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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 ELECTRONICALLY VIA EFS-WEB

- [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. It is an object of the invention to go some way to satisfying this desire; and/or to at least provide the public with a useful choice.

[0004a] In this specification where reference has been made to patent specifications, other external documents, or other sources of information, this is generally for the purpose of providing a context for discussing the features of the invention. Unless specifically stated otherwise, reference to such external documents is not to be construed as an admission that such documents, or such sources of information, in any jurisdiction, are prior art, or form part of the common general knowledge in the art.

SUMMARY OF DISCLOSURE

[0004b] In a first aspect, the invention provides a an antisense oligonucleotide (ASO) comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length, wherein the ASO is capable of reducing a calcium/calmodulin-dependent protein kinase type II delta (*CAMK2D*) protein and/or *CAMK2D* transcript expression in a cell expressing the *CAMK2D* protein and/or *CAMK2D* transcript, and wherein the contiguous nucleotide sequence comprises the sequence set forth in SEQ ID NO: 1688, SEQ ID NO: 24, 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: 822, SEQ ID NO: 827, SEQ ID NO: 981, SEQ ID NO: 982, SEQ ID NO: 983, SEQ ID NO: 984, SEQ ID NO: 986, SEQ ID NO: 989, SEQ ID NO: 1247, SEQ ID NO: 1249, SEQ ID NO: 1326, SEQ ID NO: 1359, SEQ ID NO: 1363, SEQ ID NO: 1371, SEQ ID NO: 1387, SEQ ID NO: 1389, SEQ ID NO: 1390, SEQ ID NO: 1409, SEQ ID NO: 1415, SEQ ID NO: 1420, SEQ ID NO: 1429, SEQ ID NO: 1524, SEQ ID NO: 1530, SEQ ID NO: 1659, SEQ ID NO: 1662, SEQ ID NO: 1663, SEQ ID NO: 1676, SEQ ID NO: 1685, SEQ ID NO: 1686, SEQ ID NO: 1687, or SEQ ID NO: 1690;

and wherein the ASO comprises at least one nucleoside analog and is a gapmer.

[0004c] In a second aspect, the invention provides a conjugate comprising the ASO of the first aspect of the invention, wherein the ASO is covalently attached to at least one non-

nucleotide or non-polynucleotide moiety, 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.

[0004d] In a third aspect, the invention provides a pharmaceutical composition comprising the ASO of the first aspect of the invention or the conjugate of the second aspect of the invention, and a pharmaceutically acceptable diluent, carrier, salt, or adjuvant, wherein the pharmaceutically acceptable salt comprises a sodium salt, a potassium salt, an ammonium salt, or any combination thereof.

[0004e] In another aspect, the invention provides a kit comprising the ASO of the first aspect of the invention, the conjugate of the second aspect of the invention, or the pharmaceutical composition of the third aspect of the invention, and instructions for use.

[0004f] Also described is a diagnostic kit comprising the ASO of the first aspect of the invention, the conjugate of the second aspect of the invention, or the pharmaceutical composition of the third aspect of the invention, and instructions for use.

[0004g] In another aspect, the invention provides a method of inhibiting or reducing CAMK2D protein expression in a cell, comprising administering the ASO of the first aspect of the invention, the conjugate of the second aspect of the invention, or the pharmaceutical composition of the third aspect of the invention to the cell expressing CAMK2D protein, wherein the CAMK2D protein expression in the cell is inhibited or reduced after the administration.

[0004h] In another aspect, the invention provides 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 the first aspect of the invention, the conjugate of the second aspect of the invention, or the pharmaceutical composition of the third aspect of the invention to the subject.

[0004i] In another aspect, the invention provides use of the ASO of the first aspect of the invention, the conjugate of the second aspect of the invention, or the pharmaceutical composition of the third aspect of the invention for the manufacture of a medicament for the treatment of a cardiovascular disease or disorder in a subject in need thereof.

[0004j] In the description in this specification reference may be made to subject matter which is not within the scope of the claims of the current application. That subject matter should be readily identifiable by a person skilled in the art and may assist in putting into practice the invention as defined in the claims of this application.

- [0004k]** The term “comprising” as used in this specification and claims means “consisting at least in part of”. When interpreting statements in this specification and claims which include the term “comprising”, other features besides the features prefaced by this term in each statement can also be present. Related terms such as “comprise” and “comprises” are to be interpreted in similar manner.
- [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'-fluro-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 inhuman 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 (HF_rEF), a heart failure with preserved ejection fraction (HF_pEF), a heart failure with mid-range ejection fraction (HF_{mr}EF), 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, pulmonarily, 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 tacatattattactcctc (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 $-C(O)-NH_2$ group.
- [0051] The term "sulfonyl", alone or in combination, means the $-SO_2$ 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 $-N_3$ group.
- [0056] The term "nitro", alone or in combination, signifies the NO_2 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

LLLDDDDDDDDDDDDDDDDLL (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 DNAb, 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 DNAa, DNAt, DNA and DNAg. 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 DNAas DNAts DNAas DNAts DNAts DNAas DNAts DNAas DNAts DNAts DNAas DNAs DNAs DNAs OxyMCs OxyTs OxyMC.
- [0087] "Potency" is normally expressed as an IC₅₀ or EC₅₀ value, in μM, 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

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 → EPQTTVIHNPDGNGKE. The sequence of CAMK2D Isoform Delta 10 (identifier: Q13557-10) differs from the canonical sequence (SEQ ID NO: 3) as follows: 329-329: E → EPQTTVIHNPDGNGKE 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 → KKRKSSSSVQMMEPQTTVIHNPDGNGK. 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 \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. In other embodiments, the target region corresponds to nucleotides 1,498 – 59,655 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. In certain embodiments, the target region corresponds to nucleotides 61,917 – 104,625 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. In some embodiments, the target region corresponds to nucleotides 112,262 – 117,921 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. In some embodiments, the target region corresponds to nucleotides 119,540 – 135,119 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. In further embodiments, the target region corresponds to nucleotides 137,687 – 157,756 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. In certain embodiments, the target region corresponds to nucleotides 159,291 – 266,074 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. 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 → EPQTTVIHNPDG NKE; 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 → KINNKANVVTSPKENIPTPALEPQTTVIHNPDG NK; 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 a 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-thiozolo-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.

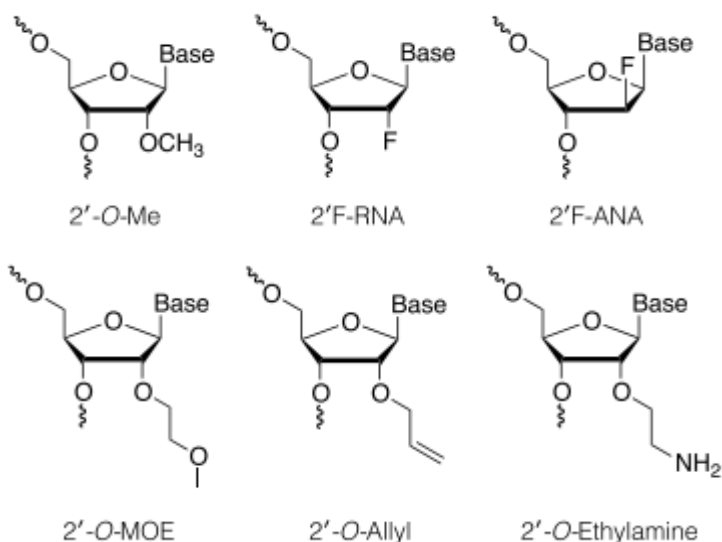
[0132] Such modifications include those where the ribose ring structure is modified, *e.g.* by replacement with a hexose ring (HNA), or a bicyclic ring, which typically have a biradical bridge between the C2' and C4' carbons on the ribose ring (LNA), or an unlinked ribose ring which typically lacks a 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'-Fluro-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).

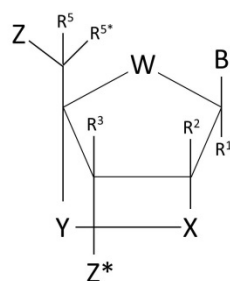
[0135] LNA nucleosides are 2'-sugar modified nucleosides which comprise a linker group (referred to as a biradical or a bridge) between C2' and C4' of the ribose sugar ring of a nucleoside (*i.e.*, 2'-4' bridge), which restricts or locks the conformation of the ribose ring. These nucleosides are also 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

