGAAAGTT GTAATGGT	ASO-0940	OxyAs OxyGs DNags DNacs DNats DNats DNats DNats DNats DNats DNats
811	206274	206292	AAGGCAGAAAGT TGTAATGG	ASO-0058	OxyAs OxyAs OxyGs OxyGs DNacs DNacs DNats DNats DNats DNats DNats DNats
812	206749	206766	ATTTCATCAGT AATAGAT	ASO-0941	OxyAs OxyTs OxyTs DNacs DNats DNats DNats DNats DNats DNats DNats
813	207074	207091	TTAGAGATTTT GTGAATA	ASO-0942	OxyTs OxyTs OxyAs OxyGs DNAas DNags DNats DNats DNats DNats DNats DNats
814	207236	207254	ATTTTCTAACTT TAACATA	ASO-0943	OxyAs OxyTs OxyTs OxyTs DNats DNats DNats DNats DNats DNats DNats DNats
815	207748	207767	TACTGATCTTT GTTATGTA	ASO-0944	OxyTs OxyAs DNacs DNats DNags DNAas DNats DNats DNats DNats DNats DNats
816	207753	207769	CTTACTGATCT TTGTTA	ASO-0945	OxyMCs OxyTs OxyTs OxyAs DNacs DNats DNats DNats DNats DNats DNats DNats
817	208449	208468	TTTTGCTTTTATT AAGTTCTG	ASO-0946	OxyTs OxyTs DNats DNats DNags DNacs DNats DNats DNats DNats DNats DNats
818	208505	208522	GAGTGAGATAA AAGGATG	ASO-0947	OxyGs OxyAs OxyGs OxyTs DNags DNags DNats DNats DNats DNats DNats DNats
819	208949	208966	GAATTTCTTGG TTATTAG	ASO-0948	OxyGs OxyAs OxyAs OxyTs DNats DNats DNats DNats DNats DNats DNats DNats
820	209096	209112	AATTTTGTAGA	ASO-	OxyAs OxyAs OxyTs OxyTs DNats DNats DNats DNats DNats DNats DNats DNats

[illegible]

FIG. 1A (cont.)

[illegible]

FIG. 1A (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
			GGGCAGA	0975	DNAas DNAgs DNAgs DNAGs OxyMCs OxyAs OxyGs OxyA
859	213182	213199	ACTGCAAGAT ACAAGGG	ASO- 0976	OxyAs OxyMCs DNAts DNAGs DNACs DNAas DNAas DNAGs DNAas DNAts DNAas DNACs OxyAs OxyGs OxyGs OxyG
860	213182	213200	GACTGCAAGA TACAAGGG	ASO- 0977	OxyGs DNAas DNACs DNAts DNAGs DNACs DNAas DNAas DNAGs DNAGs DNAts DNAas DNACs DNAas OxyGs OxyGs OxyG
861	213183	213200	GACTGCAAGA TACAAGG	ASO- 0978	OxyGs OxyAs OxyMCs DNAts DNAGs DNACs DNAas DNAas DNAGs DNAGs DNAts DNAas DNACs OxyAs OxyAs OxyGs OxyG
862	213183	213201	TGACTGCAAG ATACAAGG	ASO- 0979	OxyTs OxyGs OxyAs DNACs DNAts DNAGs DNACs DNAas DNAas DNAGs DNAGs DNAts DNAas DNACs DNAas OxyGs OxyG
863	213183	213202	ATGACTGCAAA GATACAAGG	ASO- 0980	OxyAs OxyTs DNAGs DNAas DNACs DNAts DNAGs DNACs DNAas DNAas DNAGs DNAGs DNAts DNAas DNACs OxyAs OxyAs OxyGs OxyG
864	213184	213201	TGACTGCAAG ATACAAG	ASO- 0981	OxyTs OxyGs OxyAs OxyMCs DNAts DNAGs DNACs DNAas DNAas DNAGs DNAGs DNAts DNAas OxyMCs OxyAs OxyAs OxyG
865	213184	213202	ATGACTGCAAA GATACAAG	ASO- 0982	OxyAs OxyTs OxyGs DNAas DNACs DNAts DNAGs DNACs DNAas DNAas DNAGs DNAGs DNAts DNAas OxyMCs OxyAs OxyAs OxyG
866	213184	213203	AATGACTGCAA AGATACAAG	ASO- 0983	OxyAs OxyAs OxyTs OxyGs DNAas DNACs DNAts DNAGs DNACs DNAas DNAas DNAGs DNAGs DNAts DNAas DNACs OxyAs OxyAs OxyG
867	213185	213204	CAATGACTGCA AAGATACA	ASO- 0984	OxyMCs OxyAs OxyAs OxyTs DNAGs DNAas DNACs DNAts DNAGs DNACs DNAGs DNAGs DNAts DNAas DNACs DNAts DNAas OxyA
868	213186	213204	CAATGACTGCA AAGATACA	ASO- 0985	OxyMCs OxyAs OxyAs DNAts DNAGs DNAas DNACs DNAts DNAGs DNACs DNAGs DNAGs DNAts DNAas DNACs OxyTs OxyAs OxyMCs OxyA
869	213186	213205	ACAATGACTGC AAAGATACA	ASO- 0986	OxyAs OxyMCs OxyAs OxyAs DNAts DNAGs DNAas DNACs DNAts DNAGs DNACs DNAGs DNAGs DNAts DNAas DNACs OxyAs OxyMCs OxyA
870	213187	213205	ACAATGACTGC AAAAGATAC	ASO- 0987	OxyAs OxyMCs OxyAs OxyAs DNAts DNAGs DNAas DNACs DNAts DNAGs DNACs DNAGs DNAGs DNAts DNAas DNACs OxyTs OxyAs OxyMC
871	213188	213206	TACAATGACTG CAAAGATA	ASO- 0988	OxyTs OxyAs OxyMCs OxyAs DNAas DNAts DNAGs DNACs DNAas DNAts DNAGs DNACs DNAas DNAts DNAGs OxyTs OxyA
872	213189	213208	TATACAATGAC TGCAAGAT	ASO- 0989	OxyTs OxyAs DNAts DNAas DNACs DNAts DNAGs DNACs DNAts DNAGs DNACs DNAGs DNAGs DNAts DNAas DNAts DNAGs OxyAs OxyT
873	213191	213208	TATACAATGAC TGCAAG	ASO- 0990	OxyTs OxyAs OxyTs OxyAs DNACs DNAas DNAts DNAGs DNACs DNAts DNAGs DNACs DNAGs DNAGs DNAts DNAas DNAts DNAGs OxyG
874	213240	213256	AACATGCCAT TTAGGT	ASO- 0991	OxyAs OxyAs DNACs DNAts DNAas DNAts DNAGs DNACs DNAts DNAGs DNACs DNAGs DNAts DNAts DNAts OxyGs OxyT
875	213240	213257	GAACATGCCA TTTAGGT	ASO- 0992	OxyGs OxyAs OxyAs DNACs DNAts DNAas DNAts DNAGs DNACs DNAts DNAGs DNACs DNAGs DNAts DNAts DNAts OxyGs OxyT
876	213240	213259	GTGAACATGTC CATTTAGGT	ASO- 0993	OxyGs DNAts DNAGs DNAas DNAts DNAGs DNACs DNAts DNAGs DNACs DNAGs DNAGs DNAts DNAas DNAts DNAGs OxyGs OxyT
877	213241	213257	GAACATGCCA	ASO-	OxyGs OxyAs OxyAs OxyMCs DNAts DNAas DNAts DNAGs DNACs DNAGs DNAts DNAGs DNACs DNAGs

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
			TTTAGG	0994	DNAas DNAts DNAts DNAAs OxyGs OxyG
878	213241	213258	TGAACATATGCC ATTTAGG	ASO- 0995	OxyTs DNAGs DNAAs DNAcs DNAts DNAAs DNAts DNAGs DNAcs DNAGs DNAAs DNAts DNAts DNAts OxyAs OxyGs OxyG
879	213241	213259	GTGAACATATGC CATTTAGG	ASO- 0996	OxyGs DNAts DNAGs DNAAs DNAcs DNAts DNAAs DNAts DNAGs DNAcs DNAGs DNAAs DNAts DNAts DNAts OxyAs OxyGs OxyG
880	213242	213259	GTGAACATATGC CATTAG	ASO- 0997	OxyGs OxyTs DNAGs DNAAs DNAcs DNAts DNAAs DNAts DNAGs DNAcs DNAGs DNAAs DNAts DNAts OxyTs OxyAs OxyG
881	213242	213260	TGTGAACATATG CCATTTAG	ASO- 0998	OxyTs DNAGs DNAts DNAGs DNAAs DNAcs DNAts DNAAs DNAts DNAGs DNAGs DNAcs DNAAs DNAts OxyTs OxyTs OxyAs OxyG
882	213242	213261	CTGTGAACACTAT GCCATTTAG	ASO- 0999	OxyMCs DNAts DNAGs DNAts DNAGs DNAAs DNAcs DNAts DNAAs DNAts DNAGs DNAcs DNAAs DNAAs DNAts DNAts DNAts OxyAs OxyG
883	213243	213259	GTGAACATATGC CATTTA	ASO- 1000	OxyGs OxyTs DNAGs DNAAs DNAcs DNAts DNAAs DNAts DNAGs DNAcs DNAGs DNAAs OxyTs OxyTs OxyTs OxyA
884	213243	213260	TGTGAACACTATG CCATTTA	ASO- 1001	OxyTs OxyGs OxyTs DNAGs DNAAs DNAcs DNAts DNAAs DNAts DNAGs DNAGs DNAcs DNAAs DNAts DNAts OxyTs OxyA
885	213243	213261	CTGTGAACACTAT GCCATTTA	ASO- 1002	OxyMCs DNAts DNAGs DNAts DNAGs DNAAs DNAcs DNAts DNAAs DNAts DNAGs DNAcs DNAcs DNAAs OxyTs OxyTs OxyTs OxyA
886	213246	213262	CCTGTGAACTA TGCCAT	ASO- 1003	OxyMCs OxyMCs DNAts DNAGs DNAts DNAGs DNAAs DNAcs DNAts DNAAs DNAts DNAGs DNAcs DNAGs OxyAs OxyT
887	213248	213263	CCCTGTGAACT ATGCC	ASO- 1004	OxyMCs DNAGs DNAcs DNAts DNAGs DNAts DNAGs DNAAs DNAcs DNAts DNAAs DNAts DNAGs OxyMCs OxyMC
888	213267	213283	CCATATACTGA CCTTCA	ASO- 1005	OxyMCs OxyMCs OxyAs DNAts DNAAs DNAts DNAAs DNAts DNAts DNAAs DNAGs DNAts DNAts DNAts OxyMCs OxyA
889	213267	213284	TCCATATACTG ACCTTCA	ASO- 1006	OxyTs OxyMCs DNAGs DNAAs DNAts DNAAs DNAts DNAAs DNAts DNAGs DNAAs DNAGs DNAcs DNAts OxyTs OxyMCs OxyA
890	213268	213284	TCCATATACTG ACCTTC	ASO- 1007	OxyTs OxyMCs DNAGs DNAAs DNAts DNAAs DNAts DNAAs DNAts DNAGs DNAAs DNAGs OxyMCs OxyTs OxyTs OxyMC
891	213269	213285	CTCCATATACT GACCTT	ASO- 1008	OxyMCs DNAts DNAGs DNAcs DNAAs DNAts DNAAs DNAts DNAAs DNAts DNAGs DNAAs OxyMCs OxyMCs OxyTs OxyT
892	213269	213286	ACTCCATATAC TGACCTT	ASO- 1009	OxyAs OxyMCs DNAts DNAGs DNAcs DNAAs DNAts DNAAs DNAts DNAGs DNAts DNAGs DNAAs DNAGs OxyMCs OxyTs OxyT
893	213270	213286	ACTCCATATAC TGACCT	ASO- 1010	OxyAs OxyMCs OxyTs OxyMCs DNAGs DNAAs DNAts DNAAs DNAts DNAGs DNAts DNAGs DNAAs DNAGs OxyMCs OxyT
894	213271	213287	GACTCCATATA CTGACC	ASO- 1011	OxyGs OxyAs OxyMCs DNAts DNAGs DNAcs DNAAs DNAts DNAAs DNAts DNAGs DNAts DNAGs DNAAs OxyMCs OxyMC
895	213450	213467	TTTTGCTATGAT GTATAT	ASO- 1012	OxyTs OxyTs OxyTs OxyTs DNAGs DNAGs DNAts DNAAs DNAts DNAts DNAGs DNAts OxyAs OxyTs OxyAs OxyT
896	213587	213605	AGCGGGACATA	ASO-	OxyAs DNAGs DNAGs DNAmcs DNAGs DNAGs DNAAs DNAGs DNAAs DNAts

FIG. 1A (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
			CATCACAG	1013	DNAas DNAcs DNAas DNAts DNAcs DNAas DNacs DNacs OxyAs OxyG
897	213587	213606	CAGGCGGACAT ACATCACAG	ASO-1014	OxyMCs DNAas DNags DNags DNAmcs DNags DNags DNAas DNacs DNacs DNacs OxyAs OxyG
898	213588	213605	AGGCGGACATA CATCACA	ASO-1015	OxyAs OxyGs DNags DNAmcs DNags DNags DNags DNAas DNacs DNacs DNacs DNats
899	213588	213606	CAGGCGGACAT ACATCACA	ASO-1016	OxyMCs DNAas DNags DNags DNAmcs DNags DNags DNags DNAas DNacs DNacs DNacs
900	213589	213605	AGGCGGACATA CATCAC	ASO-1017	OxyAs OxyGs DNags DNAmcs DNags DNags DNags DNags DNAas DNacs DNacs DNats
901	213589	213606	CAGGCGGACAT ACATCAC	ASO-1018	OxyMCs DNAas DNags DNags DNAmcs DNags DNags DNags DNags DNAas DNacs DNacs
902	213589	213607	ACAGGCGGAC ATACATCAC	ASO-1019	OxyAs DNacs DNAas DNags DNags DNAmcs DNags DNags DNags DNags DNacs
903	213589	213608	TACAGGCGGAC ATACATCAC	ASO-1020	OxyTs OxyAs DNacs DNAas DNags DNags DNags DNags DNags DNags DNags
904	213590	213605	AGGCGGACATA CATCA	ASO-1021	OxyAs OxyGs DNags DNAmcs DNags DNags DNags DNags DNags DNags DNats
905	213590	213606	CAGGCGGACAT ACATCA	ASO-1022	OxyMCs OxyAs DNags DNags DNAmcs DNags DNags DNags DNags DNacs DNacs
906	213590	213607	ACAGGCGGAC ATACATCA	ASO-1023	OxyAs OxyMCs DNAas DNags DNags DNAmcs DNags DNags DNags DNags DNacs
907	213590	213608	TACAGGCGGAC ATACATCA	ASO-1024	OxyTs DNAas DNacs DNAas DNags DNags DNags DNags DNags DNags DNags
908	213591	213606	CAGGCGGACAT ACATC	ASO-1025	OxyMCs OxyAs DNags DNags DNAmcs DNags DNags DNags DNags DNacs DNacs
909	213591	213607	ACAGGCGGAC ATACATC	ASO-1026	OxyAs OxyMCs DNAas DNags DNags DNAmcs DNags DNags DNags DNags DNacs
910	213591	213608	TACAGGCGGAC ATACATC	ASO-1027	OxyTs DNAas DNacs DNAas DNags DNags DNags DNags DNags DNags DNags
911	213591	213609	CTACAGGCGGA CATACATC	ASO-1028	OxyMCs DNats DNAas DNacs DNAas DNags DNags DNags DNags DNags DNags
912	213592	213608	TACAGGCGGAC ATACAT	ASO-1029	OxyTs OxyAs OxyMCs DNAas DNags DNags DNags DNags DNags DNags DNags
913	213592	213609	CTACAGGCGGA CATACAT	ASO-1030	OxyMCs DNats DNAas DNacs DNAas DNags DNags DNags DNags DNags DNags
914	213592	213610	TCTACAGGCGG ACATACAT	ASO-1031	OxyTs DNacs DNats DNAas DNacs DNAas DNags DNags DNags DNags DNags
915	213593	213608	TACAGGCGGAC	ASO-	OxyTs OxyAs OxyMCs OxyAs DNags DNags DNags DNags DNags DNags DNags

FIG. 1A (cont.)

[illegible]

FIG. 1A (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
			AAATTCCTC	1051	DNAas DNAas DNAas DNAts DNAts DNAts OxyTs OxyTs OxyMC
935	213930	213947	TCCTGGTTATA AATTCCT	ASO-1052	OxyTs OxyMCs OxyMCs DNAts DNAts DNAts DNAts DNAts DNAts
936	213930	213948	TTCTGCTTAT AAATTCCT	ASO-1053	DNAas DNAas DNAas DNAts DNAts DNAts DNAts DNAts DNAts
937	213930	213949	TTTCTGCTTA TAAATTCCT	ASO-1054	OxyTs OxyTs OxyTs OxyMCs DNAts DNAts DNAts DNAts DNAts DNAts
938	213931	213948	TTCTGCTTAT AAATTCCT	ASO-1055	DNAas DNAas DNAas DNAts DNAts DNAts DNAts DNAts DNAts
939	213931	213949	TTTCTGCTTA TAAATTCCT	ASO-1056	OxyTs OxyTs OxyTs OxyMCs DNAts DNAts DNAts DNAts DNAts DNAts
940	213931	213950	ATTTCTGCTT ATAAATTCCT	ASO-1057	OxyAs OxyTs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts
941	213932	213948	TTCTGCTTAT AAATTC	ASO-1058	DNAas DNAas DNAas DNAts DNAts DNAts DNAts DNAts DNAts
942	213932	213949	TTTCTGCTTA TAAATTC	ASO-1059	OxyTs OxyTs OxyTs OxyMCs DNAts DNAts DNAts DNAts DNAts DNAts
943	213932	213950	ATTTCTGCTT ATAAATTC	ASO-1060	OxyAs OxyTs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts
944	213932	213951	CATTCTGCTT TATAAATTC	ASO-1061	OxyMCs OxyAs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts
945	213933	213951	CATTCTGCTT TATAAATTC	ASO-1062	OxyMCs OxyAs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts
946	213933	213952	TCATTTCTGCTG TTATAAATTC	ASO-1063	OxyTs OxyMCs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts
947	213934	213951	CATTCTGCTT TATAAATTC	ASO-1064	OxyMCs OxyAs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts
948	213934	213952	TCATTTCTGCTG TTATAAATTC	ASO-1065	OxyTs OxyMCs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts
949	214149	214165	CACTGCTGTA TACCTCCT	ASO-1066	OxyMCs DNAas DNAts DNAts DNAts DNAts DNAts DNAts
950	214152	214169	CACTCACTGTC TGTATAC	ASO-1067	OxyMCs OxyAs OxyMCs DNAts DNAts DNAts DNAts DNAts DNAts
951	214152	214170	ACACTCACTGT CTGTATAC	ASO-1068	OxyAs OxyMCs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts
952	214153	214169	CACTCACTGTC TGTATA	ASO-1069	OxyMCs OxyAs OxyMCs DNAts DNAts DNAts DNAts DNAts DNAts
953	214159	214175	AGCTTACACTC	ASO-	OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts

FIG. 1A (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
			ACTGTC	1070	DNAAs DNAcs DNAts DNAGs OxyTs OxyMC
954	214160	214176	AAGCTTACACT CACTGT	ASO-1071	OxyAs OxyGs DNAcs DNAts DNAGs DNAAs DNAcs DNAts DNAGs
955	214163	214178	CCAAGCTTACA CTCAC	ASO-1072	OxyMCs OxyMCs OxyAs OxyAs DNAGs DNAcs DNAts DNAGs DNAAs DNAcs
956	214279	214295	GCATTACTCAC CTTCAG	ASO-1073	OxyGs OxyMCs DNAAs DNAts DNAts DNAGs DNAcs DNAts DNAGs DNAAs
957	214433	214451	TAGAGATGAAA TAAGAGAG	ASO-1074	OxyTs OxyAs OxyGs OxyAs DNAGs DNAAs DNAts DNAGs DNAAs DNAAs
958	214766	214784	TAATGTTAAGG GAAAGAGA	ASO-1075	OxyTs OxyAs OxyAs OxyTs DNAGs DNAts DNAts DNAGs DNAAs DNAGs DNAGs
959	214967	214984	TAAGGGTATCA GTAGGCA	ASO-1076	OxyTs OxyAs OxyAs OxyGs DNAGs DNAts DNAts DNAGs DNAAs DNAts DNAGs
960	214969	214984	TAAGGGTATCA GTAGG	ASO-1077	OxyTs OxyAs OxyAs OxyGs DNAGs DNAts DNAts DNAGs DNAAs DNAts DNAGs
961	215349	215367	GACTGGAAATA TGGATTTA	ASO-1078	OxyGs OxyAs OxyMCs OxyTs DNAGs DNAGs DNAAs DNAAs DNAts DNAts
962	215705	215724	ATATATGTTCA CTTAAAGG	ASO-1079	OxyAs OxyTs OxyAs OxyTs DNAGs DNAts DNAts DNAGs DNAts DNAts DNAts
963	215706	215724	ATATATGTTCA CTTAAAG	ASO-1080	OxyAs OxyTs OxyAs OxyTs DNAGs DNAts DNAts DNAGs DNAts DNAts DNAts
964	216351	216370	ATCATGGGTAT AAAAGGCAC	ASO-1081	OxyAs DNAts DNAts DNAts DNAts DNAGs DNAGs DNAts DNAts DNAts DNAts
965	216411	216429	TTTAACCTTTACT ATATTGG	ASO-1082	OxyTs OxyTs OxyTs OxyAs DNAGs DNAts DNAts DNAts DNAts DNAts DNAts
966	216786	216802	ATGTACTTTTG GTTGAC	ASO-1083	OxyAs OxyTs OxyGs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
967	216889	216906	ATAGTGATCTT TATTCTG	ASO-1084	OxyAs OxyTs OxyAs OxyMCs DNAts DNAts DNAts DNAts DNAts DNAts DNAts
968	217509	217528	TTACAGGCTTT TAATTCATC	ASO-1085	OxyTs OxyTs OxyAs OxyMCs DNAts DNAts DNAts DNAts DNAts DNAts DNAts
969	217513	217530	CTTTACAGGCT TTTAATT	ASO-1086	OxyMCs OxyTs OxyTs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts
970	217809	217828	ATTTATTTCTC TTTGCTC	ASO-1087	OxyAs OxyTs OxyTs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts
971	218208	218225	TTCACAAAAT CCAACAC	ASO-1088	OxyTs OxyTs OxyMCs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts
972	218211	218228	CAATTACAAA	ASO-1089	OxyMCs OxyAs OxyAs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts

FIG. 1A (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
			TATCCAA	1088	DNAas DNAts DNAas DNAts OxyMCs OxyMCs OxyAs OxyA
973	218876	218893	CCAGATTGTTG TTCATGA	ASO-1089	OxyMCs DNAs DNAs DNAs DNAs DNAts DNAts DNAts DNAts DNAts
974	218981	218997	TTCTGAATAGG GGCTAA	ASO-1090	OxyTs OxyTs OxyMCs DNAts DNAts DNAs DNAs DNAts DNAts DNAts
975	219839	219857	TATTCATTCTT GTTTATT	ASO-1091	DNAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
976	219917	219936	TATGTGCTATA AGTTTGCAA	ASO-1092	OxyTs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
977	219976	219992	TGTGTGGAATT AATGCC	ASO-1093	OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
978	220130	220147	TCTGTCACTTA TCTTTTG	ASO-1094	OxyTs OxyMCs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
979	220732	220751	TTGGGAGATAA AATAACTCA	ASO-1095	OxyTs OxyTs OxyGs OxyGs DNAts DNAts DNAts DNAts DNAts DNAts
980	220735	220752	CTTGGGAGATA AAATAAC	ASO-1096	OxyMCs OxyTs OxyTs OxyGs DNAts DNAts DNAts DNAts DNAts DNAts
981	220916	220933	CAACAACCAT TATAGCA	ASO-1097	OxyMCs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
982	220916	220934	TCAACAACCAT TTATAGCA	ASO-1098	OxyTs OxyMCs DNAs DNAs DNAts DNAts DNAts DNAts DNAts DNAts
983	220917	220934	TCAACAACCAT TTATAGC	ASO-1099	OxyTs OxyMCs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts
984	220917	220935	GTCAACAACCA TTTATAGC	ASO-1100	OxyGs OxyTs OxyMCs DNAs DNAs DNAts DNAts DNAts DNAts DNAts
985	220917	220936	TGTCAACAAC ATTTATAGC	ASO-1101	OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
986	220918	220935	GTCAACAACCA TTTATAG	ASO-1102	OxyGs OxyTs OxyMCs DNAs DNAs DNAts DNAts DNAts DNAts DNAts
987	220918	220936	TGTCAACAAC ATTTATAG	ASO-1103	OxyTs OxyGs OxyTs OxyMCs DNAs DNAs DNAts DNAts DNAts DNAts
988	220918	220937	TGTCAACAAC CATTTATAG	ASO-1104	OxyGs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
989	220919	220936	TGTCAACAAC ATTTATA	ASO-1105	OxyTs OxyGs OxyTs OxyMCs DNAs DNAs DNAts DNAts DNAts DNAts
990	220919	220937	TGTCAACAAC CATTTATA	ASO-1106	OxyGs OxyTs OxyGs DNAts DNAts DNAts DNAts DNAts DNAts DNAts
991	221023	221041	AGGTTGGTTTT	ASO-1107	OxyAs OxyGs OxyGs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts

FIG. 1A (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
			TAAATAGA	1106	DNAts DNAAAs DNAAAs DNAts DNAAAs OxyGs OxyA
992	221024	221041	AGGTTGGTTTT TAAATAG	ASO-1107	OxyAs OxyGs OxyGs DNAts DNAts DNAGs DNAGs DNAts DNAts DNAts DNAts
993	221141	221158	TTTAAATATTTGT AACTTG	ASO-1108	OxyTs OxyTs OxyAs DNAAAs DNAts DNAts DNAAAs DNAts DNAts DNAts DNAts
994	221558	221575	ATTTGCTACTAT TCCACT	ASO-1109	OxyAs DNAts DNAts DNAts DNAGs DNAGs DNAts DNAts DNAAAs DNAGs DNAts DNAAAs
995	221765	221784	CATTATTCTTAA TTTTCTCTG	ASO-1110	OxyMCs OxyAs OxyTs OxyTs DNAts DNAts DNAAAs DNAts DNAts DNAGs DNAts DNAAAs
997	221991	222007	TTAGGATGATG AGTTTA	ASO-1113	OxyTs OxyTs OxyAs OxyGs DNAGs DNAAAs DNAts DNAts DNAGs DNAAAs DNAts DNAGs
998	222173	222189	AAGCAGGGTT ATTTGA	ASO-1114	OxyAs OxyAs OxyGs OxyGs DNAGs DNAGs DNAAAs DNAGs DNAGs DNAts DNAts
999	222645	222664	CTAATTCCTTCT TCACCTTC	ASO-1115	OxyMCs DNAts DNAAAs DNAAAs DNAts DNAts DNAts DNAGs DNAts DNAts DNAts DNAts
1000	222658	222674	ATGGTTGATTC TAATTC	ASO-1116	OxyAs OxyTs OxyGs OxyGs DNAts DNAts DNAts DNAGs DNAAAs DNAts DNAts DNAts
1001	223316	223335	TCATTTTGTTTA TATGTTAA	ASO-1117	OxyTs OxyMCs OxyAs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1002	223476	223493	GATAAAATATATT GGGTTA	ASO-1118	OxyGs OxyAs OxyTs OxyAs DNAAAs DNAAAs DNAts DNAts DNAAAs DNAts DNAAAs DNAts
1003	223778	223794	TGATTCAGAGC ATTACT	ASO-1119	OxyTs OxyGs OxyAs DNAts DNAts DNAGs DNAGs DNAAAs DNAGs DNAAAs DNAGs DNAts
1004	223903	223920	GTCTTTAAGAA TCTGTTT	ASO-1120	OxyGs OxyTs OxyMCs OxyTs DNAts DNAts DNAts DNAAAs DNAAAs DNAGs DNAAAs
1005	223903	223921	TGTCTTTAAGA ATCTGTTT	ASO-1121	OxyTs OxyGs OxyTs OxyMCs DNAts DNAts DNAts DNAts DNAts DNAAAs DNAGs DNAts
1006	223903	223922	CTGCTTTTAAG AATCTGTTT	ASO-1122	OxyMCs OxyTs OxyGs DNAts DNAGs DNAts DNAts DNAts DNAts DNAts DNAAAs DNAAAs
1007	223904	223921	TGTCTTTAAGA ATCTGTT	ASO-1123	OxyTs OxyGs OxyTs DNAGs DNAts DNAts DNAts DNAts DNAts DNAAAs DNAGs DNAAAs
1008	223904	223922	CTGCTTTTAAG AATCTGTT	ASO-1124	OxyMCs OxyTs OxyGs DNAts DNAGs DNAts DNAts DNAts DNAts DNAts DNAAAs DNAAAs
1009	223904	223923	GCTGCTTTTAA GAATCTGTT	ASO-1125	OxyGs DNAGs DNAts DNAGs DNAts DNAGs DNAts DNAGs DNAts DNAts DNAts DNAAAs DNAAAs
1010	223905	223922	CTGCTTTTAAG AATCTGT	ASO-1126	OxyMCs OxyTs DNAGs DNAts DNAGs DNAts DNAts DNAts DNAts DNAts DNAts DNAAAs DNAAAs
1011	223905	223923	GCTGCTTTTAA	ASO-	OxyGs OxyMCs DNAts DNAGs DNAts DNAGs DNAts DNAGs DNAts DNAts DNAts DNAts DNAAAs