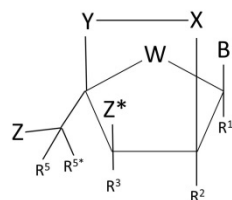
- [0138] X is oxygen, sulfur, $-\text{CR}^a\text{R}^b-$, $-\text{C}(\text{R}^a)=\text{C}(\text{R}^b)-$, $-\text{C}(=\text{CR}^a\text{R}^b)-$, $-\text{C}(\text{R}^a)=\text{N}$, $-\text{Si}(\text{R}^a)_2-$, $-\text{SO}_2-$, $-\text{NR}^a-$; $-\text{O}-\text{NR}^a-$, $-\text{NR}^a-\text{O}-$, $>\text{C}=\text{J}$, Se; $-\text{cPr}-$, $-\text{O}-\text{NR}^a-$, $\text{NR}^a-\text{CR}^a\text{R}^b-$, $-\text{N}(\text{R}^a)-\text{O}-$, or $\text{O}-\text{CR}^a\text{R}^b-$;
- [0139] Y is oxygen, sulfur, $-(\text{CR}^a\text{R}^b)_n-$, $-\text{CR}^a\text{R}^b-\text{O}-\text{CR}^a\text{R}^b-$, $-\text{C}(\text{R}^a)=\text{C}(\text{R}^b)-$, $-\text{C}(\text{R}^a)=\text{N}$, $-\text{Si}(\text{R}^a)_2-$, $-\text{SO}_2-$, $-\text{NR}^a-$, or $>\text{C}=\text{J}$ Se; $-\text{cPr}-$, $-\text{O}-\text{NR}^a-$, $-\text{O}-\text{CR}^a\text{R}^b-$, or $\text{NR}^a-\text{CR}^a\text{R}^b-$; wherein n is 1 or 2;
- [0140] with the proviso that $-\text{X}-\text{Y}-$ is not $-\text{O}-\text{O}-$, $\text{Si}(\text{R}^a)_2-\text{Si}(\text{R}^a)_2-$, $-\text{SO}_2-\text{SO}_2-$, $-\text{C}(\text{R}^a)=\text{C}(\text{R}^b)-\text{C}(\text{R}^a)=\text{C}(\text{R}^b)-$, $-\text{C}(\text{R}^a)=\text{N}-\text{C}(\text{R}^a)=\text{N}-$, $-\text{C}(\text{R}^a)=\text{N}-\text{C}(\text{R}^a)=\text{C}(\text{R}^b)-$, $-\text{C}(\text{R}^a)=\text{C}(\text{R}^b)-\text{C}(\text{R}^a)=\text{N}-$, or $-\text{Se}-\text{Se}-$;
- [0141] J is oxygen, sulfur, CH_2 , or $=\text{N}(\text{R}^a)$;
- [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, thioisulfidealkylsulfanyl, aryloxycarbonyl, aryloxy, arylcarbonyl, heteroaryl, heteroaryloxycarbonyl, heteroaryloxy, heteroarylcarbonyl, $-\text{OC}(=\text{X}^a)\text{R}^c$, $-\text{OC}(=\text{X}^a)\text{NR}^c\text{R}^d$ and $-\text{NR}^c\text{C}(=\text{X}^a)\text{NR}^c\text{R}^d$; 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 $-\text{NR}^c$;
- 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, $-\text{NR}^a-$, $-\text{CR}^a\text{R}^b-$ or $-\text{C}(=\text{CR}^a\text{R}^b)-$, particularly oxygen, sulfur, $-\text{NH}-$, $-\text{CH}_2-$ or $-\text{C}(=\text{CH}_2)-$, more particularly oxygen.
- [0144] In some embodiments, Y is $-\text{CR}^a\text{R}^b-$, $-\text{CR}^a\text{R}^b-\text{CR}^a\text{R}^b-$ or $-\text{CR}^a\text{R}^b-\text{CR}^a\text{R}^b-\text{CR}^a\text{R}^b-$, 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, $-\text{X}-\text{Y}-$ 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 $-\text{CH}_2\text{-O-CH}_3$, in particular, hydrogen, methyl and $-\text{CH}_2\text{-O-CH}_3$.
- [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, $-\text{X-Y-}$ is $-\text{O-CH}_2-$, $-\text{S-CH}_2-$, $-\text{S-CH}(\text{CH}_3)-$, $-\text{NH-CH}_2-$, $-\text{O-CH}_2\text{CH}_2-$, $-\text{O-CH}(\text{CH}_2\text{-O-CH}_3)-$, $-\text{O-CH}(\text{CH}_2\text{CH}_3)-$, $-\text{O-CH}(\text{CH}_3)-$, $-\text{O-CH}_2\text{-O-CH}_2-$, $-\text{O-CH}_2\text{-O-CH}_2-$, $-\text{CH}_2\text{-O-CH}_2-$, $-\text{C}(=\text{CH}_2)\text{CH}_2-$, $-\text{C}(=\text{CH}_2)\text{CH}(\text{CH}_3)-$, $-\text{N}(\text{-O-CH}_3)-$ or $-\text{N}(\text{CH}_3)-$;
- [0151] In some embodiments, $-\text{X-Y-}$ is $-\text{O-CR}^a\text{R}^b-$ wherein R^a and R^b are independently selected from the group consisting of hydrogen, alkyl and alkoxyalkyl, in particular, hydrogen, methyl and $-\text{CH}_2\text{-O-CH}_3$.
- [0152] In some embodiments, $-\text{X-Y-}$ is $-\text{O-CH}_2-$ or $-\text{O-CH}(\text{CH}_3)-$, particularly $-\text{O-CH}_2-$.
- [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:



β -D

or



α -L

Formula II

Formula III

wherein

W is selected from $-\text{O-}$, $-\text{S-}$, $-\text{N}(\text{R}^a)-$, $-\text{C}(\text{R}^a\text{R}^b)-$, in particular $-\text{O-}$;

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, R¹, R², R³, are all hydrogen at the same time, one of R⁵ and R^{5*} is hydrogen and the other one is azide..

- [0162] In some embodiments, -X-Y- is -O-CH₂-, W is oxygen and R¹, R², R³, R⁵ 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 R¹, R², R³, R⁵ 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 R¹, R², R³, R⁵ 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 R¹, R², R³, R⁵ 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, R¹, R², R³ are all hydrogen at the same time, one of R⁵ 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, R¹, R², R³ are all hydrogen at the same time, one of R⁵ 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 R¹, R², R³, R⁵ 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

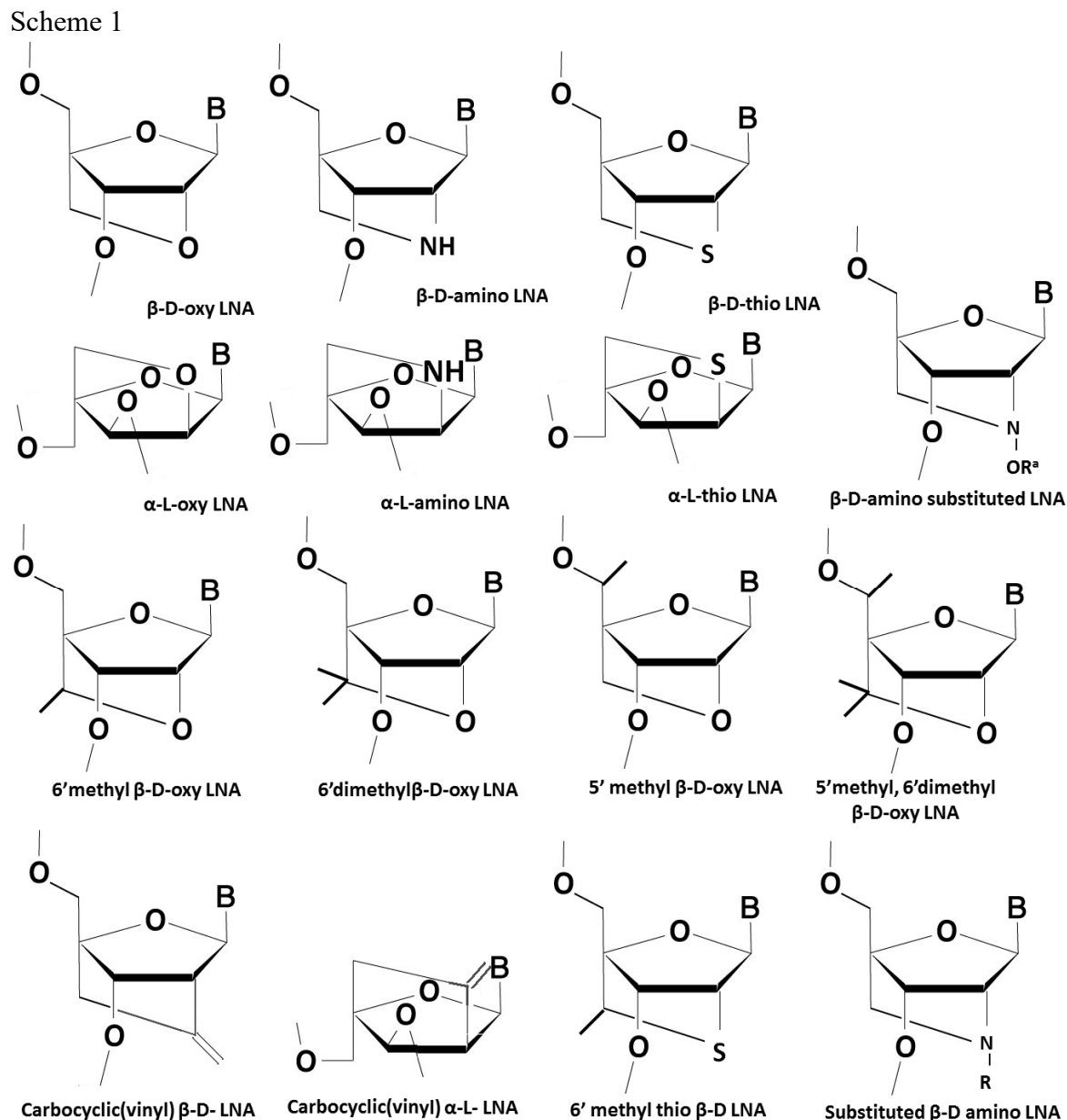
such embodiments, R^1 , R^2 and R^3 can be in particular hydrogen and $-X-Y-$ can be in particular $-O-CH_2-$ or $-O-CHC(R^a)_3-$, such as $-O-CH(CH_3)-$.

[0181] In some embodiments, $-X-Y-$ is $-CR^aR^b-O-CR^aR^b-$, such as $-CH_2-O-CH_2-$, 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 $-O-CH_2-O-CH_2-$, 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.



[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'-Fluro-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 in 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 carditis, 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 entireties.

[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 (qScript[™]MXLE 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 Viia[™] 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

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

The claims defining the invention are as follows:

1. An antisense oligonucleotide (ASO) comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length, wherein the ASO is capable of reducing a calcium/calmodulin-dependent protein kinase type II delta (*CAMK2D*) protein and/or *CAMK2D* transcript expression in a cell expressing the *CAMK2D* protein and/or *CAMK2D* transcript, and wherein the contiguous nucleotide sequence comprises the sequence set forth in SEQ ID NO: 1688, SEQ ID NO: 24, 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: 822, SEQ ID NO: 827, SEQ ID NO: 981, SEQ ID NO: 982, SEQ ID NO: 983, SEQ ID NO: 984, SEQ ID NO: 986, SEQ ID NO: 989, SEQ ID NO: 1247, SEQ ID NO: 1249, SEQ ID NO: 1326, SEQ ID NO: 1359, SEQ ID NO: 1363, SEQ ID NO: 1371, SEQ ID NO: 1387, SEQ ID NO: 1389, SEQ ID NO: 1390, SEQ ID NO: 1409, SEQ ID NO: 1415, SEQ ID NO: 1420, SEQ ID NO: 1429, SEQ ID NO: 1524, SEQ ID NO: 1530, SEQ ID NO: 1659, SEQ ID NO: 1662, SEQ ID NO: 1663, SEQ ID NO: 1676, SEQ ID NO: 1685, SEQ ID NO: 1686, SEQ ID NO: 1687, or SEQ ID NO: 1690; and wherein the ASO comprises at least one nucleoside analog and is a gapmer.
2. The ASO of claim 1, wherein the cell is a human cell.
3. The ASO of claim 2, wherein (i) 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% when the human cell is contacted with the ASO compared to *CAMK2D* protein expression in a corresponding human cell that is not contacted with the ASO; (ii) 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% when the human cell is contacted with the ASO compared to *CAMK2D* transcript expression in a corresponding human cell that is not contacted with the ASO; or (iii) both (i) and (ii).