FIG. 1A (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
			GAATCTGT	1127	DNAas DNAGs DNAAs DNAas DNAts DNACs DNAts OxyGs OxyT
1012	223906	223923	GCTGTCCTTTAA GAATCTG	ASO- 1128	OxyGs OxyMCs DNAts DNAGs DNAts DNACs DNAts DNAts DNAts DNAas DNAas DNAGs DNAAs DNAas DNAts DNACs OxyMCs OxyTs OxyG
1013	223968	223987	TCAATGTTTTCC AAACAATT	ASO- 1129	OxyTs OxyMCs OxyAs OxyAs DNAts DNAGs DNAts DNAts DNAts DNAts DNAts DNAas DNAas DNAGs DNACs DNAas DNAts OxyAs OxyTs OxyTs OxyT
1014	223969	223987	TCAATGTTTTCC AACCAATT	ASO- 1130	OxyTs OxyMCs OxyAs OxyAs DNAts DNAGs DNAts DNAts DNAts DNAts DNAts DNAas DNAas DNAGs DNACs OxyAs OxyAs OxyTs OxyT
1015	223970	223987	TCAATGTTTTCC AACAAT	ASO- 1131	OxyTs OxyMCs OxyAs OxyAs DNAts DNAGs DNAts DNAts DNAts DNAts DNAts DNAas DNAas DNAGs OxyMCs OxyAs OxyAs OxyT
1016	224012	224030	TTAACCTCAAG AGTTTGGA	ASO- 0073	OxyTs DNAts DNAas DNAas DNACs DNAts DNAts DNAts DNAts DNAts DNAts DNAas DNAGs DNAts DNAts OxyTs OxyGs OxyGs OxyA
1017	224015	224031	GTTAACTTCAA GAGTTT	ASO- 1132	OxyGs OxyTs OxyTs OxyAs DNAts DNAGs DNAts DNAts DNAts DNAts DNAts DNAGs DNAas OxyGs OxyTs OxyTs OxyT
1018	224056	224073	CTACAGACATT TGCCAAA	ASO- 1133	OxyMCs OxyTs DNAts DNAts DNAts DNAts DNAGs DNAts DNAts DNAts DNAts DNAts DNAts DNAGs DNAGs OxyMCs OxyAs OxyAs OxyA
1019	224397	224413	ATTTACAGGA TTAGGG	ASO- 1134	OxyAs OxyTs OxyTs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts OxyAs OxyGs OxyGs OxyG
1020	224468	224485	GCTTTATTTAG AAAGAAA	ASO- 1135	OxyGs OxyMCs OxyTs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAas DNAas DNAGs OxyGs OxyAs OxyAs OxyA
1021	224468	224487	AGGCTTTATTT AGAAAAGAA	ASO- 1136	OxyAs OxyGs OxyGs OxyMCs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAas DNAGs DNAas DNAts DNAts DNAGs DNAts OxyAs OxyAs OxyA
1022	224469	224487	AGGCTTTATTT AGAAAAGAA	ASO- 1137	OxyAs OxyGs OxyGs OxyMCs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAas DNAGs DNAas DNAts DNAts DNAGs OxyGs OxyAs OxyA
1023	224469	224488	CAGGCTTTATT TAGAAAAGAA	ASO- 1138	OxyMCs OxyAs OxyGs DNAGs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAas DNAGs DNAas DNAts DNAts OxyAs OxyGs OxyAs OxyA
1024	224470	224487	AGGCTTTATTT AGAAAAGA	ASO- 1139	OxyAs OxyGs OxyGs OxyMCs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAas DNAGs DNAas DNAts DNAts DNAGs OxyGs OxyA
1025	224470	224488	CAGGCTTTATT TAGAAAAGA	ASO- 1140	OxyMCs OxyAs OxyGs DNAGs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAas DNAGs DNAas DNAts DNAts OxyAs OxyGs OxyA
1026	224470	224489	TCAGGCTTTAT TTAGAAAAGA	ASO- 1141	OxyTs OxyMCs OxyAs DNAGs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAGs DNAas DNAts DNAts DNAts OxyAs OxyGs OxyA
1027	224471	224489	TCAGGCTTTAT TTAGAAAAG	ASO- 1142	OxyTs OxyMCs OxyAs OxyGs DNAGs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAGs DNAas DNAts DNAts OxyAs OxyAs OxyG
1028	224471	224490	CTCAGGCTTTA TTTAGAAAAG	ASO- 1143	OxyMCs OxyTs DNAts DNAts DNAts DNAGs DNAts DNAts DNAts DNAts DNAts DNAas DNAts DNAts DNAts DNAts DNAGs DNAts OxyAs OxyAs OxyG
1029	224472	224490	CTCAGGCTTTA TTTAGAAA	ASO- 1144	OxyMCs OxyTs OxyMCs OxyAs DNAGs DNAts DNAts DNAts DNAts DNAts DNAts DNAas DNAts DNAts DNAts DNAts DNAGs DNAts OxyAs OxyAs OxyA
1030	224472	224491	TCTCAGGCTTT	ASO-	OxyTs OxyMCs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts

[illegible]

FIG. 1A (cont.)

[illegible]

FIG. 1A (cont.)

[illegible]

[illegible]

FIG. 1A (cont.)

[illegible]

FIG. 1A (cont.)

[illegible]

FIG. 1A (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
			GACACCTG	1255	DNAGs DNAAAs DNACs DNAAAs OxyMCs OxyTs OxyG
1145	244268	244287	AATATAGAGAA TGACACCTG	ASO- 1256	OxyAs OxyTs DNAAAs DNATs DNAAAs DNAGs DNAAAs DNAAAs DNAAAs DNATs DNAGs DNAAAs DNACs DNAAAs OxyMCs OxyTs OxyG
1146	244269	244286	ATATAGAGAAT GACACCT	ASO- 1257	OxyAs OxyTs DNAAAs DNATs DNAAAs DNAGs DNAAAs DNAAAs DNATs DNAGs DNAAAs DNACs OxyMCs OxyT
1147	244269	244287	AATATAGAGAA TGACACCT	ASO- 1258	OxyAs OxyTs OxyAs DNATs DNAAAs DNAGs DNAAAs DNAGs DNAAAs DNATs DNAGs DNAAAs DNACs OxyAs OxyMCs OxyT
1148	244269	244288	GAATATAGAGA ATGACACCT	ASO- 1259	OxyGs OxyAs OxyAs DNATs DNAAAs DNATs DNAAAs DNAGs DNAAAs DNAGs DNAAAs DNATs DNAGs DNAAAs DNACs DNAAAs OxyMCs OxyT
1149	244270	244286	ATATAGAGAAT GACACC	ASO- 1260	OxyAs OxyTs OxyAs OxyTs DNAAAs DNAGs DNAAAs DNAGs DNAAAs DNATs DNAGs DNAAAs OxyMCs OxyMC
1150	244270	244287	AATATAGAGAA TGACACC	ASO- 1261	OxyAs OxyTs OxyAs DNATs DNAAAs DNAGs DNAAAs DNAGs DNAAAs DNATs DNAGs DNAAAs OxyMCs OxyAs OxyMCs
1151	244270	244288	GAATATAGAGA ATGACACC	ASO- 1262	OxyGs OxyAs OxyAs OxyTs DNAAAs DNATs DNAAAs DNAGs DNAAAs DNAGs DNAAAs DNATs DNAGs DNAAAs OxyMCs OxyAs OxyMCs
1152	244270	244289	AGAAATATAGAG AATGACACC	ASO- 1263	OxyAs OxyGs DNAAAs DNAAAs DNATs DNAAAs DNATs DNAAAs DNAGs DNAAAs DNAGs DNAAAs DNATs DNAGs DNAAAs DNACs DNAAAs OxyMCs OxyT
1153	244271	244288	GAATATAGAGA ATGACAC	ASO- 1264	OxyGs OxyAs OxyAs OxyTs DNAAAs DNATs DNAAAs DNAGs DNAAAs DNAGs DNAAAs DNATs DNAGs DNAAAs OxyMCs OxyAs OxyMC
1154	244271	244290	TAGAATATAGA GAATGACAC	ASO- 1265	OxyTs OxyAs OxyGs OxyAs DNAAAs DNATs DNAAAs DNATs DNAAAs DNAGs DNAAAs DNAGs DNAAAs DNATs DNAGs DNAAAs DNACs DNAAAs OxyAs OxyMCs
1155	244274	244291	GTAGAATATAG AGAAATGA	ASO- 1266	OxyGs OxyTs OxyAs OxyGs DNAAAs DNAAAs DNATs DNAAAs DNATs DNAAAs DNAGs DNAAAs DNAGs DNAAAs OxyTs OxyGs OxyA
1156	244351	244367	ACATCATAAAGC TCCAGC	ASO- 1267	OxyAs OxyMCs OxyAs DNATs DNACs DNAAAs DNATs DNAAAs DNAAAs DNAGs DNAAAs DNATs DNAGs DNAAAs DNACs DNAAAs OxyGs OxyMC
1157	244351	244368	TACATCATAAAG CTCCAGC	ASO- 1268	OxyTs DNAAAs DNACs DNAAAs DNATs DNACs DNAAAs DNATs DNAAAs DNAAAs DNAGs DNAAAs DNATs DNAGs DNAAAs OxyAs OxyGs OxyMC
1158	244351	244369	ATACATCATAA GCTCCAGC	ASO- 1269	OxyAs DNATs DNAAAs DNACs DNAAAs DNATs DNACs DNAAAs DNATs DNAAAs DNAGs DNAAAs DNAGs DNAAAs DNACs OxyAs OxyGs OxyMC
1159	244352	244369	ATACATCATAA GCTCCAG	ASO- 1270	OxyAs OxyTs OxyAs DNACs DNAAAs DNATs DNACs DNAAAs DNATs DNAAAs DNAGs DNAAAs DNAGs DNAAAs DNATs DNAGs DNAAAs OxyAs OxyG
1160	244352	244370	CATACATCATAA AGCTCCAG	ASO- 1271	OxyMCs OxyAs DNATs DNAAAs DNACs DNAAAs DNATs DNACs DNAAAs DNATs DNAAAs DNATs DNAGs DNAAAs DNACs DNAAAs OxyAs OxyG
1161	244352	244371	ACATACATCAT AAGCTCCAG	ASO- 1272	OxyAs OxyMCs OxyAs DNATs DNAAAs DNATs DNAAAs DNATs DNAAAs DNATs DNAGs DNAAAs DNAGs DNAAAs DNACs DNAAAs OxyAs OxyG
1162	244353	244369	ATACATCATAA GCTCCA	ASO- 1273	OxyAs OxyTs DNAAAs DNACs DNAAAs DNATs DNACs DNAAAs DNATs DNAAAs DNAGs DNAAAs DNAGs DNAAAs OxyTs OxyMCs OxyA
1163	244353	244370	CATACATCATAA	ASO-	OxyMCs OxyAs DNATs DNAAAs DNACs DNAAAs DNATs DNAAAs DNATs DNAAAs DNATs

FIG. 1A (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
			AGCTCCA	1274	DNAas DNAas DNAGs DNACs DNAts OxyMCs OxyA
1164	244353	244371	ACATACATCAT AAGCTCCA	ASO- 1275	OxyAs OxyMCs OxyAs DNAts DNAas DNACs DNAts DNAas DNACs DNAts
1165	244353	244372	TACATACATCA TAAGCTCCA	ASO- 1276	OxyTs OxyAs DNACs DNAts DNAas DNACs DNAts DNAas DNACs DNAts
1166	244354	244370	CATACATCAT AGCTCC	ASO- 1277	OxyMCs OxyAs DNAts DNAas DNACs DNAts DNACs DNAts DNAas DNAts
1167	244354	244371	ACATACATCAT AAGCTCC	ASO- 1278	OxyAs OxyMCs OxyAs DNAts DNAas DNACs DNAts DNACs DNAts DNAas DNAts
1168	244354	244372	TACATACATCA TAAGCTCC	ASO- 1279	OxyTs OxyAs DNACs DNAts DNAas DNACs DNAts DNACs DNAts DNAas DNAts
1169	244354	244373	TTACATACATC ATAAGCTCC	ASO- 1280	OxyTs DNAts DNAas DNACs DNAts DNAas DNACs DNAts DNACs DNAts DNACs
1170	244355	244371	ACATACATCAT AAGCTC	ASO- 1281	OxyAs OxyMCs OxyAs DNAts DNAas DNACs DNAts DNACs DNAts DNAas DNAts
1171	244355	244372	TACATACATCA TAAGCTC	ASO- 1282	OxyTs OxyAs OxyMCs OxyAs DNAts DNAas DNACs DNAts DNACs DNAts DNAas DNAts
1172	244355	244373	TTACATACATC ATAAGCTC	ASO- 1283	OxyTs OxyTs OxyAs OxyMCs DNAts DNAas DNACs DNAts DNACs DNAts DNACs
1173	244355	244374	ATTACATACAT CATAAGCTC	ASO- 1284	OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1174	244356	244373	TTACATACATC ATAAGCT	ASO- 1285	OxyTs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1175	244356	244374	ATTACATACAT CATAAGCT	ASO- 1286	OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1176	244356	244375	TATTACATACAT CATAAGCT	ASO- 1287	OxyTs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1177	244357	244373	TTACATACATC ATAAGC	ASO- 1288	OxyTs OxyTs OxyAs OxyMCs DNAts DNAts DNAts DNAts DNAts DNAts
1178	244357	244374	ATTACATACAT CATAAGC	ASO- 1289	OxyAs OxyTs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1179	244357	244375	TATTACATACAT CATAAGC	ASO- 1290	OxyTs OxyAs OxyTs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts
1180	244357	244376	TTTACATACATA TCATAAGC	ASO- 1291	OxyTs OxyTs OxyAs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts
1181	244358	244375	TATTACATACAT CATAAG	ASO- 1292	OxyTs OxyAs OxyTs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts
1182	244358	244376	TTTACATACATA	ASO-	OxyTs OxyTs OxyAs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts

[illegible]