4. The ASO of any one of claims 1 to 3, 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.
5. The ASO of any one of claims 1 to 4, 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'-fluro-RNA; 2'-fluoro-DNA; arabino nucleic acid (ANA); 2'-fluoro-ANA; or bicyclic nucleoside analog.
6. The ASO of any one of claims 1 to 5, wherein one or more of the nucleoside analog is a sugar modified nucleoside.
7. The ASO of claim 6, wherein the sugar modified nucleoside is an affinity enhancing 2' sugar modified nucleoside.
8. The ASO of claim 7, wherein the affinity enhancing 2' sugar modified nucleoside is a locked nucleic acid (LNA), 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.
9. The ASO of any one of claims 1 to 8, wherein the ASO comprises one or more 5'-methyl-cytosine nucleobases.
10. The ASO of any one of claims 1 to 9, 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.
11. The ASO of any one of claims 1 to 10, wherein the cell comprises a hiPSC-CM cell which is expressing the CAMK2D protein and/or *CAMK2D* transcript.
12. The ASO of any one of claims 1 to 11, wherein the nucleotide sequence comprises one or more modified internucleoside linkages.
13. The ASO of any one of claims 1 to 12, wherein the one or more modified internucleoside linkages is a phosphorothioate linkage.

14. The ASO of claim 12 or 13, wherein at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or 100% of internucleoside linkages are modified.
15. The ASO of claim 14, wherein each of the internucleoside linkages in the ASO is a phosphorothioate linkage.
16. A conjugate comprising the ASO of any one of claims 1 to 15, wherein the ASO is covalently attached to at least one non-nucleotide or non-polynucleotide moiety, 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.
17. A pharmaceutical composition comprising the ASO of any one of claims 1 to 15 or the conjugate of claim 16, and a pharmaceutically acceptable diluent, carrier, salt, or adjuvant, wherein the pharmaceutically acceptable salt comprises a sodium salt, a potassium salt, an ammonium salt, or any combination thereof.
18. The pharmaceutical composition of claim 17, which further comprises at least one further therapeutic agent, wherein the further therapeutic agent is a CAMK2D antagonist.
19. A kit comprising the ASO of any one of claims 1 to 15, the conjugate of claim 16, or the pharmaceutical composition of any one of claims 17 or 18, and instructions for use.
20. A method of inhibiting or reducing CAMK2D protein expression in a cell, comprising administering the ASO of any one of claims 1 to 15, the conjugate of claim 16, or the pharmaceutical composition of any one of claims 17 or 18 to the cell expressing CAMK2D protein, wherein the CAMK2D protein expression in the cell is inhibited or reduced after the administration.
21. The method of claim 20, wherein the cell is a cardiac cell.
22. The method of claim 21, wherein the cell is a hiPSC-CM.
23. 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 15, the conjugate of claim 16, or the pharmaceutical composition of any one of claims 17 or 18 to the subject.

24. Use of the ASO of any one of claims 1 to 15, the conjugate of claim 16, or the pharmaceutical composition of any one of claims 17 or 18 for the manufacture of a medicament for the treatment of a cardiovascular disease or disorder in a subject in need thereof.
25. The ASO of any one of claims 1 to 15, the conjugate of claim 16, or the pharmaceutical composition of any one of claims 17 or 18 when used in therapy of a cardiovascular disease or disorder in a subject in need thereof.
26. The method of claim 23, the use of claim 24, or the ASO when used of claim 27, 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.
27. The method, use, or ASO of claim 26, wherein the cardiovascular disease or disorder is heart failure, 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.
28. The method of any one of claims 23, 26, and 27, the use of any one of claims 24, 26, and 27, or the ASO when used of any one of claims 25 to 27, wherein the ASO, the conjugate, or the pharmaceutical composition is administered intracardially, orally, parenterally, intrathecally, intra-cerebroventricularly, pulmonarily, 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
			AATAATTAG	0111	DNAcs DNAas DNAAs DNAts DNAas DNAAs DNAts DNAts OxyAs OxyG
22	2497	2514	CCTGGAAACCA ATAATTA	ASO-0112	OxyMCs OxyMCs OxyTs DNAGs DNAas DNAas DNAas DNAas DNACs DNACs DNAas DNAas DNAts DNAas DNAas OxyTs OxyTs OxyA
23	2497	2515	CCCTGGAAACC AATAATTA	ASO-0113	OxyMCs OxyMCs DNACs DNAts DNAGs DNAGs DNAas DNAas DNACs DNACs DNAas DNAts DNAts OxyTs OxyTs OxyA
24	2566	2583	GATAATTTTGG CAGCATA	ASO-0002	OxyGs OxyAs DNAts DNAas DNAas DNAts DNAts DNAts DNAts DNAGs DNAGs DNACs DNAas DNAGs OxyMCs OxyAs OxyTs OxyA
25	2566	2584	TGATAATTTTG GCAGCATA	ASO-0003	OxyTs OxyGs OxyAs DNAts DNAas DNAas DNAts DNAts DNAts DNAts DNAGs DNAGs DNACs DNAGs DNACs OxyAs OxyTs OxyA
26	2566	2585	TTGATAATTTTG GCAGCATA	ASO-0004	OxyTs DNAts DNAGs DNAas DNAts DNAas DNAas DNAts DNAts DNAts DNAts DNAGs DNAGs DNACs DNAGs OxyMCs OxyAs OxyTs OxyA
27	2567	2584	TGATAATTTTG GCAGCAT	ASO-0005	OxyTs OxyGs OxyAs DNAts DNAas DNAas DNAts DNAts DNAts DNAts DNAGs DNAGs DNACs DNAGs OxyMCs OxyAs OxyT
28	2568	2585	TTGATAATTTTG GCAGCA	ASO-0006	OxyTs OxyTs OxyGs OxyAs DNAts DNAas DNAas DNAts DNAts DNAts DNAts DNAGs DNAGs DNACs DNAGs OxyMCs OxyA
29	2570	2586	GTTGATAATTTT GGCAG	ASO-0007	OxyGs OxyTs DNAts DNAGs DNAas DNAts DNAas DNAas DNAts DNAts DNAts DNAts DNAGs DNAGs OxyGs OxyMCs OxyAs OxyG
30	2571	2588	GTGTGATAAT TTTGGCA	ASO-0008	OxyGs OxyTs DNAGs DNAts DNAts DNAGs DNAas DNAts DNAas DNAas DNAts DNAts DNAts DNAts DNAGs DNAts DNAGs OxyGs OxyMCs OxyA
31	2571	2590	TGGTGTGATA ATTTTGGCA	ASO-0009	OxyTs OxyGs DNAGs DNAts DNAGs DNAts DNAts DNAts DNAGs DNAas DNAts DNAas DNAts DNAas DNACs DNAts DNAts DNAts DNAts DNAGs OxyMCs OxyA
32	2572	2590	TGGTGTGATA ATTTTGGC	ASO-0010	OxyTs OxyGs DNAGs DNAts DNAGs DNAts DNAts DNAts DNAGs DNAas DNAts DNAas DNAts DNAas DNACs DNAts DNAts DNAts DNAts DNAGs OxyGs OxyMC
33	2572	2591	TTGGTGTGAT AATTTTGGC	ASO-0011	OxyTs DNAts DNAGs DNAGs DNAts DNAGs DNAts DNAts DNAts DNAGs DNAas DNAts DNAs DNACs DNAts DNAts DNAts DNAts DNAGs DNAGs OxyGs OxyMC
34	2574	2592	TTTGGTGTGA TAATTTTG	ASO-0114	OxyTs OxyTs OxyTs OxyGs DNAGs DNAts DNAGs DNAts DNAts DNAts DNAGs DNAas DNAts DNAs DNACs DNAts DNAts DNAts DNAts DNAGs DNAGs OxyTs OxyTs OxyG
35	2575	2594	TTTTTGGTGTT GATAATTTT	ASO-0115	OxyTs OxyTs OxyTs DNAts DNAGs DNAGs DNAts DNAts DNAts DNAGs DNAts DNAts DNAts DNAGs DNAGs DNACs DNAts DNAts DNAts DNAts DNAGs DNAts DNAGs OxyTs OxyTs OxyT
36	2576	2594	TTTTTGGTGTT GATAATTTT	ASO-0116	OxyTs OxyTs OxyTs DNAts DNAGs DNAGs DNAts DNAts DNAts DNAGs DNAts DNAts DNAts DNAGs DNAGs DNACs DNAts DNAts DNAts DNAts DNAGs DNAts DNAGs OxyTs OxyTs OxyT
37	2576	2595	CTTTTGGTGT TGATAATTT	ASO-0117	OxyMCs OxyTs OxyTs OxyTs DNAts DNAts DNAts DNAts DNAGs DNAGs DNAts DNAts DNAts DNAts DNAGs DNAGs DNACs DNAts DNAts DNAts DNAts DNAGs DNAts DNAGs OxyTs OxyTs OxyT
38	2577	2595	CTTTTGGTGT TGATAATTT	ASO-0118	OxyMCs OxyTs OxyTs OxyTs DNAts DNAts DNAts DNAts DNAGs DNAGs DNAts DNAts DNAts DNAts DNAGs DNAGs DNACs DNAts DNAts DNAts DNAts DNAGs DNAts DNAGs OxyTs OxyTs OxyT
39	2577	2596	GCTTTTGGTG TTGATAATTT	ASO-0119	OxyGs OxyMCs OxyTs DNAts DNAts DNAts DNAts DNAGs DNAGs DNAts DNAts DNAts DNAts DNAGs DNAGs DNACs DNAts DNAts DNAts DNAts DNAGs DNAts DNAGs OxyTs OxyTs OxyT
40	2578	2595	CTTTTGGTGT	ASO-	OxyMCs OxyTs OxyTs DNAts DNAts DNAts DNAts DNAGs DNAGs DNAts DNAts DNAts DNAts DNAGs DNAGs DNACs DNAts DNAts DNAts DNAts DNAGs DNAts DNAGs OxyTs OxyTs OxyT

FIG. 1A (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
60	4982	4998	ACAATACTT TGACCATTTTG AAGGAA	0139 ASO-0140	DNAas DNAcs DNAas DNAcs OxyAs OxyMCs OxyTs OxyT OxyTs OxyGs OxyAs OxyMCs DNAcs DNAas DNats DNats DNats DNats DNats DNags
61	5256	5274	GATTTATTTCA GTATTTG	ASO-0141	OxyGs OxyAs OxyTs OxyTs DNats DNAas DNats DNats DNats DNats DNats DNacs DNAas DNags DNats DNAas OxyTs OxyTs OxyTs OxyG
62	5798	5814	TATGGTATGTA TGACTA	ASO-0142	OxyTs OxyAs OxyTs OxyGs DNags DNats DNAas DNats DNats DNats DNats DNags DNats DNags DNAas OxyMCs OxyTs OxyA
63	6204	6221	ACTTTATATAAT TTGACA	ASO-0143	OxyAs OxyMCs OxyTs OxyTs DNats DNAas DNats DNats DNats DNats DNags DNats DNats DNats OxyGs OxyAs OxyMCs OxyA
64	6209	6228	TTCTTGGACTT TATATAAT	ASO-0012	OxyTs OxyTs OxyMCs OxyTs DNats DNags DNags DNAas DNacs DNats DNats DNats DNAas DNats DNAas DNats OxyAs OxyAs OxyT
65	6211	6228	TTCTTGGACTT TATATAA	ASO-0144	OxyTs OxyTs OxyMCs OxyTs DNats DNags DNags DNAas DNacs DNats DNats DNats DNAas DNats OxyAs OxyTs OxyAs OxyA
66	6797	6813	GTAGCAAGAAT TAGTTT	ASO-0145	OxyGs OxyTs OxyAs OxyGs DNacs DNAas DNAas DNags DNags DNAas DNags DNats DNAas OxyGs OxyTs OxyTs OxyT
67	7148	7164	TTAATATCAAG ACCTAT	ASO-0146	OxyTs OxyTs OxyAs OxyAs DNats DNAas DNats DNacs DNAas DNAas DNags DNAas DNAcs OxyMCs OxyTs OxyAs OxyT
68	7248	7264	CTGGAAGTGTG GATATA	ASO-0147	OxyMCs OxyTs OxyGs OxyGs DNAas DNAas DNags DNats DNags DNats DNats DNags DNags DNAas DNats DNAas OxyTs OxyA
69	7738	7756	TGTAACCTAAA ATCTTTAA	ASO-0148	OxyTs OxyGs OxyTs OxyAs DNAas DNacs DNats DNats DNats DNats DNags DNAas DNats DNacs DNats OxyTs OxyTs OxyAs OxyA
70	7987	8006	TAGTACTTTATT CATGCTTG	ASO-0149	OxyTs DNAas DNags DNats DNAas DNacs DNats DNats DNats DNats DNats DNats DNacs DNAas DNats DNags OxyMCs OxyTs OxyTs OxyG
71	8068	8085	TTTTCTTTAAATC AATACT	ASO-0150	OxyTs OxyTs OxyTs OxyMCs DNats DNats DNats DNats DNAas DNags DNats DNacs DNAas DNAas OxyTs OxyAs OxyMCs OxyT
72	8560	8577	AGGAGTTAAAA TGAGACT	ASO-0151	OxyAs OxyGs OxyGs OxyAs DNags DNats DNats DNats DNAas DNAas DNags DNats DNags DNAas DNags OxyAs OxyMCs OxyT
73	8994	9012	AATGGGAAGAT AAAATGTA	ASO-0152	OxyAs OxyAs OxyTs OxyGs DNags DNags DNAas DNAas DNags DNags DNats DNAas DNAas DNAas OxyTs OxyGs OxyTs OxyA
74	9181	9199	AACCATTTTCC TACCATTT	ASO-0153	OxyAs OxyAs OxyMCs DNacs DNats DNats DNats DNats DNats DNats DNacs DNats DNAas DNacs DNacs DNAas DNats DNats OxyTs OxyT
75	9246	9263	TGTATAGTGAG ATATTTT	ASO-0154	OxyTs OxyGs OxyTs OxyAs DNats DNAas DNags DNats DNats DNags DNags DNAas DNats DNAas OxyTs OxyTs OxyTs OxyT
76	9752	9768	AAGTAGGGAGA ATGTTCC	ASO-0155	OxyAs OxyAs OxyGs OxyTs DNags DNags DNags DNags DNags DNags DNags DNAas DNats OxyGs OxyTs OxyTs OxyMC
77	10016	10033	CTAATATATGA GAAGTAA	ASO-0156	OxyMCs OxyTs OxyAs OxyAs DNats DNats DNAas DNats DNats DNats DNags DNAas DNags DNAas DNAas OxyGs OxyTs OxyAs OxyA
78	10465	10484	TTCATGCTTTAT	ASO-	OxyTs OxyTs OxyMCs OxyAs DNats DNags DNacs DNats DNats DNats 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
			TTCAATGT	0157	DNAts DNAts DNAts DNAts DNAts DNAts OxyGs OxyT
79	10665	10684	GAAATTCAAAT TATCCAGAA	ASO-0158	OxyGs OxyAs OxyAs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
80	10856	10874	AGAGTTCAAAT TGGGATGG	ASO-0013	OxyAs DNAGs DNAGs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
81	10862	10881	AGAAAAGAGAG TTCAAAATTG	ASO-0159	OxyAs OxyGs OxyAs OxyAs DNAGs DNAGs DNAts DNAts DNAts DNAts DNAts DNAts
82	11520	11539	TTATTCAAAATA CAACCTCA	ASO-0160	OxyTs OxyTs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
83	11881	11897	TATTAATTACTG TGCCA	ASO-0161	OxyTs OxyAs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
84	12135	12154	AGAAAATAC TG AATTATACA	ASO-0162	OxyAs OxyGs OxyAs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
85	12329	12346	GTAGAAATGGAT CAAAAATT	ASO-0163	OxyGs OxyTs OxyAs OxyGs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
86	12722	12741	GAATAGGTATT AGAAAATATG	ASO-0164	OxyGs OxyAs OxyAs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
87	13070	13089	TATTTATGATA TGATTATT	ASO-0165	OxyTs OxyAs OxyTs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
88	13270	13286	TTGCAGTACAT AGGGAA	ASO-0166	OxyTs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
89	13559	13573	CTCGCATACTT TGTC	ASO-0167	OxyMCs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
90	13722	13740	TAATTTTACTTG ACTTTTAC	ASO-0168	OxyTs OxyAs OxyAs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
91	14250	14266	TACTTAGTCAC TCTTAA	ASO-0169	OxyTs OxyAs OxyMCs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
92	14390	14407	ATCTTAGTTTTG GATTTTG	ASO-0170	OxyAs OxyTs OxyMCs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
93	14747	14766	ATTTAAATCGA AGTTGTCIT	ASO-0171	OxyAs OxyTs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
94	14764	14780	TAGGGAGGCTA AATATT	ASO-0172	OxyTs OxyAs OxyGs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
95	15458	15475	TGGACATTATG ATTATCA	ASO-0173	OxyTs OxyGs OxyGs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
96	15470	15487	ATTGGGAGATT ATGGACA	ASO-0014	OxyAs OxyTs OxyTs OxyGs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
97	15644	15663	TTTGGTTTGGG	ASO-	OxyTs OxyTs OxyTs 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
98	15669	15686	TTATTTCAA TGGTATTTCTA AGTTTAG	0174 ASO-0175	DNAts DNAAAs DNAAAs DNAAAs OxyTs OxyMCs OxyAs OxyA OxyTs OxyGs OxyTs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs OxyAs OxyG
99	16298	16315	TTCCTCATTAAAT AGTAGA	ASO-0176	OxyTs OxyTs OxyMCs OxyMCs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs OxyGs OxyAs OxyA
100	16504	16523	ACTTTCCTCTG ATACTGAAG	ASO-0177	OxyAs OxyMCs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs OxyGs OxyAs OxyG
101	16574	16590	CCTCAATGTTA CCTTTC	ASO-0178	OxyMCs OxyMCs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs OxyTs OxyMC
102	17218	17235	ACAGTTTTATA GATAAGA	ASO-0179	OxyAs OxyMCs OxyAs OxyGs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs OxyAs OxyGs OxyA
103	17404	17419	TATCTAAACT AGCCC	ASO-0180	OxyTs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs OxyMCs OxyMCs OxyMC
104	17654	17671	AATGCTAGG TTCTGAG	ASO-0181	OxyAs OxyAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs OxyTs OxyGs OxyAs OxyG
105	17708	17725	AGTCATTAATT CTTTATC	ASO-0182	OxyAs OxyGs OxyTs OxyMCs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs OxyTs OxyAs OxyTs OxyMC
106	19162	19179	TGTAAGCAAGG CACAAGA	ASO-0183	OxyTs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs OxyAs OxyAs OxyGs OxyA
107	19372	19388	ACACCTACCTC AATAAC	ASO-0184	OxyAs OxyMCs OxyAs OxyMCs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs OxyAs OxyAs OxyA OxyMC