FIG. 1A (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
			CAGATCCA	1330	DNAas DNAcs DNAas DNags DNAas DNats DNacs OxyMCs OxyA
1221	246852	246868	TTTACTTACACA GATCC	ASO- 1331	OxyTs OxyTs OxyTs DNAas DNacs DNats DNats DNats DNacs DNacs DNacs
1222	246852	246869	TTTTACTTACAC AGATCC	ASO- 1332	DNAas DNags OxyAs OxyTs OxyMCs OxyMC
1223	246852	246870	GTTTTACTTACA CAGATCC	ASO- 1333	OxyTs OxyTs DNats DNats DNats DNats DNats DNats DNats DNats DNacs
1224	246852	246871	AGTTTTACTTAC ACAGATCC	ASO- 1334	DNAas DNacs DNats DNats DNats DNats DNats DNats DNats DNats DNacs
1225	246853	246870	GTTTTACTTACA CAGATC	ASO- 1335	OxyGs OxyTs OxyTs DNats DNats DNats DNats DNats DNats DNats DNats DNacs
1226	246853	246871	AGTTTTACTTAC ACAGATC	ASO- 1336	DNAas DNacs DNats DNats DNats DNats DNats DNats DNats DNats DNacs
1227	246853	246872	AAGTTTTACTTA CACAGATC	ASO- 1337	OxyAs OxyAs OxyGs OxyTs DNats DNats DNats DNats DNats DNats DNats DNats DNacs
1228	246854	246871	AGTTTTACTTAC ACAGAT	ASO- 1338	DNAas DNacs DNats DNats DNats DNats DNats DNats DNats DNats DNacs
1229	246854	246872	AAGTTTTACTTA CACAGAT	ASO- 1339	OxyAs OxyAs OxyGs OxyTs DNats DNats DNats DNats DNats DNats DNats DNats DNacs
1230	246854	246873	GAAGTTTACT TACACAGAT	ASO- 1340	OxyGs OxyAs OxyAs DNags DNats DNats DNats DNats DNats DNats DNats DNats DNacs
1231	246855	246874	AGAAGTTTAC TTACACAGA	ASO- 1341	DNats DNats DNats DNats DNats DNats DNats DNats DNats DNats DNacs
1232	246856	246874	AGAAGTTTAC TTACACAG	ASO- 1342	OxyAs OxyGs OxyAs DNags DNats DNats DNats DNats DNats DNats DNats DNats DNacs
1233	246856	246875	GAGAAGTTTAA CTTACACAG	ASO- 1343	OxyGs OxyAs DNags DNats DNats DNats DNats DNats DNats DNats DNats DNacs
1234	246857	246875	GAGAAGTTTAA CTTACACA	ASO- 1344	DNats DNats DNats DNats DNats DNats DNats DNats DNats DNats DNacs
1235	246858	246875	GAGAAGTTTAA CTTACAC	ASO- 1345	OxyGs OxyAs OxyGs OxyAs DNags DNats DNats DNats DNats DNats DNats DNats DNats DNacs
1236	247171	247188	AAATCTTTCTT CTGGGA	ASO- 1346	OxyAs OxyAs OxyAs DNats DNats DNats DNats DNats DNats DNats DNats DNacs
1237	247399	247415	GCCTTTCATTT ACTTAG	ASO- 1347	DNats DNats DNats DNats DNats DNats DNats DNats DNats DNats DNacs
1238	247440	247459	AATTATCTTTAT TTTAAATGT	ASO- 1348	OxyAs OxyAs OxyTs DNats DNats DNats DNats DNats DNats DNats DNats DNacs
1239	247882	247899	TTCTAAGTATTC	ASO-	OxyTs OxyTs OxyMCs OxyTs DNats DNats DNats DNats DNats DNats DNats DNats DNacs

FIG. 1A (cont.)

[illegible]

FIG. 1A (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
			GCAGTCTAC	1368	DNAGs DNACs DNAAs DNAGs DNAts DNACs OxyTs OxyAs OxyMC
1259	248058	248076	AATTTCTTCAA GCAGTCTA	ASO-1369	OxyAs OxyAs OxyTs DNAts DNAts DNACs DNAts DNAts DNACs DNAAs DNACs DNAGs DNACs DNAGs DNAts DNACs OxyTs OxyA
1260	248060	248077	AAATTTCTTCAA GCAGTCTC	ASO-1370	OxyAs OxyAs DNAAs DNAts DNAts DNACs DNAts DNAts DNACs DNAAs DNAGs DNACs OxyAs OxyGs OxyTs OxyMC
1261	248060	248078	TAAATTTCTTCA AGCAGTCTC	ASO-1371	OxyTs DNAGs DNAGs DNAGs DNAts DNAts DNACs DNAts DNAts DNACs DNAGs DNAGs DNAGs DNACs OxyAs OxyGs OxyTs OxyMC
1262	248060	248079	TTAAATTTCTTC AAGCAGTCTC	ASO-1372	OxyTs DNAts DNAGs DNAGs DNAGs DNAts DNAts DNACs DNAts DNAts DNACs DNAGs DNAGs DNAGs DNACs OxyAs OxyGs OxyTs OxyMC
1263	248061	248078	TAAATTTCTTCA AGCAGTCTC	ASO-1373	OxyTs OxyAs OxyAs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNACs DNAts DNAts DNACs DNAGs DNAGs DNAGs OxyAs OxyGs OxyT
1264	248061	248079	TTAAATTTCTTC AAGCAGTCTC	ASO-1374	OxyTs DNAts DNAGs DNAGs DNAGs DNAts DNAts DNACs DNAts DNAts DNACs DNAGs DNAGs DNAGs DNACs OxyAs OxyGs OxyT
1265	248061	248080	ATTAAATTTCTT CAAGCAGTCTC	ASO-1375	OxyAs OxyTs DNAts DNAGs DNAGs DNAGs DNAts DNAts DNACs DNAts DNAts DNACs DNAGs DNAGs DNAGs DNACs OxyAs OxyGs OxyT
1266	248062	248079	TTAAATTTCTTC AAGCAGTCTC	ASO-1376	OxyTs OxyTs OxyAs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNACs DNAts DNAts DNACs DNAGs DNAGs DNAGs OxyAs OxyG
1267	248062	248080	ATTAAATTTCTT CAAGCAGTCTC	ASO-1377	OxyAs OxyTs DNAts DNAGs DNAGs DNAGs DNAts DNAts DNACs DNAts DNAts DNACs DNAGs DNAGs DNAGs DNACs OxyAs OxyG
1268	248062	248081	CATTAAATTTCTT TCAAGCAGTCTC	ASO-1378	OxyMCs OxyAs DNAts DNAts DNAts DNAGs DNAGs DNAts DNAts DNAts DNAts DNACs DNAts DNAts DNACs DNAGs DNAGs DNAGs DNACs OxyAs OxyG
1269	248063	248080	ATTAAATTTCTT CAAGCAGTCTC	ASO-1379	OxyAs OxyTs DNAts DNAGs DNAGs DNAGs DNAts DNAts DNACs DNAts DNAts DNACs DNAGs DNAGs DNAGs DNACs OxyAs OxyG
1270	248063	248081	CATTAAATTTCTT TCAAGCAGTCTC	ASO-1380	OxyMCs OxyAs DNAts DNAts DNAts DNAGs DNAGs DNAts DNAts DNAts DNAts DNACs DNAts DNAts DNACs DNAGs DNAGs DNAGs DNACs OxyAs OxyG
1271	248063	248082	GCATTAAATTTT CTTCAAGCAGTCTC	ASO-1381	OxyGs OxyMCs OxyAs DNAts DNAts DNAts DNAGs DNAGs DNAts DNAts DNAts DNAts DNACs DNAts DNAts DNACs DNAGs DNAGs DNAGs DNACs OxyA
1272	248064	248081	CATTAAATTTCTT TCAAGCAGTCTC	ASO-1382	OxyMCs OxyAs OxyTs DNAts DNAts DNAts DNAGs DNAGs DNAts DNAts DNAts DNAts DNACs DNAts DNAts DNACs DNAGs DNAGs DNAGs DNACs OxyMC
1273	248064	248082	GCATTAAATTTT CTTCAAGCAGTCTC	ASO-1383	OxyGs OxyMCs DNAGs DNAts DNAts DNAts DNAGs DNAGs DNAts DNAts DNAts DNAts DNACs DNAts DNAts DNACs DNAGs DNAGs DNAGs DNACs OxyMC
1274	248064	248083	AGCATTAAATTTT CTTCAAGCAGTCTC	ASO-1384	OxyAs OxyGs DNAGs DNAts DNAts DNAts DNAGs DNAGs DNAts DNAts DNAts DNAts DNACs DNAts DNAts DNACs DNAGs DNAGs DNAGs DNACs OxyMC
1275	248065	248082	GCATTAAATTTT CTTCAAGCAGTCTC	ASO-1385	OxyGs OxyMCs OxyAs OxyTs DNAts DNAts DNAts DNAGs DNAGs DNAts DNAts DNAts DNAts DNACs DNAts DNAts DNACs DNAGs DNAGs DNAGs DNACs OxyG
1276	248065	248083	AGCATTAAATTTT CTTCAAGCAGTCTC	ASO-1386	OxyAs OxyGs OxyMCs DNAGs DNAts DNAts DNAts DNAGs DNAGs DNAts DNAts DNAts DNAts DNACs DNAts DNAts DNACs DNAGs DNAGs DNAGs DNACs OxyAs OxyG
1277	248066	248083	AGCATTAAATTTT	ASO-	OxyAs OxyGs OxyMCs OxyAs DNAts DNAts DNAts DNAGs DNAGs DNAts DNAts DNAts DNAts DNACs DNAts DNAts DNACs DNAGs DNAGs DNAGs DNACs

[illegible]

FIG. 1A (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
			CTTACC	1406	DNats DNacs DNAts OxyTs OxyAs OxyMCs OxyMC
1297	248098	248116	AAATGTAATAATT TCTTACC	ASO- 1407	OxyAs OxyAs OxyAs OxyTs DNags DNAts DNAas DNAas DNAts DNAas DNAts
1298	248181	248198	ACATAATTGAA AGCCTTT	ASO- 1408	OxyAs OxyMCs OxyAs DNats DNAas DNAas DNats DNats DNags DNAas
1299	248540	248559	CCCTGTGAAAA AAATTAGAA	ASO- 1409	OxyMCs OxyMCs OxyMCs DNats DNags DNats DNats DNags DNAas DNAas
1300	248541	248560	ACCCTGTGAAA AAAAATTAGA	ASO- 1410	OxyAs OxyMCs OxyMCs OxyMCs DNats DNags DNats DNats DNags DNAas
1301	248542	248559	CCCTGTGAAAA AAATTAG	ASO- 1411	OxyMCs OxyMCs OxyMCs DNats DNags DNats DNats DNags DNAas DNAas
1302	248542	248560	ACCCTGTGAAA AAAAATTAG	ASO- 1412	OxyAs OxyMCs OxyMCs OxyMCs DNats DNags DNats DNats DNags DNAas
1303	248542	248561	CACCCTGTGAA AAAAATTAG	ASO- 1413	OxyMCs OxyAs OxyMCs OxyMCs DNacs DNats DNats DNats DNats DNags
1304	248543	248560	ACCCTGTGAAA AAAAATTA	ASO- 1414	OxyAs OxyMCs OxyMCs OxyMCs DNats DNags DNats DNats DNags DNAas
1305	248543	248561	CACCCTGTGAA AAAAATTA	ASO- 1415	OxyMCs OxyAs OxyMCs OxyMCs DNacs DNats DNats DNats DNats DNags
1306	248544	248561	CACCCTGTGAA AAAAATT	ASO- 1416	OxyMCs OxyAs OxyMCs OxyMCs DNacs DNats DNats DNats DNats DNags
1307	248545	248562	GCACCCGTGTA AAAAAAT	ASO- 1417	OxyGs OxyMCs OxyAs OxyMCs DNacs DNats DNats DNats DNats DNags
1308	248563	248579	GCATAGTTGTC AAGATG	ASO- 1418	OxyGs OxyMCs DNAas DNats DNAas DNags DNats DNats DNats DNats
1309	248563	248580	AGCATAGTTGT CAAGATG	ASO- 1419	OxyAs OxyGs DNacs DNats DNats DNAas DNags DNats DNats DNats
1310	248563	248581	CAGCATAGTTG TCAAGATG	ASO- 1420	OxyMCs OxyAs OxyGs DNacs DNats DNAas DNats DNags DNats DNats
1311	248564	248580	AGCATAGTTGT CAAGAT	ASO- 1421	OxyAs OxyGs OxyMCs DNAas DNats DNats DNAas DNags DNats DNags
1312	248564	248581	CAGCATAGTTG TCAAGAT	ASO- 1422	OxyMCs OxyAs OxyGs DNacs DNats DNAas DNats DNags DNats DNats
1313	248565	248581	CAGCATAGTTG TCAAGA	ASO- 1423	OxyMCs OxyAs OxyGs DNacs DNats DNAas DNats DNags DNats DNats
1314	249516	249533	CATGGAATCAT TTTGAGG	ASO- 1424	OxyMCs OxyAs DNats DNags DNags DNAas DNats DNats DNacs DNAas
1315	249969	249985	ATTGGTTGAAG	ASO-	OxyAs OxyTs OxyTs OxyGs DNags DNats DNats DNats DNags DNAas

FIG. 1A (cont.)

[illegible]

FIG. 1A (cont.)