108	19703	19720	CAATATAAGAC ATGAGAG	ASO-0185	OxyMCs OxyAs OxyAs OxyTs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs OxyAs OxyGs OxyAs OxyG
109	19868	19884	CTTATCTATCC AAATGC	ASO-0186	OxyMCs OxyTs OxyTs OxyAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs OxyTs OxyGs OxyMC
110	20246	20263	ATCCTATCACA TTACTTC	ASO-0187	OxyAs OxyTs OxyMCs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs OxyTs OxyTs OxyMC
111	20497	20515	TGTTCTATTTTA TTAGTAC	ASO-0188	OxyTs OxyGs OxyTs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs OxyGs OxyTs OxyAs OxyMC
112	21423	21441	GAGAGGTAAGA ATGATGAA	ASO-0015	OxyGs OxyAs OxyGs OxyAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs OxyGs OxyAs OxyA
113	21444	21461	CTGGGTTTGG GGAGAGG	ASO-0189	OxyMCs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs OxyGs OxyG
114	21808	21826	TCCTTTGTATTT CTTGAAT	ASO-0190	OxyTs OxyMCs OxyMCs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs OxyAs OxyAs OxyT
115	22289	22308	ATAGGTTGATG TTTTCTTGA	ASO-0191	OxyAs OxyTs OxyAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs DNAAAs OxyGs OxyA
116	22294	22310	TAATAGGTTGA	ASO-	OxyTs OxyAs OxyAs OxyTs 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
			TGTTTC	0192	DNAts DNAGs OxyTs OxyTs OxyTs OxyMC
117	22342	22358	GCCAAATTCCTT TCTAGT	ASO-0193	OxyGs OxyMCs DNACs DNAas DNAas DNAts DNAts DNAts DNACs DNAts DNAts DNAts DNACs DNAts DNAts DNAas OxyGs OxyT
118	22992	23011	AAAATAAATAA CACATCCCA	ASO-0194	OxyAs OxyAs OxyAs DNAts DNAas DNAas DNAts DNAts DNAts DNAas DNACs DNAas DNACs DNAas DNAts OxyMCs OxyMCs OxyMCs OxyA
119	23373	23392	TTTTAATGTGTT ATTATCCT	ASO-0195	OxyTs OxyTs DNAts DNAts DNAas DNAas DNAts DNAts DNAts DNAts DNAts DNAas DNAts DNAts DNAas OxyTs OxyMCs OxyMCs OxyT
120	23595	23614	GACCTAAATAT TATACAAGA	ASO-0196	OxyGs OxyAs OxyMCs OxyMCs DNAts DNAts DNAas DNAas DNAts DNAts DNAts DNAts DNAas DNAts DNAas DNACs OxyAs OxyAs OxyGs OxyA
121	23727	23744	TGAAGAATCTA AATATGT	ASO-0197	OxyTs OxyGs OxyAs OxyAs DNAGs DNAas DNAas DNAts DNAts DNAts DNAas DNAas DNAts OxyAs OxyTs OxyGs OxyT
122	24150	24166	ATCATCTGGTT GTGAAT	ASO-0198	OxyAs OxyTs OxyMCs OxyAs DNAts DNACs DNAts DNAGs DNAGs DNAts DNAGs DNAts OxyGs OxyAs OxyAs OxyT
123	24404	24423	CTTAATGAATAT AGAGTTCT	ASO-0016	OxyMCs OxyTs OxyTs OxyAs DNAas DNAts DNAGs DNAas DNAts DNAts DNAas DNAts DNAas DNAGs DNAas DNAGs OxyTs OxyTs OxyMCs OxyT
124	24407	24424	ACTTAATGAAT ATAGAGT	ASO-0199	OxyAs OxyMCs OxyTs OxyTs DNAas DNAas DNAts DNAts DNAGs DNAas DNAts DNAas DNAts DNAas OxyGs OxyAs OxyGs OxyT
125	24747	24764	TTAATAATCATA TATACC	ASO-0200	OxyTs OxyTs OxyAs OxyAs DNAts DNAas DNAts DNAts DNACs DNAts DNAas DNAts DNAas OxyTs OxyAs OxyMCs OxyMC
126	24874	24891	CATAATAATAG TATTTGG	ASO-0201	OxyMCs OxyAs OxyTs OxyAs DNAas DNAts DNAts DNAas DNAts DNAts DNAGs DNAts DNAas DNAts OxyTs OxyTs OxyGs OxyG
127	26041	26060	AATAAGAAATTT CCATAACTT	ASO-0202	OxyAs OxyAs OxyTs OxyAs DNAas DNAGs DNAas DNAts DNAts DNAts DNACs DNACs DNAas DNAts DNAas OxyAs OxyMCs OxyTs OxyT
128	26381	26397	GAGATCAATAA AGTATA	ASO-0203	OxyGs OxyAs OxyGs OxyAs DNAts DNACs DNAas DNAts DNAts DNAts DNAas DNAGs OxyTs OxyAs OxyTs OxyA
129	27197	27215	ATTTGAAAGGC TGATGGGA	ASO-0204	OxyAs DNAts DNAts DNAts DNAGs DNAas DNAas DNAts DNAGs DNAts DNAts DNAGs DNAas DNAts DNAGs OxyGs OxyGs OxyA
130	27363	27380	ATGTAAATCAA ATAGTTC	ASO-0205	OxyAs OxyTs OxyGs OxyTs DNAas DNAas DNAts DNAts DNACs DNAas DNAas DNAts DNAas OxyGs OxyTs OxyTs OxyMC
131	27712	27731	GAAGAGTAATT TAAAAGCTT	ASO-0206	OxyGs OxyAs OxyAs OxyGs DNAas DNAGs DNAts DNAts DNAas DNAts DNAts DNAas DNAas DNAas OxyGs OxyGs OxyMCs OxyTs OxyT
132	28063	28080	TTGACATCTGA CTTTTAA	ASO-0207	OxyTs OxyTs OxyGs DNAas DNACs DNAas DNAts DNAts DNAts DNAts DNACs DNAts DNAts OxyTs OxyTs OxyAs OxyA
133	28249	28265	AGATATAGTTA CTTAAC	ASO-0208	OxyAs OxyGs OxyAs OxyTs DNAas DNAts DNAas DNAts DNAts DNAts DNACs DNAts OxyTs OxyAs OxyAs OxyMC
134	28369	28385	GTCAAAGTTATC AGGTAT	ASO-0209	OxyGs OxyTs OxyMCs OxyAs DNAas DNAGs DNAts DNAts DNAts DNAts DNACs DNAas DNAGs DNAGs OxyTs OxyAs OxyT
135	28782	28801	GACAGAGACTG	ASO-	OxyGs OxyAs OxyMCs OxyAs DNAGs 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
136	28857	28873	AAATGATAA CTGGAGAAAGTT TTGAAG	0017 ASO-0210	DNAGs DNAas DNAas DNAts DNAGs DNAGs OxyTs OxyAs OxyA OxymCs OxyTs OxyGs DNAas DNAGs DNAGs DNAas DNAGs DNAts DNAts DNAts DNAts DNAGs OxyAs OxyG
137	28897	28915	TAAAAGAGTTT GCATAGGA	ASO-0211	OxyTs OxyAs OxyAs DNAas DNAGs DNAGs DNAGs DNAts DNAts DNAGs DNAGs DNAts DNAts DNAas OxyGs OxyG
138	29430	29446	AATATTATTGGT TGAGC	ASO-0212	OxyAs OxyAs OxyTs OxyAs DNAts DNAts DNAts DNAts DNAGs DNAGs DNAts DNAts OxyGs OxyAs OxyGs OxyMC
139	30003	30020	TCTCATAAACTT CATTCC	ASO-0213	OxyTs OxymCs DNAts DNAGs DNAas DNAts DNAas DNAGs DNAGs DNAts DNAts DNAGs DNAts DNAts OxyTs OxymCs OxyMC
140	30007	30024	CCTCTCTCATA AACTTCA	ASO-0214	OxymCs DNAGs DNAts DNAGs DNAts DNAGs DNAts DNAGs DNAts DNAas DNAas DNAas DNAGs OxyTs OxyTs OxymCs OxyA
141	30420	30439	ACATTATCTTCA TTAAACAA	ASO-0215	OxyAs OxymCs OxyAs OxyTs DNAts DNAas DNAts DNAGs DNAts DNAGs DNAas DNAts DNAts DNAas DNAas OxyAs OxymCs OxyAs OxyA
142	30634	30653	ATAACTCTGTG TATTAGCAT	ASO-0216	OxyAs DNAts DNAas DNAGs DNAts DNAts DNAGs DNAts DNAGs DNAts DNAas DNAts DNAts DNAas OxyGs OxymCs OxyAs OxyT
143	30870	30888	CAGATTTTATTT GTCATTC	ASO-0217	OxymCs OxyAs OxyGs DNAas DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAGs DNAts DNAGs OxyAs OxyTs OxyTs OxyMC
144	31207	31225	AGAAAAGAATG AAACTGTT	ASO-0218	OxyAs OxyGs OxyAs OxyAs DNAas DNAGs DNAGs DNAGs DNAts DNAGs DNAas DNAas DNAas DNAGs OxyTs OxyGs OxyTs OxyT
145	31565	31582	TGAATTAAAAT GAGAGTA	ASO-0219	OxyTs OxyGs OxyAs OxyAs DNAts DNAts DNAts DNAas DNAas DNAts DNAGs DNAas DNAGs OxyAs OxyGs OxyTs OxyA
146	31711	31728	TAACCTTTTCAG ATGGCAT	ASO-0220	OxyTs OxyAs OxyAs OxymCs DNAts DNAts DNAts DNAts DNAts DNAts DNAas DNAts DNAGs DNAGs OxymCs OxyAs OxyT
147	32776	32793	TAAGTCATCAT CATCGTC	ASO-0221	OxyTs OxyAs OxyAs OxyGs DNAts DNAGs DNAts DNAts DNAGs DNAts DNAGs DNAas DNAts DNAGs DNAGs OxyTs OxyMC
148	33003	33022	AAAGAACAGTC CTAATACAA	ASO-0222	OxyAs OxyAs OxyAs OxyGs DNAas DNAGs DNAGs DNAGs DNAts DNAGs DNAGs DNAts DNAGs DNAts DNAts OxyAs OxymCs OxyAs OxyA
149	33008	33024	CCAAAGAACAG TCCTAA	ASO-0223	OxymCs OxymCs OxyAs DNAas DNAGs DNAGs DNAas DNAGs DNAGs DNAGs DNAts DNAGs DNAGs OxyTs OxyAs OxyA
150	33577	33596	ATAAGTAACAA CACAGATGA	ASO-0224	OxyAs OxyTs OxyAs DNAas DNAGs DNAts DNAas DNAGs DNAGs DNAts DNAGs DNAts DNAGs DNAts DNAGs OxyAs OxyTs OxyGs OxyA
151	33580	33598	CAATAAGTAAC AACACAGA	ASO-0018	OxymCs OxyAs OxyTs DNAas DNAGs DNAGs DNAts DNAts DNAGs DNAts DNAGs DNAts DNAGs DNAts DNAas OxymCs OxyAs OxyGs OxyA
152	34058	34077	GCAAAAAGTCTT AAATACTTC	ASO-0225	OxyGs OxymCs OxyAs OxyAs DNAas DNAGs DNAGs DNAts DNAts DNAts DNAts DNAas DNAts DNAts DNAts DNAas OxymCs OxyTs OxyTs OxyMC
153	34060	34077	GCAAAAAGTCTT AAATACT	ASO-0226	OxyGs OxymCs OxyAs OxyAs DNAas DNAGs DNAGs DNAts DNAts DNAts DNAts DNAas DNAts DNAts OxyTs OxyAs OxymCs OxyT
154	34238	34256	ATCAATATTTAAA	ASO-	OxyAs OxyTs OxymCs OxyAs DNAas DNAts DNAts DNAts DNAts DNAts DNAas 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
174	40947	40963	GAAATAGCA TGTTAAGATGT AATTGG	0245 0246	DNAGs DNAas DNAas DNAas DNATs OxyAs OxyGs OxyMCs OxyA OxyTs OxyGs OxyTs OxyTs DNAas DNAas DNAGs DNAas DNATs DNAGs DNATs
175	40998	41017	AACATATTAAG TACAAGTGA	ASO-0020	OxyAs OxyAs OxyMCs OxyAs DNATs DNAas DNATs DNATs DNAas DNAas DNAGs DNATs DNAas DNACs DNAas DNAas OxyGs OxyTs OxyGs OxyA
176	40999	41016	ACATATTAAGT ACAAGTG	ASO-0247	OxyAs OxyMCs OxyAs OxyTs DNAas DNATs DNATs DNATs DNAas DNAGs DNATs DNAas DNACs DNAas OxyAs OxyGs OxyTs OxyG
177	41740	41757	ACAAATCATT GTCTATT	ASO-0248	OxyAs OxyMCs OxyAs OxyAs DNAas DNATs DNATs DNACs DNAas DNATs DNAas DNAGs DNATs DNACs OxyTs OxyAs OxyTs OxyT
178	41742	41758	CACAAATCATT AGCTA	ASO-0249	OxyMCs OxyAs OxyMCs OxyAs DNAas DNATs DNATs DNACs DNAas DNATs DNATs DNAas DNAGs OxyTs OxyMCs OxyTs OxyA
179	42527	42546	CATATTATGCT GTTTTCTG	ASO-0250	OxyMCs OxyAs DNATs DNAas DNATs DNATs DNATs DNAGs DNACs DNATs DNAGs DNATs DNATs DNATs DNATs DNACs DNACs OxyTs OxyG
180	42531	42548	TTCATATTATGC TGTTTT	ASO-0251	OxyTs OxyTs OxyMCs OxyAs DNATs DNAas DNATs DNATs DNATs DNAGs DNACs DNATs DNAGs OxyTs OxyTs OxyTs OxyT
181	42952	42969	CAGTGAAAATC TAAATTA	ASO-0252	OxyMCs OxyAs OxyGs OxyTs DNAGs DNAas DNAas DNAas DNAas DNATs DNACs DNATs DNAas DNAas OxyAs OxyTs OxyTs OxyA
182	43391	43408	AATTTGGGAAG GTTTAGA	ASO-0253	OxyAs OxyAs OxyTs OxyTs DNATs DNAGs DNAGs DNAGs DNAas DNAGs DNAGs DNATs DNATs OxyTs OxyAs OxyGs OxyA
183	43393	43410	GCAATTTGGGA AGGTTTA	ASO-0254	OxyGs OxyMCs DNAas DNAas DNATs DNATs DNATs DNAGs DNAGs DNAGs DNAas DNAas DNAGs DNAGs OxyTs OxyTs OxyTs OxyA
184	43931	43949	AGGAGAAGACT TAAATTTT	ASO-0255	OxyAs OxyGs OxyAs DNAGs DNAas DNATs DNATs DNAGs DNAas DNATs DNATs DNAas DNAas OxyTs OxyTs OxyTs OxyT
185	44247	44264	GTGGAGAGAGT TGAATTT	ASO-0256	OxyGs OxyTs OxyGs DNAGs DNAas DNAGs DNAas DNAGs DNAas DNAGs DNATs DNATs DNAGs DNAas OxyAs OxyTs OxyTs OxyT
186	44345	44361	AAAGTGAGTGT TAAAGGT	ASO-0257	OxyAs OxyAs OxyAs OxyGs DNATs DNAGs DNAas DNAGs DNATs DNAGs DNATs DNAas OxyAs OxyGs OxyGs OxyT
187	44714	44731	ATTTTAATTTGT GAGTAG	ASO-0258	OxyAs OxyTs OxyTs DNATs DNAas DNATs DNATs DNATs DNATs DNAGs DNATs DNAGs DNAas OxyGs OxyTs OxyAs OxyG
188	44982	45001	AAATTGAACAA GTGAATAGT	ASO-0259	OxyAs OxyAs OxyTs DNATs DNAGs DNAas DNAas DNATs DNATs DNAGs DNAGs DNATs DNAGs DNAas DNATs OxyTs OxyAs OxyGs OxyT
189	45144	45160	AGTGAACTTAG TGATAT	ASO-0260	OxyAs OxyGs OxyTs OxyGs DNAas DNATs DNATs DNATs DNATs DNAGs DNATs DNAGs OxyTs OxyAs OxyT
190	46568	46586	TGTTTCTAGGT TTTCATTTT	ASO-0261	OxyTs OxyGs OxyTs DNATs DNATs DNATs DNATs DNATs DNAGs DNATs DNATs DNATs DNACs DNAas DNATs OxyTs OxyTs OxyT
191	46816	46835	TACTTTACATTC TTTTATGT	ASO-0262	OxyTs OxyAs OxyMCs OxyTs DNATs DNATs DNATs DNATs DNATs DNATs DNACs DNATs DNATs DNATs DNATs DNAas DNATs OxyGs OxyT
192	46826	46845	TCTTCTCAATTA	ASO-	OxyTs OxyMCs DNATs DNATs DNATs DNATs DNATs DNAas 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 DNAts
194	47167	47183	CTAGTCATTTC TTTTGGG	ASO-0264	OxyMCs DNAts DNAas DNAGs DNAts DNAts DNAcs DNAts DNAts DNAts DNAts
195	47770	47788	TAATTTATCATG TATTCAG	ASO-0265	OxyTs OxyAs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
196	47915	47931	CATTACCACTA TATCAT	ASO-0266	OxyMCs OxyAs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
197	48166	48183	TTTTCTTATCAA TATGCA	ASO-0267	OxyTs OxyTs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
198	48838	48855	TGAATAATGTTT TACTAA	ASO-0268	OxyTs OxyGs OxyAs OxyAs DNAts DNAts DNAas DNAts DNAts DNAts DNAts DNAts
199	49269	49286	ATCTGTGAATA CTTTGAA	ASO-0269	OxyAs OxyTs OxyMCs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
200	49272	49289	GAAATCTGTGA ATACTTT	ASO-0270	OxyGs OxyAs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
201	50015	50034	TATACTTGTTCT CTCACATTT	ASO-0271	OxyTs OxyAs DNAts DNAas DNAts DNAts DNAts DNAts DNAts DNAts DNAts
202	50024	50041	CATTAAATATAC TTGTTC	ASO-0272	OxyMCs OxyAs OxyTs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
203	50265	50283	ATGAAAATAAA TGATCTAG	ASO-0273	OxyAs OxyTs OxyGs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
204	50610	50628	TCATTCTTAAAA TACTAAC	ASO-0274	OxyTs OxyMCs OxyAs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
205	50889	50907	CTTGTTTTAAAT TCTAATA	ASO-0275	OxyMCs OxyTs OxyTs OxyGs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
206	51319	51337	TGATATAGCAA AGCAATGT	ASO-0276	OxyTs OxyGs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
207	51570	51588	TTATGACTGGA AGAACAAA	ASO-0277	OxyTs OxyTs OxyAs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
208	51576	51594	TGTTTATTATGA CTGGAAG	ASO-0022	DNAas DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
209	51789	51807	ATTTTGACAAG ACTTACAT	ASO-0278	OxyAs OxyTs OxyTs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
210	51976	51993	TGCACTTTTAT CTTTAAC	ASO-0279	OxyTs OxyGs OxyMCs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
211	52383	52401	ATGATTTAAATA	ASO-	OxyAs OxyTs OxyGs 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
212	52840	52859	TTTTGGG TGAAATTTAA GGACAGAAA	0280 ASO-0281	DNAas DNAts DNAts OxyTs OxyGs OxyGs OxyG OxyTs OxyGs OxyAs OxyAs DNAs DNAts DNAts DNAts DNAts DNAs DNAs DNAs DNAs DNAs DNAs DNAs DNAs DNAs OxyGs OxyAs OxyAs OxyA
213	52861	52879	TTTAATGGAAC TAAACTAT	ASO-0282	OxyTs OxyTs OxyAs DNAs DNAts DNAts DNAs DNAs DNAs DNAs DNAs DNAts DNAs DNAs DNAs OxyMCs OxyTs OxyAs OxyT
214	53490	53507	AAATGAACGAG GAACTGG	ASO-0283	OxyAs OxyAs OxyAs DNAts DNAs DNAs DNAs DNAs DNAmcs DNAs DNAs DNAs DNAs DNAs DNAs DNAs OxyMCs OxyTs OxyGs OxyG
215	53682	53698	TGTTACTAGTC ATCATG	ASO-0284	OxyTs OxyGs OxyTs DNAts DNAs DNAs DNAts DNAts DNAs DNAs DNAs DNAs DNAts OxyMCs OxyAs OxyTs OxyG
216	54402	54421	AGGAAAATTGT GGAATCTTT	ASO-0285	OxyAs OxyGs DNAs DNAs DNAs DNAs DNAs DNAts DNAts DNAs DNAts DNAs DNAs DNAs DNAs DNAs DNAts OxyMCs OxyTs OxyTs OxyT
217	54418	54434	ATTTGGGTTAC TAAGGA	ASO-0286	OxyAs OxyTs OxyTs DNAs DNAs DNAs DNAs DNAs DNAts DNAts DNAs DNAts DNAs DNAs OxyGs OxyGs OxyA
218	54752	54770	AATAGAAAATT AGTTTAGA	ASO-0287	OxyAs OxyAs OxyTs OxyAs DNAs DNAs DNAs DNAs DNAs DNAs DNAts DNAs DNAs DNAts DNAts OxyTs OxyAs OxyGs OxyA
219	54932	54950	TTGCAAAAATA TATGTTCT	ASO-0288	OxyTs OxyTs OxyGs OxyMCs DNAs DNAs DNAs DNAs DNAs DNAts DNAs DNAs DNAts DNAs DNAs DNAs OxyTs OxyTs OxyMCs OxyT
220	55303	55319	TAAAGGATGGT ATGGCT	ASO-0289	OxyTs OxyAs DNAs DNAs DNAs DNAs DNAs DNAs DNAts DNAs DNAts DNAs DNAts OxyGs OxyMCs OxyT