[illegible]

FIG. 1A (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
			CTTACC	1462	DNAas DNAcs DNAts DNAts OxyAs OxyMCs OxyMC
1354	252290	252307	GCATCTGTTTA ACTTACC	ASO-1463	OxyGs DNAcs DNAas DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1355	252336	252355	TAACATTTAAA GATTATCCA	ASO-1464	DNAas DNAcs DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1356	252624	252643	TTATTTGGAAG AGCATTTGG	ASO-1465	OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1357	252879	252897	TATTATTTGTT TAGAAAG	ASO-1466	OxyTs OxyAs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1358	253054	253071	GTGTTGATGAA GAATGTA	ASO-1467	OxyGs OxyTs OxyGs DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1359	253080	253097	ATTAAATTAATTC CCAAGA	ASO-1468	OxyAs OxyTs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1360	253537	253553	TATAAGTTGAA TGAAG	ASO-1469	OxyTs OxyAs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1361	253645	253661	TTCTGAATTGA CCAGTC	ASO-1470	OxyTs OxyTs OxyMCs DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1362	253645	253662	TTTCTGAATTG ACCAGTC	ASO-1471	OxyTs OxyTs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1363	253647	253664	CTTTTCTGAATT GACCAG	ASO-1472	OxyMCs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1364	253648	253665	CCTTTCTGAA TTGACCA	ASO-1473	OxyMCs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1365	253649	253666	TCCTTTTCTGA ATTGACC	ASO-1474	OxyTs OxyMCs DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1366	253649	253667	TTCTTTTCTGA ATTGACC	ASO-1475	OxyTs OxyTs OxyMCs DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1367	253673	253689	CATCTGAACAC TCGAAC	ASO-1476	OxyMCs OxyAs OxyTs OxyMCs DNAts DNAts DNAts DNAts DNAts DNAts
1368	253673	253690	TCATCTGAACA CTCGAAC	ASO-1477	OxyTs OxyMCs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1369	253673	253691	ATCATCTGAAC ACTCGAAC	ASO-1478	OxyAs OxyTs OxyMCs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts
1370	253673	253692	CATCATCTGAA CACTCGAAC	ASO-1479	DNAas DNAcs DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1371	253676	253691	ATCATCTGAAC ACTCG	ASO-1480	OxyAs OxyTs OxyMCs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts
1372	253676	253692	CATCATCTGAA	ASO-	OxyMCs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts

FIG. 1A (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
			CACCTCG	1481	DNAas DNAcs DNAas DNacs OxyTs OxyMCs OxyG
1373	253861	253879	CAAATTCAATTT CAGAGAA	ASO-1482	OxyMCs OxyAs OxyAs DNats DNats DNacs DNAas DNats DNats DNats
1374	254164	254183	AGGTGTTAAAT TTATTGTTT	ASO-1483	OxyAs OxyGs OxyGs DNats DNats DNats DNats DNats DNats DNats
1375	254301	254319	GTGTGATATAA TTATTTTA	ASO-1484	OxyGs OxyTs OxyGs OxyTs DNats DNats DNats DNats DNats DNats
1376	254884	254903	TAAATGAATAT GTGCCTCA	ASO-1485	OxyTs OxyTs OxyAs OxyAs DNats DNats DNats DNats DNats DNats
1377	254916	254933	TTCTTTATTGTT AGGTAT	ASO-1486	OxyTs OxyTs OxyMCs DNats DNats DNats DNats DNats DNats
1378	255212	255231	TATTTAATATGC TATATTTA	ASO-1487	OxyTs OxyAs OxyTs OxyTs DNats DNats DNats DNats DNats DNats
1379	255431	255448	AGAAATTTAACA TGATATT	ASO-1488	OxyAs OxyGs OxyAs OxyAs DNats DNats DNats DNats DNats DNats
1380	255686	255703	TAGTATTGAGA GGAAGAT	ASO-1808	OxyTs OxyAs OxyGs OxyTs DNats DNats DNats DNats DNats DNats
1381	255869	255888	TATTTATTATTT TCTAAAGG	ASO-1489	OxyTs OxyAs OxyTs OxyTs DNats DNats DNats DNats DNats DNats
1382	256137	256155	TAAAGAATATAT CATTACC	ASO-1490	OxyTs OxyAs OxyAs OxyAs DNats DNats DNats DNats DNats DNats
1383	256310	256326	TTCAAATTATTAG TGGGG	ASO-1491	OxyTs OxyTs OxyMCs OxyAs DNats DNats DNats DNats DNats DNats
1384	256760	256778	GATGAACGTGA AAGACATG	ASO-1492	OxyGs OxyAs OxyTs OxyGs DNats DNats DNats DNats DNats DNats
1385	256864	256883	TGCAGAAAATA GAAACAGAG	ASO-1493	OxyTs OxyGs OxyMCs DNats DNats DNats DNats DNats DNats
1386	256865	256884	ATGCAGAAAAT AGAAACAGA	ASO-1494	OxyAs OxyTs OxyGs OxyMCs DNats DNats DNats DNats DNats DNats
1387	256887	256904	TTTGTTGTTTAT CTGTGG	ASO-1495	OxyTs DNats DNats DNats DNats DNats DNats DNats DNats
1388	256887	256905	CTTTGTTGTTTA TCTGTGG	ASO-1496	OxyMCs OxyTs DNats DNats DNats DNats DNats DNats DNats
1389	256888	256905	CTTTGTTGTTTA TCTGTG	ASO-1497	OxyMCs DNats DNats DNats DNats DNats DNats DNats DNats
1390	256889	256906	GCTTTGTGTTT TATCTGT	ASO-1498	OxyGs OxyMCs DNats DNats DNats DNats DNats DNats DNats
1391	256890	256908	TGGCTTTGTTG	ASO-	OxyTs DNats DNats DNats DNats DNats DNats DNats DNats

FIG. 1A (cont.)

[illegible]

[illegible]

FIG. 1A (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
			GATTAC	1537	DNAGs DNAGs DNAAs OxyTs OxyTs OxyAs OxyMC
1430	258967	258982	TCAGGGTTGTG GATTA	ASO-1538	OxyTs OxyMCs DNAAs DNAGs DNAGs DNAts DNAGs DNAts
1431	258984	259001	TCTGAATACCT TGTTTCC	ASO-1539	OxyTs OxyMCs DNAts DNAGs DNAAs DNAts DNAGs DNAts DNAGs DNAts
1432	259095	259111	GTGGTAGAAAA TGGTTA	ASO-1540	OxyGs OxyTs OxyGs DNAGs DNAts DNAGs DNAAs DNAGs DNAAs
1433	259409	259426	ACTCAAAAGTA ACACTAA	ASO-1541	OxyAs OxyMCs OxyTs OxyMCs DNAAs DNAGs DNAts DNAGs DNAts
1434	259752	259769	AATTGGACACA TGGAAATA	ASO-1542	OxyAs OxyAs OxyTs OxyTs DNAGs DNAGs DNAts DNAGs DNAts DNAGs DNAts
1435	260259	260275	TTAATGTGACC TAGTAT	ASO-1543	OxyTs OxyTs OxyAs DNAAs DNAts DNAGs DNAts DNAGs DNAAs DNAts
1436	260398	260417	ATTTAGAGATT CAGTATTC	ASO-0080	OxyAs OxyTs OxyTs DNAts DNAts DNAGs DNAAs DNAGs DNAts
1437	260451	260468	TCAGTAATGGA AAACAGA	ASO-1544	OxyTs OxyMCs OxyAs OxyGs DNAts DNAts DNAGs DNAts DNAGs DNAts
1438	260810	260828	TGGAATTATAA TGAATAAT	ASO-1545	OxyTs OxyGs OxyGs OxyAs DNAAs DNAts DNAts DNAts DNAts DNAts
1439	261157	261173	TGTAGAAGCAG CGGAAG	ASO-1546	OxyTs DNAGs DNAts DNAAs DNAGs DNAAs DNAts DNAGs DNAts
1440	261162	261179	GTGATTTGTAG AAGCAGC	ASO-1547	OxyGs OxyTs DNAGs DNAAs DNAts DNAts DNAts DNAts DNAts
1441	261398	261417	CCTGATGAGAA GAAAACACA	ASO-1548	OxyMCs OxyMCs DNAts DNAGs DNAAs DNAts DNAGs DNAAs DNAts
1442	261399	261417	CCTGATGAGAA GAAAACAC	ASO-1549	OxyMCs OxyMCs DNAts DNAGs DNAAs DNAts DNAGs DNAAs DNAts
1443	261399	261418	TCCTGATGAGA AGAAAACAC	ASO-1550	OxyTs OxyMCs OxyMCs DNAts DNAGs DNAAs DNAts DNAGs DNAAs
1444	261400	261417	CCTGATGAGAA GAAAACA	ASO-1551	OxyMCs OxyMCs OxyTs OxyGs DNAAs DNAts DNAts DNAts DNAts
1445	261400	261418	TCCTGATGAGA AGAAAACA	ASO-1552	OxyTs OxyMCs OxyMCs OxyTs DNAGs DNAAs DNAts DNAGs DNAAs
1446	261401	261418	TCCTGATGAGA AGAAAAC	ASO-1553	OxyTs OxyMCs OxyMCs OxyTs DNAGs DNAAs DNAts DNAGs DNAAs
1447	261451	261469	ATACCTTTTAC ATCTTCAT	ASO-1554	OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1448	261451	261470	CATACCTTTCA	ASO-	OxyMCs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts

FIG. 1A (cont.)

[illegible]

[illegible]

FIG. 1A (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
			TAAAGGGT	0081	DNAas DNAts DNAas DNAas OxyGs OxyGs OxyGs OxyT
1487	264912	264928	AAAATGTGGTT AGAGCT	ASO- 1593	OxyAs OxyAs OxyAs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts
1488	266049	266067	AGTGAGATACT GGAAACAG	ASO- 0082	OxyGs OxyTs OxyGs DNAas DNAts DNAts DNAts DNAts DNAts DNAts
1489	266049	266066	GTGAGATACTG GAAACAG	ASO- 1594	DNAgs DNAas DNAas OxyAs OxyMCs OxyAs OxyG
1490	266057	266074	GAGCTGAAGTG AGATACT	ASO- 1595	OxyAs OxyGs OxyTs DNAts DNAas DNAts DNAts DNAts DNAts DNAts
1491	272888	272905	ATGAAACTGTG TTACATT	ASO- 1596	DNAgs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1492	272889	272906	AATGAAACTGT GTTACAT	ASO- 1597	OxyAs OxyAs OxyTs OxyGs DNAas DNAas DNAts DNAts DNAts DNAts
1493	273186	273203	AAGAAAAGCTA TTTATAG	ASO- 1598	DNAgs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1494	273436	273452	CGATAATGGAA CAGTAG	ASO- 1599	OxyMCs OxyGs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts
1495	273657	273676	ATAAAGTAAATT ATATTGG	ASO- 1600	DNAas DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1496	273952	273970	CTGCTGTTATG AGGAAACC	ASO- 0083	OxyAs OxyTs OxyAs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts
1497	274086	274104	GTTTTATAATAA TATGTAT	ASO- 1601	DNAgs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1498	274365	274384	AATATTAAATTTA ATTTTGA	ASO- 1602	DNAas DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1499	274705	274724	TATTAATAATTGC ACAGGATT	ASO- 1603	OxyTs OxyAs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts
1500	274973	274992	TCATCTTCTTTT TCTAAATC	ASO- 1604	DNAcs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1501	275483	275502	ATTATAATCTTT TCTTACCT	ASO- 1605	OxyAs OxyTs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts
1502	275484	275502	ATTATAATCTTT TCTTACC	ASO- 1606	DNAcs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1503	275895	275912	CATTGGTGAAG AGATATG	ASO- 1607	OxyMCs OxyAs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts
1504	276227	276246	CTTGGTACATT ATCTTGACAG	ASO- 1608	DNAgs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1505	276472	276491	TACTTGTCCTTT	ASO-	OxyTs OxyAs OxyMCs DNAts DNAts DNAts DNAts DNAts DNAts

FIG. 1A (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
			ATCATTAG	1609	DNats DNAs DNats DNacs DNAs DNats DNats OxyAs OxyG
1506	276737	276753	TGTAAGGTAAA GTCTTT	ASO- 1610	OxyTs OxyGs OxyTs OxyAs DNAs DNags DNats DNAs DNAs DNAs
1507	277053	277072	GTAAGATTAGA CTGTGCTAC	ASO- 1611	DNags DNats OxyMCs OxyTs OxyTs OxyT
1508	277421	277440	ATTGTAATTCCT GATTTTAC	ASO- 1612	OxyGs DNats DNAs DNags DNAs DNats DNats DNats DNAs DNAs
1509	277611	277627	CCAGGAATAGC TTTTAA	ASO- 1613	OxyAs OxyTs OxyGs DNats DNats DNats DNats DNats DNats
1510	277919	277936	ATCTGAATTTT GTGTTAG	ASO- 1614	DNacs DNats DNats OxyTs OxyAs OxyAs OxyA
1511	278181	278200	TATTAATTCCTG TTTTAGCC	ASO- 0084	OxyAs OxyTs OxyMCs OxyTs DNags DNAs DNats DNats DNats DNats
1512	278185	278203	ACATAATTATTC TTGTTTT	ASO- 1615	OxyTs OxyAs DNats DNats DNats DNats DNats DNats DNats DNats
1513	278624	278643	TTTAAATGAAT GAATCCAAG	ASO- 1616	OxyAs OxyTs OxyTs OxyAs DNAs DNAs DNats DNats DNats DNats
1514	278626	278644	TTTTAAATGAAT GAAATCCA	ASO- 1617	DNags DNAs DNAs DNAs DNats DNats DNats DNats DNats DNats
1515	279074	279090	GATAATATAGC TTTGCG	ASO- 1618	OxyGs OxyAs OxyTs OxyAs DNAs DNats DNats DNats DNats DNats
1516	279461	279480	TTCAGTTTTCTT AGATGCAT	ASO- 1619	OxyTs OxyTs DNacs DNAs DNags DNats DNats DNats DNats DNats
1517	279663	279679	AATGGAGTTGG TGAGCA	ASO- 1620	DNats DNAs DNags DNAs DNats DNats DNats DNats DNats DNats
1518	280077	280093	GATAACAATTTG GTCAGA	ASO- 1621	OxyGs OxyAs DNats DNAs DNAs DNacs DNats DNats DNats DNats
1519	280136	280152	TCTGGAGGGAT GTAATT	ASO- 1622	DNags DNats OxyMCs OxyAs OxyGs OxyA
1520	280658	280676	TCTACCAATTA AATATTTA	ASO- 1623	OxyTs OxyMCs OxyTs OxyAs DNacs DNats DNAs DNAs DNats DNats
1521	280662	280679	TCCTCTACCAA TTAAATA	ASO- 1624	DNAs DNAs DNAs DNats DNats DNats DNats DNats DNats DNats
1522	281482	281499	CTATGATATGA ATGTATG	ASO- 1625	OxyMCs OxyTs OxyAs OxyTs DNags DNAs DNats DNats DNats DNats
1523	281493	281509	TGACTTAATGC TATGAT	ASO- 1626	DNAs DNAs DNats DNags OxyTs OxyAs OxyTs OxyG
1524	282021	282039	GTTATTATTATT	ASO-	OxyTs OxyGs OxyAs DNacs DNats DNats DNats DNats DNats DNats

FIG. 1A (cont.)

[illegible]

FIG. 1A (cont.)

[illegible]

FIG. 1A (cont.)