221	55457	55473	TGGAGTAACAA AATGAG	ASO-0290	OxyTs OxyGs OxyGs OxyAs DNAs DNAts DNAts DNAs DNAs DNAs DNAs DNAs DNAs DNAts OxyGs OxyAs OxyG
222	55843	55862	GTTAAGAAAATT TTGAAGTGC	ASO-0023	OxyGs OxyTs OxyTs OxyAs DNAs DNAs DNAs DNAs DNAs DNAs DNAts DNAts DNAts DNAs DNAs DNAs DNAs OxyTs OxyGs OxyMC
223	55912	55929	AGATCAAGGCT AAAGAGA	ASO-0291	OxyAs OxyGs OxyAs DNAts DNAs DNAs DNAs DNAs DNAs DNAs DNAts DNAs DNAs DNAs DNAs DNAs OxyAs OxyGs OxyA
224	56166	56184	TTGATAGTGAA TGAAATTT	ASO-0292	OxyTs OxyTs OxyGs OxyAs DNAts DNAs DNAs DNAs DNAts DNAs DNAs DNAts DNAs DNAs DNAs OxyAs OxyTs OxyTs OxyT
227	56918	56935	TATATTTAATCA GATATC	ASO-0297	OxyTs OxyAs OxyTs OxyAs DNAts DNAts DNAts DNAs DNAs DNAts DNAs DNAs DNAs DNAs OxyTs OxyAs OxyTs OxyMC
228	57034	57051	TGCCTGAATAA AGTAAGA	ASO-0298	OxyTs OxyGs OxyMCs OxyMCs DNAts DNAs DNAs DNAs DNAs DNAs DNAs DNAs DNAs DNAts DNAs DNAs DNAs OxyGs OxyA
229	57343	57361	TAAATTTACTTGA CATTTTC	ASO-0299	OxyTs OxyAs OxyAs OxyTs DNAts DNAts DNAts DNAs DNAs DNAts DNAs DNAs DNAs DNAs DNAts OxyTs OxyTs OxyTs OxyMC
230	57600	57617	ATTATTAATGAC TATTTG	ASO-0300	OxyAs OxyTs OxyTs OxyAs DNAts DNAts DNAts DNAs DNAs DNAs DNAs DNAs DNAts DNAs OxyTs OxyTs OxyTs OxyG
231	57859	57876	TAAATGATATAA AGTAGC	ASO-0301	OxyTs OxyAs OxyAs OxyTs DNAts DNAs DNAs DNAs DNAs DNAts DNAs DNAs DNAs DNAs OxyTs OxyAs OxyGs OxyMC
232	58265	58282	AAGAACTTCTT	ASO-	OxyAs OxyAs DNAs DNAs DNAs DNAs DNAs DNAts DNAts DNAs DNAts DNAs 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
			CAATGCA	0302	DNacs DNAs DNAs DNats OxyGs OxyMCs OxyA
233	58617	58633	AAAATAGGTTA GGTCTG	ASO-0303	OxyAs OxyAs OxyAs OxyAs DNats DNAs DNags DNats DNats DNAs DNAs DNags DNags OxyTs OxyMCs OxyTs OxyG
234	58780	58796	GTTGAGAAATAC AGATTG	ASO-0304	OxyGs OxyTs OxyTs OxyGs DNAs DNags DNAs DNAs DNats DNAs DNAs DNAs DNags OxyAs OxyTs OxyTs OxyG
235	58919	58937	AGACACATTTTC ATTTTAAG	ASO-0305	OxyAs OxyGs OxyAs OxyMCs DNAs DNacs DNAs DNats DNats DNats DNats DNacs DNAs DNats DNats DNats DNats DNats DNAs OxyAs OxyG
236	59562	59581	TTTATTTACAAT CCTTTAAA	ASO-0306	OxyTs OxyTs OxyAs DNats DNats DNats DNAs DNAs DNAs DNAs DNAs DNats DNacs DNacs DNats DNats OxyTs OxyAs OxyAs OxyA
237	59636	59654	TTTATATTAAGG ACCAGAC	ASO-0024	OxyTs OxyTs OxyAs DNats DNAs DNats DNats DNats DNAs DNAs DNags DNags DNAs DNacs DNacs OxyAs OxyGs OxyAs OxyMC
238	59638	59655	TTTTATAITTAAG GACCAG	ASO-0307	OxyTs OxyTs OxyTs DNAs DNats DNAs DNats DNats DNats DNAs DNAs DNags DNags DNAs OxyMCs OxyMCs OxyAs OxyG
239	61917	61935	TGCTATAATAT CTCCATC	ASO-0308	OxyTs DNags DNats DNacs DNats DNAs DNats DNats DNAs DNAs DNAs DNats DNacs DNats DNacs OxyMCs OxyAs OxyTs OxyMC
240	62140	62158	CATTATGATATA AACATGT	ASO-0309	OxyMCs OxyAs OxyTs OxyTs DNAs DNats DNats DNags DNAs DNats DNats DNAs DNAs DNAs DNacs DNacs OxyAs OxyTs OxyGs OxyT
241	62487	62506	TAATCTAAGGT TTACTAAGA	ASO-0310	OxyTs OxyAs OxyAs OxyTs DNacs DNats DNAs DNAs DNAs DNags DNags DNats DNats DNAs DNacs DNats OxyAs OxyAs OxyGs OxyA
242	62667	62683	ATGGCTACTTT GGTTTT	ASO-0311	OxyAs OxyTs OxyGs DNags DNacs DNats DNats DNAs DNacs DNats DNats DNags DNags DNats DNats OxyTs OxyT
243	62877	62894	ATTGCCTAGAA GAAATGA	ASO-0312	OxyAs OxyTs OxyTs OxyGs DNacs DNacs DNats DNAs DNAs DNags DNAs DNags DNAs DNAs DNAs OxyTs OxyTs OxyGs OxyA
244	63189	63205	TTTGTGATAGG TATATG	ASO-0313	OxyTs OxyTs OxyTs OxyGs DNats DNags DNAs DNats DNAs DNAs DNags DNats DNAs OxyTs OxyAs OxyTs OxyG
245	63479	63496	GTTTCTGTGAT AATTTAA	ASO-0314	OxyGs OxyTs OxyTs OxyTs DNacs DNats DNags DNats DNats DNags DNats DNAs DNAs DNats OxyTs OxyTs OxyAs OxyA
246	63973	63991	TATAAATGGCA GTACAGAT	ASO-0315	OxyTs OxyAs OxyTs DNAs DNAs DNAs DNats DNats DNags DNags DNacs DNags DNats DNAs DNacs OxyAs OxyGs OxyAs OxyT
247	63976	63994	ATTTATAAATG GCAGTACA	ASO-0316	OxyAs OxyTs OxyTs DNAs DNags DNats DNAs DNAs DNAs DNats DNats DNags DNacs DNAs DNags OxyTs OxyAs OxyMCs OxyA
248	64358	64377	TATTTTCTTCTT TCTGTACT	ASO-0317	OxyTs OxyAs DNats DNats DNats DNats DNats DNats DNats DNats DNats DNats DNats DNacs DNats DNags DNats DNAs OxyMCs OxyT
249	64756	64775	AGGGAAGGCA AAATCTACAT	ASO-0318	OxyAs OxyGs OxyGs DNags DNAs DNAs DNAs DNags DNags DNacs DNAs DNAs DNAs DNAs DNats DNats DNacs DNats DNAs DNacs OxyAs OxyT
250	64986	65003	ACAGAGAAAGGT AATGCAT	ASO-0319	OxyAs OxyMCs OxyAs OxyGs DNAs DNags DNags DNAs DNAs DNags DNats DNAs DNAs DNats DNats DNags OxyMCs OxyAs OxyT
251	65329	65348	TAAGTGATTTT	ASO-	OxyTs DNAs DNAs DNags DNats DNags DNats DNAs 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
			ATCTGTAAA	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 DNAts DNAts OxyTs OxyGs OxyTs OxyA
309	78259	78278	AAGGAA TAGCA TGATTAACA	ASO-0393	OxyAs OxyAs OxyGs OxyAas DNAas DNAts DNAts DNAGs DNAas DNAts DNAGs DNAas DNAts DNAts OxyAs OxyMCs OxyA
310	78542	78558	TGGCTGAGAG GTGAATC	ASO-0394	OxyTs OxyGs OxyGs DNACs DNAts DNAGs DNAas DNAGs DNAas DNAGs DNAts DNAGs DNAas DNAas OxyTs OxyMC
311	78838	78855	TCTAAATTA GTGAAGA	ASO-0395	OxyTs OxyMCs OxyTs OxyAs DNAas DNAts DNAts DNAts 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 DNAas DNAGs DNAts OxyMCs OxyAs OxyTs OxyMC
313	79090	79107	TGAAGTCAAAA TTAGTCA	ASO-0396	OxyTs OxyGs OxyAs OxyAas DNAGs DNAts DNACs DNAas DNAas DNAts DNAts DNAas OxyGs OxyTs OxyMCs OxyA
314	79400	79417	ATTTACTTCAGT ACCAT	ASO-0397	OxyAs OxyTs OxyTs 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 DNAas DNAGs OxyAs OxyTs OxyGs OxyA
316	81553	81570	GTGCTGGGGT CTTAACCT	ASO-0399	OxyGs DNAts DNAGs DNACs DNAts DNAGs DNAGs DNAts DNAts DNAts DNAts DNAas DNAas DNACs OxyTs OxyT
317	81771	81787	TATTTAAGTTCT TGTC	ASO-0400	OxyTs OxyAs OxyTs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts OxyGs OxyTs OxyMCs OxyA
318	82146	82165	ACTTCATAGTA GGTGCAGA	ASO-0401	OxyAs DNACs DNAts DNAts DNACs DNAas DNAts DNAts DNAts DNAGs DNAGs DNAts DNAGs DNAts DNACs DNAas OxyGs OxyA
319	82479	82498	TTAATTCCTCCC TAGATGTC	ASO-0402	OxyTs DNAts DNAas DNAas DNAts DNAts DNAts DNAts DNAts DNACs DNAts DNAas DNAGs DNAas DNAts DNAGs OxyTs OxyMC
320	82701	82720	AAGGTTGTTAA TGCTAAAGA	ASO-0403	OxyAs OxyAs OxyGs DNAGs DNAts DNAts DNAGs DNAts DNAts DNAts DNAGs DNACs DNAts DNAas OxyAs OxyAs OxyGs OxyA
321	82880	82897	TAATACCTTTATG TAATAG	ASO-0404	OxyTs 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 DNAas DNAas DNAts DNAGs DNAts DNACs OxyTs OxyAs OxyAs OxyG
323	83423	83441	TAGTTGACACA TATTATAA	ASO-0029	OxyTs OxyAs OxyGs OxyTs DNAts DNAGs DNAas DNACs DNAas DNAts DNAts DNAts DNAts OxyAs OxyTs OxyAs OxyA
324	83475	83491	GTGATTTTATA GTTGGT	ASO-0406	OxyGs OxyTs OxyGs OxyAs DNAts DNAts DNAts DNAts DNAts DNAGs DNAts DNAts DNAGs OxyGs OxyT
325	83877	83895	GAATATTTTATA ATTTGAT	ASO-0407	OxyGs OxyAs OxyAs OxyTs 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