[illegible]

FIG. 1A (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
			ACAGTAA	1680	DNAts DNAAs DNACs DNAAs OxyGs OxyTs OxyAs OxyA
1582	298036	298053	TGCTTCAGTAT ATATCTT	ASO- 1681	OxyTs OxyGs DNACs DNAts DNAts DNACs DNAAs DNAGs DNAts DNAAs DNAts DNAAs DNAts DNAAs OxyTs OxyMCs OxyTs OxyT
1583	299320	299338	CAAAGATATTA GTGAACCTG	ASO- 1682	OxyMCs OxyAs OxyAs OxyAs DNAGs DNAAs DNAts DNAAs DNAts DNAts DNAAs DNAGs DNAts DNAGs DNAAs OxyAs OxyMCs OxyTs OxyG
1584	299326	299342	TAGGCAAGAT ATTAGT	ASO- 1683	OxyTs OxyAs OxyGs OxyGs DNACs DNAAs DNAAs DNAGs DNAts DNAAs DNAts DNAAs DNAts DNAts OxyAs OxyGs OxyT
1585	299788	299807	TCCTCTATAAAT ATGGTTTT	ASO- 1684	OxyTs OxyMCs OxyMCs DNAts DNAts DNACs DNAts DNAts DNAts DNAAs DNAts DNAAs DNAts DNAAs DNAts DNAGs DNAGs DNAts DNAts OxyTs OxyT
1586	299887	299905	GCTTAAATCA AATATATA	ASO- 1685	OxyGs OxyMCs OxyTs OxyTs DNAAs DNAAs DNAAs DNAts DNAts DNAts DNACs DNAAs DNAAs DNAts DNAts DNAAs OxyTs OxyAs OxyTs OxyA
1587	300239	300255	AAGGTAGATCA AATGGA	ASO- 1686	OxyAs OxyAs OxyGs OxyGs DNAts DNAAs DNAGs DNAts DNAts DNAts DNAts DNAAs DNAAs OxyTs OxyGs OxyGs OxyA
1588	300543	300560	AAGGTTTAAGA GAGGAAG	ASO- 1687	OxyAs OxyAs OxyGs OxyGs DNAts DNAts DNAts DNAts DNAAs DNAts DNAGs DNAAs DNAGs DNAAs DNAGs OxyGs OxyAs OxyAs OxyG
1589	300798	300816	TATTGTGTTTAA GTTTATT	ASO- 0089	OxyTs OxyAs OxyTs OxyTs DNAGs DNAts DNAGs DNAts DNAts DNAts DNAAs DNAAs DNAGs DNAts DNAts OxyTs OxyAs OxyTs OxyT
1590	300801	300819	TATTATTGTGTT TAAGTTT	ASO- 1688	OxyTs OxyAs OxyTs OxyTs DNAAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAAs DNAAs OxyGs OxyTs OxyTs OxyT
1591	301617	301636	TTTTGTTGTTTC ATGTGTAA	ASO- 1689	OxyTs OxyTs OxyTs DNAts DNAGs DNAts DNAts DNAts DNAts DNAts DNAts DNACs DNAAs DNAts DNAGs DNAts DNAGs OxyTs OxyAs OxyA
1592	301676	301694	AGATTTTCTCTG AAAAGAA	ASO- 1690	OxyAs OxyGs OxyAs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAAs DNAAs DNAAs OxyAs OxyGs OxyAs OxyA
1593	301775	301793	GAATAAATGTA CCATTTTC	ASO- 1691	OxyGs OxyAs OxyAs OxyTs DNAAs DNAAs DNAAs DNAts DNAts DNAts DNAts DNACs DNACs DNAAs DNAts OxyTs OxyTs OxyMC
1594	301776	301795	AGGAATAAATG TACCATTT	ASO- 1692	OxyAs OxyGs OxyGs DNAAs DNAts DNAts DNAts DNAAs DNAts DNAts DNAts DNAts DNAAs DNACs DNACs OxyTs OxyTs OxyTs OxyT
1595	301777	301795	AGGAATAAATG TACCATTT	ASO- 1693	OxyAs OxyGs OxyGs OxyAs DNAts DNAts DNAts DNAAs DNAts DNAts DNAts DNAts DNAAs DNACs DNACs OxyAs OxyTs OxyTs OxyT
1596	301777	301796	TAGGAATAAAT GTACCATTT	ASO- 1694	OxyTs OxyAs OxyGs OxyGs DNAAs DNAts DNAts DNAts DNAAs DNAts DNAts DNAGs DNAts DNAAs DNACs DNACs OxyTs OxyTs OxyT
1597	301778	301795	AGGAATAAATG TACCATTT	ASO- 1695	OxyAs OxyGs OxyGs OxyAs DNAts DNAts DNAts DNAAs DNAts DNAts DNAts DNAts DNAAs DNACs OxyMCs OxyAs OxyTs OxyT
1598	301778	301796	TAGGAATAAAT GTACCATTT	ASO- 1696	OxyTs OxyAs OxyGs DNAGs DNAAs DNAts DNAts DNAts DNAAs DNAts DNAts DNAGs DNAts DNAAs DNACs OxyMCs OxyAs OxyTs OxyT
1599	301778	301797	TTAGGAATAAA TGTACCATTT	ASO- 1697	OxyTs OxyTs OxyAs OxyGs DNAGs DNAAs DNAts DNAts DNAts DNAAs DNAts DNAts DNAGs DNAts DNAAs DNACs OxyMCs OxyAs OxyTs OxyT
1600	301779	301796	TAGGAATAAAT	ASO-	OxyTs OxyAs OxyGs DNAGs DNAAs DNAts DNAts DNAts DNAAs DNAts DNAts

FIG. 1A (cont.)

[illegible]

FIG. 1A (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
			GAAAAACAT	1717	DNAas DNAGs DNAas DNAas DNAas OxyAs OxyMCs OxyAs OxyT
1620	304374	304392	TGGATTGGTTT ATTGCTTT	ASO- 1718	OxyTs OxyGs DNAGs DNAas DNAts DNAts DNAGs DNAts DNAts DNAts
1621	304458	304474	CATGTACTGTG TGAGCC	ASO- 1719	OxyMCs OxyAs DNAts DNAGs DNAts DNAas DNAts DNAts DNAGs DNAts
1622	304459	304475	CCATGTACTGT GTGAGC	ASO- 1720	OxyMCs DNACs DNAas DNAts DNAGs DNAts DNAas DNACs DNAts DNAGs
1623	304584	304600	TATTTACTTGAT GGGTA	ASO- 1721	OxyTs OxyAs OxyTs DNAts DNAts DNAas DNACs DNAts DNAts DNAGs DNAas
1624	304584	304601	ATATTTACTTGA TGGTA	ASO- 1722	OxyAs OxyTs OxyAs OxyTs DNAts DNAts DNAas DNACs DNAts DNAts DNAGs
1625	304584	304602	AATATTTACTTG ATGGTA	ASO- 1723	OxyAs OxyTs DNAas DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1626	304585	304602	AA TATTTACTTG ATGGGT	ASO- 1724	OxyAs OxyTs DNAas DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1627	304648	304665	AACAAATGGAAT AAGTAGA	ASO- 1725	OxyAs OxyAs OxyMCs OxyAs DNAas DNAts DNAGs DNAGs DNAas DNAas
1628	304966	304984	CTCCTGATAAT ATATTGGC	ASO- 1726	OxyMCs OxyTs OxyMCs DNACs DNAts DNAts DNAts DNAts DNAts DNAts
1629	305066	305082	TAGAGTGGTGA GGTGAG	ASO- 1727	OxyTs DNAas DNAGs DNAas DNAGs DNAts DNAts DNAts DNAts DNAts
1630	305517	305534	CCTATTTTCAAT TATTCC	ASO- 1728	OxyMCs OxyMCs OxyTs DNAas DNAts DNAts DNAts DNAts DNAts DNAts
1631	305595	305613	AAGAGATCAAC AGTGGACC	ASO- 0090	OxyAs OxyAs DNAGs DNAas DNAGs DNAts DNAts DNAts DNAts DNAts
1632	305842	305859	TTGGGAATAAA TTTCAGC	ASO- 1729	OxyTs OxyTs OxyGs DNAGs DNAGs DNAas DNAas DNAts DNAts DNAts
1633	305982	305998	TACTGTATGAA TGTAAC	ASO- 1730	OxyTs OxyAs OxyMCs OxyTs DNAGs DNAts DNAts DNAts DNAts DNAts
1634	306082	306098	AGAAGCCCCAT TTAAGC	ASO- 1731	OxyAs DNAGs DNAas DNAas DNAGs DNAts DNAts DNAts DNAts DNAts
1635	306087	306104	ATTAAGAGAAAG CCCCATT	ASO- 1732	OxyAs DNAts DNAts DNAts DNAas DNAts DNAts DNAts DNAts DNAts
1636	306087	306105	TATTAAGAGAA GCCCCATT	ASO- 1733	OxyTs DNAas DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1637	306088	306104	ATTAAGAGAAAG CCCCAT	ASO- 1734	OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1638	306088	306105	TATTAAGAGAA	ASO-	OxyTs DNAas DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts

FIG. 1A (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
			GCCCCAT	1735	DNAas DNAGs DNACs DNACs OxyMCs OxyMCs OxyAs OxyT
1639	306088	306106	CTATTAAGAGA AGCCCCAT	ASO-1736	OxyMCs DNAts DNAas DNAts DNAts DNAts DNAas DNAts DNAGs DNAas DNAGs
1640	306089	306105	TATTAAGAGAA GCCCCA	ASO-1737	OxyTs OxyAs DNAts DNAts DNAas DNAts DNAGs DNAas DNAGs DNAas DNAGs
1641	306089	306106	CTATTAAGAGA AGCCCCA	ASO-1738	OxyMCs DNAts DNAas DNAts DNAts DNAts DNAas DNAts DNAGs DNAas DNAGs
1642	306090	306106	CTATTAAGAGA AGCCCC	ASO-1739	OxyMCs OxyTs OxyAs DNAts DNAts DNAts DNAas DNAts DNAGs DNAas DNAGs
1643	306090	306107	CCTATTAAGAG AAGCCCC	ASO-1740	OxyMCs DNACs DNAts DNAas DNAts DNAts DNAts DNAas DNAts DNAGs DNAas
1644	306091	306107	CCTATTAAGAG AAGCCC	ASO-1741	DNAGs DNAas DNAts DNAas DNAts DNAts DNAts DNAas DNAts DNAGs DNAas
1645	306091	306108	GCCTATTAAGA GAAGCCC	ASO-1742	OxyGs DNACs DNAts DNAas DNAts DNAts DNAts DNAts DNAas DNAts DNAGs DNAas
1646	306092	306108	GCCTATTAAGA GAAGCC	ASO-1743	OxyGs DNACs DNAts DNAas DNAts DNAts DNAts DNAts DNAas DNAts DNAGs DNAas
1647	306109	306126	CATTGGGAATA CAGGGTG	ASO-1744	OxyMCs OxyAs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAas DNAts DNAts
1648	306110	306126	CATTGGGAATA CAGGGT	ASO-1745	OxyMCs OxyAs OxyTs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAas DNAts
1649	306471	306488	ATTACTTTTGA TGTGAA	ASO-1746	OxyAs OxyTs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1650	306687	306704	TTTAAATTTCAG CTTGAC	ASO-1747	OxyTs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1651	306870	306887	ATTGTGTA GCTCTGA	ASO-1748	OxyAs OxyTs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1652	307270	307287	TATGTATAAGA GATGTTT	ASO-1749	OxyTs OxyAs OxyTs OxyGs DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1653	307498	307515	ATGCACCTCAGA AACATGC	ASO-1750	OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1654	307499	307517	TCATGCACCTCA GAAACATG	ASO-1751	OxyTs OxyMCs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1655	307500	307517	TCATGCACCTCA GAAACAT	ASO-1752	OxyTs OxyMCs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1656	307500	307518	TTCATGCACCTC AGAAACAT	ASO-1753	OxyTs OxyTs OxyMCs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1657	307584	307600	GTTGAAGTGTA	ASO-	OxyGs OxyTs OxyTs OxyGs DNAas DNAts DNAts DNAts DNAts DNAts DNAts

FIG. 1A (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
			AACAAT	1754	DNAas DNAas OxyMCs OxyAs OxyTs
1658	307687	307703	TGATGAAGAGT TGTAAT	ASO-1755	OxyTs OxyGs OxyAs DNAts DNAs DNAas DNAs DNAs DNAts
1659	308035	308052	GATGTGAATTT TTCCAGT	ASO-1756	OxyGs DNAas DNAts DNAs DNAts DNAs DNAas DNAts DNAts DNAts
1660	308141	308158	ACAGGATAAAG AAAAGAG	ASO-1757	OxyAs OxyMCs OxyAs OxyGs DNAs DNAs DNAts DNAs DNAas DNAs
1661	308374	308393	ATTATAAACCTT TAAATCT	ASO-1758	OxyAs OxyTs OxyAs DNAts DNAs DNAas DNAs DNAts DNAts DNAts
1662	308896	308912	AGGACTGTGAA TTACTA	ASO-1759	OxyAs OxyGs DNAs DNAts DNAts DNAts DNAts DNAts DNAts DNAs
1663	309052	309069	ATCAGAAAAGC TTCAACC	ASO-1760	OxyAs OxyTs OxyMCs DNAs DNAs DNAts DNAs DNAs DNAs DNAs
1664	309052	309070	TATCAGAAAAG CTTCAACC	ASO-1761	OxyTs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1665	309052	309071	TTATCAGAAA GCTTCAACC	ASO-1762	OxyTs OxyTs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1666	309053	309070	TATCAGAAAAG CTTCAAC	ASO-1763	OxyTs OxyAs OxyTs OxyMCs DNAs DNAs DNAts DNAts DNAts DNAts
1667	309053	309071	TTATCAGAAA GCTTCAAC	ASO-1764	OxyTs OxyTs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1668	309053	309072	ATTATCAGAAA AGCTTCAAC	ASO-1765	OxyAs OxyTs OxyTs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts
1669	309054	309072	ATTATCAGAAA AGCTTCAA	ASO-1766	OxyAs OxyTs OxyTs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts
1670	309056	309074	TAATTATCAGA AAAGCTTC	ASO-1767	OxyTs OxyAs OxyAs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts
1671	309057	309074	TAATTATCAGA AAAGCTT	ASO-1768	OxyTs OxyAs OxyAs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts
1672	309065	309082	TTGTGTAATAAT TATCAG	ASO-1769	OxyTs OxyTs OxyGs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts
1673	309383	309402	TAGAAGATAAT AAATGTGTA	ASO-1770	OxyTs OxyAs OxyGs OxyAs DNAs DNAs DNAts DNAts DNAts DNAts
1674	309427	309443	ATATACAGTGT CCCATG	ASO-1771	OxyAs OxyTs DNAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1675	309427	309444	TATATACAGTG TCCCATG	ASO-1772	OxyTs DNAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1676	309428	309444	TATATACAGTG	ASO-	OxyTs OxyAs OxyTs DNAs DNAts DNAts DNAts DNAts DNAts DNAts

FIG. 1A (cont.)

[illegible]

FIG. 1A (cont.)

[illegible]

FIG. 1B

[illegible]

FIG. 1B (cont.)

[illegible]

FIG. 1B (cont.)

SEQ ID No.	Start #1 (SEQ ID NO: 1)	End #1 (SEQ ID NO: 1)	Start #2 (SEQ ID NO: 1)	End #2 (SEQ ID NO: 1)	Start #3 (SEQ ID NO: 1)	End #3 (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
									OxyAs OxyG
303	76160	76178	77753	77771	--	--	ATGGAACCCAG AGAAATGAAA	ASO-0386	OxyAs OxyTs OxyGs OxyGs DNAas DNAas DNacs DNacs DNAas DNacs DNacs DNacs DNAas DNacs OxyAs OxyA
385	102012	102028	103215	103231	--	--	AATGTAACCTTG TTGAGT	ASO-0463	OxyAs OxyTs OxyGs DNats DNats DNAas DNacs DNats DNats DNacs DNats DNats OxyGs OxyTs
386	102012	102029	103215	103232	--	--	AAATGTAACCTT GTTGAGT	ASO-0465	OxyAs OxyTs OxyGs DNats DNats DNacs DNacs DNats DNats DNats DNats OxyGs OxyTs
387	102012	102030	103215	103233	--	--	GAAATGTAACCT TGTTGAGT	ASO-0467	OxyGs OxyAs OxyTs OxyGs DNats DNats DNacs DNacs DNats DNats DNats DNats OxyGs OxyTs
388	102012	102031	103215	103234	--	--	AGAAATGTAA CTTGTTGAGT	ASO-0469	OxyAs OxyGs OxyTs OxyAs DNAas DNats DNats DNats DNacs DNats DNats DNats DNats OxyGs OxyTs
389	102013	102029	103216	103232	--	--	AAATGTAACCTT GTTGAG	ASO-0471	OxyAs OxyTs OxyGs DNats DNats DNacs DNats DNats DNats DNats DNats OxyGs OxyTs
390	102013	102030	103216	103233	--	--	GAAATGTAACCT TGTTGAG	ASO-0473	OxyGs OxyAs OxyTs OxyGs DNats DNats DNacs DNats DNats DNats DNats DNats OxyGs OxyTs
391	102013	102031	103216	103234	--	--	AGAAATGTAA CTTGTTGAG	ASO-0475	OxyAs OxyGs OxyTs OxyGs DNats DNats DNacs DNats DNats DNats DNats DNats OxyGs OxyTs
392	102013	102032	103216	103235	--	--	TAGAAATGTAA CTTGTTGAG	ASO-0477	OxyTs OxyAs OxyGs OxyTs OxyGs DNats DNats DNacs DNats DNats DNats DNats DNats OxyGs OxyTs
393	102014	102031	103217	103234	--	--	AGAAATGTAA CTTGTTGA	ASO-0479	OxyAs OxyGs OxyTs OxyGs DNats DNats DNacs DNats DNats DNats DNats DNats OxyGs OxyTs
394	102014	102032	103217	103235	--	--	TAGAAATGTAA	ASO-	OxyTs OxyAs OxyGs OxyTs OxyGs DNats DNats DNacs DNats DNats DNats DNats DNats OxyGs OxyTs

FIG. 1B (cont.)

SEQ ID No.	Start #1 (SEQ ID NO: 1)	End #1 (SEQ ID NO: 1)	Start #2 (SEQ ID NO: 1)	End #2 (SEQ ID NO: 1)	Start #3 (SEQ ID NO: 1)	End #3 (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
							CTTGTTGA	0481	DNAts DNAGs DNAts DNAAAs DNAAcs DNAAcs DNAts DNAGs DNAts OxyTs OxyGs OxyA
395	102014	102033	103217	103236	--	--	CTAGAAATGTA ACTTGTTGA	ASO-0483	OxyMCs OxyTs OxyAs DNAGs DNAAAs DNAAAs DNAts DNAGs DNAts DNAAcs DNAAcs DNAts DNAGs DNAts OxyTs OxyGs OxyA
396	102015	102032	103218	103235	--	--	TAGAAATGTAA CTTGTTG	ASO-0485	OxyTs OxyAs OxyGs OxyAs DNAAAs DNAAAs DNAts DNAGs DNAts DNAAcs DNAAcs DNAts DNAGs DNAts OxyTs OxyG
397	102015	102033	103218	103236	--	--	CTAGAAATGTA ACTTGTTG	ASO-0487	OxyMCs OxyTs OxyAs OxyGs DNAAAs DNAAAs DNAts DNAGs DNAts DNAAcs DNAAcs DNAts DNAGs DNAts OxyTs OxyTs OxyG
398	102015	102034	103218	103237	--	--	CCTAGAAATG TAACTTGTTG	ASO-0489	OxyMCs OxyMCs DNAts DNAAAs DNAGs DNAAAs DNAAAs DNAts DNAGs DNAts DNAAcs DNAAcs DNAts DNAGs DNAts OxyGs OxyTs OxyG
399	102016	102033	103219	103236	--	--	CTAGAAATGTA ACTTGTT	ASO-0491	OxyMCs OxyTs OxyAs OxyGs DNAAAs DNAAAs DNAts DNAGs DNAts DNAAcs DNAAcs DNAts DNAGs DNAts OxyTs OxyG
400	102016	102034	103219	103237	--	--	CCTAGAAATG TAACTTGTT	ASO-0493	OxyMCs OxyMCs OxyTs OxyAs DNAGs DNAAAs DNAAAs DNAts DNAGs DNAts DNAAcs DNAAcs DNAts DNAGs DNAts OxyTs OxyT
401	102016	102035	103219	103238	--	--	ACCTAGAAAT GTAACCTGTT	ASO-0495	OxyAs OxyMCs OxyMCs DNAts DNAAAs DNAGs DNAAAs DNAAAs DNAts DNAGs DNAts DNAAcs DNAAcs DNAts DNAGs DNAts OxyGs OxyTs OxyT
402	102017	102034	103220	103237	--	--	CCTAGAAATG TAACTTGT	ASO-0497	OxyMCs OxyMCs OxyTs DNAAAs DNAGs DNAAAs DNAAAs DNAts DNAGs DNAts DNAAcs DNAAcs OxyTs OxyTs OxyGs OxyT
403	102017	102035	103220	103238	--	--	ACCTAGAAAT GTAACCTGT	ASO-0499	OxyAs OxyMCs OxyMCs DNAts DNAAAs DNAGs DNAAAs DNAAAs DNAts DNAGs DNAts DNAAcs DNAAcs DNAts DNAGs DNAts OxyGs OxyT

FIG. 1B (cont.)

SEQ ID No.	Start #1 (SEQ ID NO: 1)	End #1 (SEQ ID NO: 1)	Start #2 (SEQ ID NO: 1)	End #2 (SEQ ID NO: 1)	Start #3 (SEQ ID NO: 1)	End #3 (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
404	102017	102036	103220	103239	--	--	CACCTAGAAA TGTAAC TTGT	ASO-0501	OxyMCs OxyAs DNAcs DNAcs DNAts DNAts DNAAs DNags DNAts DNAAs DNacs DNAts OxyTs OxyGs OxyT
405	102018	102035	103221	103238	--	--	ACCTAGAAAT GTAAC TTG	ASO-0503	OxyAs OxyMCs OxyMCs OxyTs DNAs DNags DNAs DNAs DNAs DNAts DNAts DNAts OxyTs OxyTs OxyG
406	102018	102036	103221	103239	--	--	CACCTAGAAA TGTAAC TTG	ASO-0505	OxyMCs OxyAs OxyMCs OxyMCs DNAts DNAs DNags DNAs DNAs DNAts DNAts DNAts DNAts DNAts DNAts OxyTs OxyG
407	102018	102037	103221	103240	--	--	ACACCTAGAA ATGTAAC TTG	ASO-0507	OxyAs OxyMCs OxyAs OxyMCs DNacs DNAts DNAs DNags DNAs DNAs DNAs DNAts DNAts DNAts DNAts OxyTs OxyG
408	102019	102036	103222	103239	--	--	CACCTAGAAA TGTAAC TT	ASO-0509	OxyMCs OxyAs OxyMCs OxyMCs DNAts DNAs DNags DNAs DNAs DNAts DNAts DNAts DNAts DNAts OxyTs OxyG
409	102019	102037	103222	103240	--	--	ACACCTAGAA ATGTAAC TT	ASO-0511	OxyAs OxyMCs OxyAs OxyMCs DNacs DNAts DNAs DNags DNAs DNAs DNAts DNAts DNAts DNAts OxyTs OxyT
410	102020	102036	103223	103239	--	--	CACCTAGAAA TGTAAC T	ASO-0513	OxyMCs OxyAs OxyMCs OxyMCs DNAts DNAs DNags DNAs DNAs DNAts DNAts DNAts OxyAs OxyMCs OxyT
411	102020	102037	103223	103240	--	--	ACACCTAGAA ATGTAAC T	ASO-0515	OxyAs OxyMCs OxyAs OxyMCs DNacs DNAts DNAs DNags DNAs DNAs DNAts DNAts DNAts DNAts OxyTs OxyG
412	102024	102041	103227	103244	--	--	CTATACACCTA GAAATGT	ASO-0517	OxyMCs OxyTs OxyAs DNAts DNAs DNacs DNAs DNacs DNAts DNAs DNags DNAs DNAs OxyAs OxyTs OxyGs OxyT
413	102024	102042	103227	103245	--	--	ACTATACACCT AGAAATGT	ASO-0519	OxyAs OxyMCs OxyTs OxyAs DNAts DNAs DNacs DNAs DNacs DNAts DNAs DNags DNAs DNAs DNAs DNAs OxyTs OxyGs

FIG. 1B (cont.)

SEQ ID No.	Start #1 (SEQ ID NO: 1)	End #1 (SEQ ID NO: 1)	Start #2 (SEQ ID NO: 1)	End #2 (SEQ ID NO: 1)	Start #3 (SEQ ID NO: 1)	End #3 (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
									OxyT
414	102024	102043	103227	103246	--	--	TACTATACACC TAGAAATGT	ASO-0521	OxyTs OxyAs OxyMCs DNAts DNAas DNAts DNAas DNacs DNAAas DNacs DNAts DNAts DNags DNAAas DNAAas OxyTs OxyGs OxyT
415	102025	102043	103228	103246	--	--	TACTATACACC TAGAAATG	ASO-0523	OxyTs OxyAs OxyMCs OxyTs DNAas DNAts DNAas DNacs DNAAas DNacs DNAts DNAts DNags DNAAas OxyAs OxyAs OxyTs OxyG
416	102026	102043	103229	103246	--	--	TACTATACACC TAGAAAT	ASO-0525	OxyTs OxyAs OxyMCs OxyTs DNAts DNAas DNAts DNAas DNacs DNAAas DNacs DNAts DNAts DNags OxyAs OxyAs OxyT
417	102026	102044	103229	103247	--	--	CTACTATACAC CTAGAAAT	ASO-0527	OxyMCs OxyTs OxyAs OxyMCs DNAts DNAAas DNAts DNAAas DNacs DNAAas DNacs DNacs DNAts DNAAas DNags OxyAs OxyAs OxyAs OxyT
418	102026	102045	103229	103248	--	--	CCTACTATACA CCTAGAAAT	ASO-0529	OxyMCs OxyMCs DNAts DNAts DNAas DNacs DNAts DNAAas DNAts DNAAas DNacs DNacs DNAts DNAts DNAAas DNags OxyAs OxyAs OxyT
419	102027	102044	103230	103247	--	--	CTACTATACAC CTAGAAA	ASO-0531	OxyMCs OxyTs OxyAs OxyMCs DNAts DNAAas DNAts DNAAas DNacs DNAAas DNacs DNacs DNAts DNAAas DNags OxyAs OxyAs OxyA
420	102027	102045	103230	103248	--	--	CCTACTATACA CCTAGAAA	ASO-0533	OxyMCs OxyMCs DNAts DNAts DNAas DNacs DNAts DNAAas DNAts DNAAas DNacs DNacs DNAts DNAts DNAAas DNags OxyAs OxyAs OxyA
421	102027	102046	103230	103249	--	--	TCCTACTATAC ACCTAGAAA	ASO-0535	OxyTs OxyMCs OxyMCs DNAts DNAts DNAAas DNacs DNAts DNAAas DNAts DNAAas DNacs DNAAas DNacs DNAts DNAts DNAAas DNags DNAAas OxyAs OxyA
422	102028	102047	103231	103250	--	--	TTCCTACTATA CACCTAGAA	ASO-0537	OxyTs OxyTs OxyMCs DNacs DNAts DNAts DNAAas DNacs DNAts DNAts DNAAas DNAts DNAAas DNags DNAAas OxyA
423	102029	102046	103232	103249	--	--	TCCTACTATAC	ASO-	OxyTs OxyMCs DNacs DNAts DNAts DNAAas DNacs

FIG. 1B (cont.)

[illegible]

FIG. 1B (cont.)

[illegible]

FIG. 1B (cont.)

[illegible]

FIG. 2

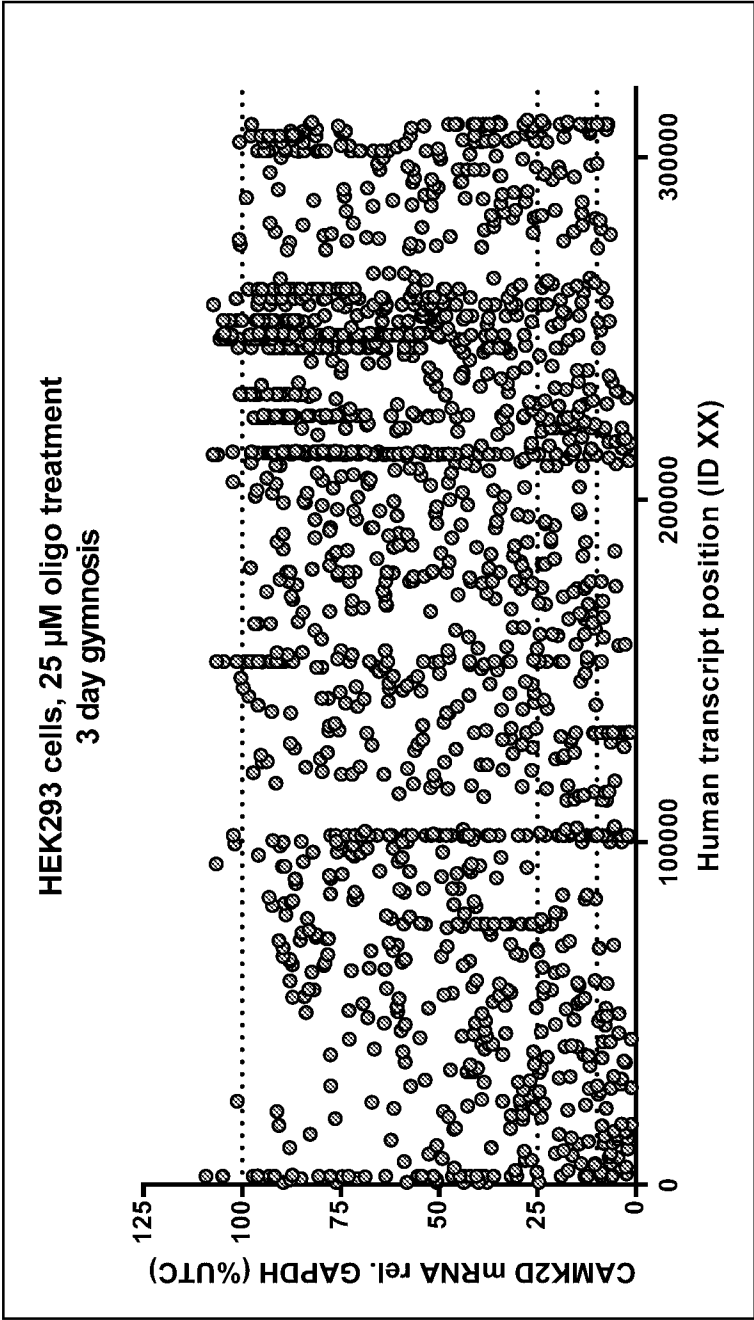


FIG. 3

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	DES No.	ASO with Design	ASO No.
24	2566	2583	DES-0002	GAtaattttggcagCATA	ASO-0002
25	2566	2584	DES-0003	TGAtaattttggcagcATA	ASO-0003
27	2567	2584	DES-0005	TGAtaattttggcagCAT	ASO-0005
55	3576	3593	DES-0135	ATTTgcaataaataTGGA	ASO-0135
61	5256	5274	DES-0141	GATTtattttcagtaTTTG	ASO-0141
63	6204	6221	DES-0143	ACTTtatataatttGACA	ASO-0143
71	8068	8085	DES-0150	TTTCtttaaatacaTACT	ASO-0150
75	9246	9263	DES-0154	TGTAtagtgagataTTTT	ASO-0154
79	10665	10684	DES-0158	GAAAttcaaattatccAGAA	ASO-0158
84	12135	12154	DES-0162	AGAAaataactgaattaTACA	ASO-0162
85	12329	12346	DES-0163	GTAGaatggatcaaAATT	ASO-0163
92	14390	14407	DES-0170	ATCTtagttttggaTTTG	ASO-0170
102	17218	17235	DES-0179	ACAGttttatagataAGA	ASO-0179
105	17708	17725	DES-0182	AGTCattaattcttTATC	ASO-0182
114	21808	21826	DES-0190	TCCTttgtatttctgAAT	ASO-0190
128	26381	26397	DES-0203	GAGAtcaataaagTATA	ASO-0203
130	28249	28265	DES-0208	AGATatagttactTAAC	ASO-0208
138	29430	29446	DES-0212	AATAttattgggtGAGC	ASO-0212
158	35743	35762	DES-0231	TACatattatattactcCTC	ASO-0231

FIG. 3 (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	DES No.	ASO with Design	ASO No.
161	37100	37119	DES-0234	ATTTAgcacatacattTAAC	ASO-0234
178	41742	41758	DES-0249	CACAAatcattagTCTA	ASO-0249
180	42531	42548	DES-0251	TTCAatattatgctgTTTT	ASO-0251
186	44345	44361	DES-0257	AAAGtgagtggttaAGGT	ASO-0257
190	46568	46586	DES-0261	TGTttctaggttcatTTT	ASO-0261
195	47770	47788	DES-0265	TAATttatcatgtatTCAG	ASO-0265
200	49272	49289	DES-0270	GAAAtctgtgaataCTTT	ASO-0270
202	50024	50041	DES-0272	CATTaaatatacttGTTC	ASO-0272
234	58780	58796	DES-0304	GTTGagaatacagATTG	ASO-0304
264	69068	69086	DES-0332	ATACattttacattaTTCT	ASO-0332
327	84562	84581	DES-0409	TTTgtttcaccattttaTAC	ASO-0409
387	102012	102030	DES-0467	GAAAtgtaactgttGAGT	ASO-0467
390	102013	102030	DES-0473	GAAAtgtaactgtTGAG	ASO-0473
396	102015	102032	DES-0485	TAGAAatgtaacttGTTG	ASO-0485
441	103690	103708	DES-0570	AAATcgttctttacaTGAA	ASO-0570
446	104608	104625	DES-0574	ATTAttatggtgtTTGT	ASO-0574
457	114694	114710	DES-0583	TAGAttataaggATTG	ASO-0583
463	116502	116519	DES-0589	TTTatgaagtttctgTGG	ASO-0589
467	117904	117921	DES-0593	GTCTtatattacatCAAA	ASO-0593
513	131977	131995	DES-0637	GTGgagatttaggataTTG	ASO-0637

FIG. 3 (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	DES No.	ASO with Design	ASO No.
516	131978	131997	DES-0643	CAGtggagatttaggatATT	ASO-0643
519	131980	131997	DES-0649	CAGtggagatttaggATA	ASO-0649
523	132017	132034	DES-0657	TGTAtaattcacaoTGTT	ASO-0657
524	132017	132035	DES-0659	ATGTataattcacaoTGTT	ASO-0659
636	157447	157465	DES-0769	TTTAtaatctcattTACT	ASO-0769
640	159834	159851	DES-0773	ACACtatttagttCTTT	ASO-0773
657	165142	165160	DES-0788	ATTtattgagtacaggCAG	ASO-0788
659	166220	166239	DES-0790	ATGgtctattaaatgtgCAA	ASO-0790
700	176162	176178	DES-0836	GTATagtatagatTAGT	ASO-0836
740	184958	184975	DES-0874	TTGTttagtattcaTTTC	ASO-0874
822	209852	209868	DES-0951	TGccactatgtcttCAA	ASO-0951
827	210416	210435	DES-0956	TTAgatattcattgttcAGT	ASO-0956
832	211327	211344	DES-0960	TTTTaattcaaccAGTA	ASO-0960
965	216411	216429	DES-1081	TTTAactttactataTTGG	ASO-1081
981	220916	220933	DES-1096	CAACaaccatttatAGCA	ASO-1096
982	220916	220934	DES-1097	TCaacaaccatttataGCA	ASO-1097
983	220917	220934	DES-1098	TCAACaaccatttatAGC	ASO-1098
984	220917	220935	DES-1099	GTCaacaaccatttataGC	ASO-1099
986	220918	220935	DES-1101	GTCACaacaaccatttaTAG	ASO-1101
989	220919	220936	DES-1104	TGTCaacaaccatttaTA	ASO-1104

FIG. 3 (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	DES No.	ASO with Design	ASO No.
1015	223970	223987	DES-1131	TCAAgtttccaaaCAAT	ASO-1131
1065	227969	227987	DES-1179	ATTAtctattatgttGTTT	ASO-1179
1071	229629	229646	DES-1185	TCTTttctattaccATTC	ASO-1185
1155	244274	244291	DES-1266	GTAGaatatagagaATGA	ASO-1266
1247	248053	248069	DES-1357	TCaagcagtctacaGTC	ASO-1357
1249	248054	248070	DES-1359	TTCaagcagtctacAGT	ASO-1359
1326	251988	252004	DES-1435	CAGttgtgtttattGGA	ASO-1435
1359	253080	253097	DES-1468	ATTAAattaattcccAAGA	ASO-1468
1363	253647	253664	DES-1472	CttttctgaattgaCCAG	ASO-1472
1371	253676	253691	DES-1480	ATCAAtctgaacacTCG	ASO-1480
1387	256887	256904	DES-1495	TttgtgtttatctGTGG	ASO-1495
1389	256888	256905	DES-1497	CttgtgtttatcTGTG	ASO-1497
1390	256889	256906	DES-1498	GCttgtgtttatctGT	ASO-1498
1409	258296	258315	DES-1517	TAAAtcactataattgaGGC	ASO-1517
1415	258714	258732	DES-1523	GCAAaagaccttattctTG	ASO-1523
1420	258716	258732	DES-1528	GCAAaagaccttatTCT	ASO-1528
1429	258966	258982	DES-1537	TCaggggtgtggaTTAC	ASO-1537
1475	261720	261737	DES-1582	TCATtattagttgtCATT	ASO-1582
1508	277421	277440	DES-1612	ATTGtatttcttgattTTAC	ASO-1612
1524	282021	282039	DES-1627	GTTattattattttcaGGT	ASO-1627

FIG. 3 (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	DES No.	ASO with Design	ASO No.
1530	283532	283549	DES-1632	TGTtagttttattctCAG	ASO-1632
1659	308035	308052	DES-1756	GatgtgaatttttcCAGT	ASO-1756
1662	308896	308912	DES-1759	AGGactgtgaattaCTA	ASO-1759
1663	309052	309069	DES-1760	ATCagaaaagcttcAACC	ASO-1760
1676	309428	309444	DES-1773	TATatacagtggtccCAT	ASO-1773
1685	309482	309501	DES-1782	CACAaatttattaactCTTA	ASO-1782
1686	309483	309501	DES-1783	CACAaatttattaacTCTT	ASO-1783
1687	309483	309502	DES-1784	TCACaaatttattaacTCTT	ASO-1784
1688	309484	309501	DES-1785	CACAaatttattaaCTCT	ASO-1785
1690	309484	309503	DES-1787	ATCAcaaatttattaaCTCT	ASO-1787

FIG. 4

ASO_NO	Single point, 25 μ M, HEK293, mRNA, %UTC	Single point, 500 nM, human iPSC-CM, mRNA, %UTC
ASO-0003	12.99	
ASO-0005	12.40	
ASO-0190	17.39	
ASO-0231	2.69	12.27
ASO-0261	7.88	43.24
ASO-0409	18.68	
ASO-0589	17.40	
ASO-0637	4.23	17.48
ASO-0643	10.78	
ASO-0649	8.04	
ASO-0788	13.01	
ASO-0790	11.02	
ASO-0956	5.12	15.39
ASO-1359	14.79	19.47
ASO-1435	6.76	12.42
ASO-1517	19.20	
ASO-1627	10.31	
ASO-1632	13.79	
ASO-1759	12.88	
ASO-1773	12.70	

FIG. 5

ASO_NO	CAMK2D/GAPDH (% ctrl)
ASO-0002	82
ASO-1104	56
ASO-1099	87
ASO-1096	69
ASO-1101	65
ASO-1097	77
ASO-1098	77
ASO-0951	75
ASO-1528	81
ASO-1756	76
ASO-1784	70
ASO-1472	83
ASO-1787	69
ASO-1760	71
ASO-1783	59
ASO-1782	74
ASO-1497	70
ASO-1498	67
ASO-1785	66
ASO-1523	73
ASO-1468	70
ASO-1357	88
ASO-1537	78
ASO-1495	70
ASO-1480	70

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2019/018947

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
- a. ☒ forming part of the international application as filed:
- ☒ in the form of an Annex C/ST.25 text file.
- ☐ on paper or in the form of an image file.
- b. ☐ furnished together with the international application under PCT Rule 13~~ter~~.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
- c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
- ☐ in the form of an Annex C/ST.25 text file (Rule 13~~ter~~.1(a)).
- ☐ on paper or in the form of an image file (Rule 13~~ter~~.1(b) and Administrative Instructions, Section 713).
2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2019/018947

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-24, 27-61(all partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/018947

A. CLASSIFICATION OF SUBJECT MATTER

INV. C12N15/113 A61K31/712 A61K31/7125
ADD. C07H21/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C12N A61K C07H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data, Sequence Search, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/059533 A2 (MYOGEN INC [US]; BACKS JOHANNES [US] ET AL.) 24 May 2007 (2007-05-24)	1,3,4,6, 19,30, 39,44, 46-48, 51-58,60
Y	the whole document	1-24, 27-61
Y	----- WO 2014/207232 A1 (SANTARIS PHARMA AS [DK]) 31 December 2014 (2014-12-31) the whole document ----- -/-	1-24, 27-61



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

23 May 2019

Date of mailing of the international search report

13/08/2019

Name and mailing address of the ISA/

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Authorized officer

Andres, Serge

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2019/018947

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE EMBL [Online] 27 August 2008 (2008-08-27), "Sequence 234707 from patent US 7374927.", XP002791545, retrieved from EBI accession no. EM PAT:GC034707 Database accession no. GC034707 sequence & US 2005/272080 A1 (PALMA JOHN F [US] ET AL) 8 December 2005 (2005-12-08) -----	1-7, 19-24, 28-32, 37,44,45
X	DATABASE EMBL [Online] 8 July 2015 (2015-07-08), "Sequence 96675 from Patent EP2850184.", XP002791546, retrieved from EBI accession no. EM PAT:JD784807 Database accession no. JD784807 sequence -& WO 2013/173637 A1 (RANA THERAPEUTICS INC [US]; GEN HOSPITAL CORP D B A [US]) 21 November 2013 (2013-11-21) -----	1-3,8, 20, 32-36, 39,53, 55,60
A	L.S. MAIER: "CaMKII[delta] overexpression in hypertrophy and heart failure: cellular consequences for excitation-contraction coupling", BRAZILIAN JOURNAL OF MEDICAL AND BIOLOGICAL RESEARCH, vol. 38, 2005, pages 1293-1302, XP055589943, the whole document -----	1-24, 27-61
A	ANIL PUROHIT ET AL: "Oxidized Ca²⁺ /Calmodulin-Dependent Protein Kinase II Triggers Atrial Fibrillation", CIRCULATION, vol. 128, no. 16, 15 October 2013 (2013-10-15), pages 1748-1757, XP055589939, US ISSN: 0009-7322, DOI: 10.1161/CIRCULATIONAHA.113.003313 the whole document -----	1-24, 27-61
A	WO 2004/046160 A2 (SANTARIS PHARMA AS [DK]; CHRISTENSEN SIGNE M [DK] ET AL.) 3 June 2004 (2004-06-03) cited in the application the whole document -----	1-24, 27-61
	-/--	

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2019/018947

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	INKYEOM KIM: "Ca²⁺+calmodulin-dependent protein kinase II-dependent activation of contractility in ferret aorta", JOURNAL OF PHYSIOLOGY, vol. 526, 2000, pages 367-374, XP055589754, the whole document -----	1-24, 27-61

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2019/018947

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2019/018947

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		US 2018237777 A1	23-08-2018
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		WO 2004046160 A2	03-06-2004

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-24, 27-61(all partially)

An antisense oligonucleotide targeted to a CAMK2D (pre-)messenger nucleic acid in the region defined by nucleotides 625-842 of SEQ ID 1, i.e. SEQ IDs 4-12 in Figure 1A. Modified forms thereof, compositions and kits comprising it. Its uses in the treatment of cardiac disorders.

2-1702. claims: 1-61(partially)

As for subject 1., but concerning each and every oligonucleotide defined by SEQ IDs 13-1713 in Figures 1A and 1B, as far as applicable.