FIG. 1A (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
			TAAAGG	0408	DNats DNacs DNats DNAas OxyAs OxyGs OxyG
327	84562	84581	TTTGTTCCACC ATTTTATAC	ASO- 0409	OxyTs OxyTs OxyTs DNags DNats DNats DNacs DNAs DNacs DNacs DNAas DNats DNats DNats DNAs DNAs OxyTs OxyAs OxyMC
328	84563	84581	TTTGTTCCACC ATTTTATA	ASO- 0410	OxyTs OxyTs OxyTs OxyGs DNats DNats DNats DNacs DNacs DNacs DNAas DNats DNats DNats DNAs OxyTs OxyA
329	84941	84960	CTATGTCAATTT AATTCCTA	ASO- 0411	OxyMCs OxyTs OxyAs DNats DNags DNats DNacs DNAs DNAas DNats DNats DNats DNAs DNAas DNats DNats OxyMCs OxyTs OxyA
330	85428	85447	TTATTTACTTTG CTCCACAC	ASO- 0412	OxyTs OxyTs DNAas DNats DNats DNats DNAs DNAs DNacs DNats DNats DNags DNacs DNats DNacs DNAs DNAs OxyAs OxyMC
331	85432	85449	C TT TATTTACTT TGCTCC	ASO- 0413	OxyMCs DNats DNats DNAs DNats DNats DNats DNats DNacs DNacs DNats DNats DNags DNacs OxyTs OxyMCs OxyMC
332	86205	86223	AGTCAGAGAGG TAAAATTC	ASO- 0414	OxyAs OxyGs OxyTs OxyMCs DNAas DNags DNAs DNAs DNacs DNAs DNags DNats DNAas DNAas DNAs OxyAs OxyTs OxyMC
333	86473	86490	GAATGATAAAA GTTTACA	ASO- 0415	OxyGs OxyAs OxyAs OxyTs DNags DNAs DNats DNats DNAs DNAas DNAas DNags DNats DNats OxyTs OxyAs OxyMCs OxyA
334	86476	86495	ATGGAGAAATGA TAAAAGTTT	ASO- 0030	OxyAs OxyTs OxyGs OxyGs DNAas DNags DNAs DNAas DNats DNats DNags DNats DNAs DNAas DNAas DNAs OxyGs OxyTs OxyTs OxyT
335	86477	86494	TGGAGAAATGAT AAAAGTT	ASO- 0416	OxyTs OxyGs OxyGs OxyAs DNags DNAs DNAas DNats DNats DNags DNAs DNAas DNAs DNAs OxyAs OxyGs OxyTs OxyT
336	87943	87959	CTAGATGGTTA GAAATTC	ASO- 0417	OxyMCs OxyTs OxyAs OxyGs DNAas DNats DNags DNags DNats DNats DNAas DNags DNAs OxyAs OxyTs OxyTs OxyMC
337	89252	89271	ATATATTTTAAAT TCTATTAA	ASO- 0418	OxyAs OxyTs OxyAs OxyTs DNAas DNats DNats DNats DNats DNats DNAs DNats DNats DNacs DNats DNAs OxyTs OxyTs OxyAs OxyA
338	89426	89442	TAGCTGTTTTG GAAGAT	ASO- 0419	OxyTs OxyAs OxyGs OxyMCs DNats DNags DNats DNats DNats DNats DNags DNags DNAas DNAs DNags OxyAs OxyT
339	89534	89550	AGTTTGAGATA CTATGT	ASO- 0420	OxyAs OxyGs OxyTs OxyTs DNats DNags DNAs DNAs DNags DNAs DNats DNacs DNats OxyAs OxyTs OxyGs OxyT
340	89977	89994	TTCACTTTTGA GTTTAAAT	ASO- 0421	OxyTs OxyTs OxyMCs OxyAs DNacs DNats DNats DNats DNats DNags DNAs DNags DNats DNats OxyTs OxyAs OxyAs OxyT
341	90288	90305	TAGTTTAGGTT TAATAAA	ASO- 0422	OxyTs OxyAs OxyGs OxyTs DNats DNats DNats DNAs DNags DNags DNats DNats DNAs DNAs DNAs OxyTs OxyAs OxyAs OxyA
342	90666	90684	ATTTAGAAGAA TAAAGGGA	ASO- 0423	OxyAs OxyTs OxyTs OxyTs DNAs DNags DNAs DNAs DNAs DNags DNAs DNAs DNats DNAs DNAs DNAs OxyGs OxyGs OxyGs OxyA
343	90891	90907	CACTTACTTCA GGGATT	ASO- 0424	OxyMCs OxyAs OxyMCs DNats DNats DNats DNAs DNacs DNats DNats DNAas DNags DNags DNags OxyAs OxyTs OxyT
344	91334	91350	CTTAGATGTAA TTTTGCG	ASO- 0425	OxyMCs OxyTs OxyTs OxyAs DNags DNAs DNats DNats DNags DNats DNAs DNAas DNats DNats OxyTs OxyTs OxyGs OxyMC
345	91479	91496	AATTTGTCTATA	ASO-	OxyAs OxyAs OxyTs OxyTs DNats DNats DNags DNats DNacs 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
			GAGGGAG	0462	DNAts DNAts DNAs DNAs DNAs OxyGs OxyGs OxyAs OxyG
384	101988	102007	GAATGATATAG GTGAATTTG	ASO- 0033	OxyGs OxyAs OxyTs DNAs DNAs DNAts DNAs DNAts DNAs DNAs DNAs
436	102094	102111	CAGAGTTGTTT TGTTCTC	ASO- 0565	OxyMCs OxyAs DNAs DNAs DNAts DNAts DNAts DNAs DNAts DNAts DNAts DNAts DNAts
437	102432	102448	AGGTTATCAGT GTGGGC	ASO- 0566	OxyAs DNAs DNAs DNAts DNAts DNAs DNAs DNAts DNAs DNAs DNAs DNAs DNAs DNAs
438	102681	102700	AACAAATAACA ACTTTCTGC	ASO- 0567	OxyAs OxyAs OxyMCs DNAs DNAs DNAs DNAts DNAts DNAts DNAs DNAs DNAs DNAs DNAs
439	102859	102875	TTTATAAGTTTA GTCTG	ASO- 0568	OxyTs OxyTs OxyTs OxyAs DNAts DNAs DNAs DNAs DNAts DNAts DNAts DNAts DNAts DNAts
440	103247	103266	ATATTGGTCTG TTTTGTTC	ASO- 0569	OxyAs DNAts DNAs DNAts DNAts DNAs DNAs DNAts DNAts DNAts DNAs DNAs DNAs DNAs
441	103690	103708	AAATCGTTCTTT ACATGAA	ASO- 0570	OxyAs OxyAs OxyTs DNAmcs DNAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
442	103692	103711	TTAAAAATCGTT CTTTACATG	ASO- 0034	OxyTs OxyTs OxyAs DNAs DNAs DNAts DNAts DNAmcs DNAts DNAts DNAts DNAts DNAts
443	103695	103712	TTTAAAAATCGTT CTTTAC	ASO- 0571	OxyTs OxyTs OxyTs OxyAs DNAs DNAs DNAts DNAts DNAts DNAts DNAmcs DNAs DNAts
444	104211	104228	AGTTGGTTTAA AATGTGT	ASO- 0572	OxyAs OxyGs OxyTs OxyTs DNAs DNAs DNAts DNAts DNAts DNAts DNAs DNAs DNAs
445	104304	104321	TTCCAAATTTTC CACTAA	ASO- 0573	OxyTs OxyTs OxyMCs DNAs DNAs DNAs DNAs DNAts DNAts DNAts DNAts DNAts DNAts
446	104608	104625	ATTATTATGGT GTTTTGT	ASO- 0574	OxyAs OxyTs OxyTs OxyAs DNAts DNAts DNAs DNAs DNAts DNAts DNAs DNAs DNAts
447	112262	112280	GCATACATAAT TATTGTTC	ASO- 0575	OxyGs OxyMCs OxyAs OxyTs DNAs DNAs DNAs DNAts DNAts DNAs DNAs DNAts DNAs DNAs
448	112263	112282	TTGCATACATA ATTATTTGT	ASO- 0035	OxyTs OxyTs OxyGs DNAs DNAs DNAts DNAts DNAts DNAts DNAs DNAs DNAts DNAs DNAs
449	112345	112361	ATTCTTAGCTT GTATGT	ASO- 0576	OxyAs OxyTs OxyTs OxyMCs DNAts DNAts DNAs DNAs DNAts DNAs DNAts DNAts DNAts
450	112542	112559	TTATTTCAATC AACTTT	ASO- 0577	OxyTs OxyTs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAs DNAs DNAs DNAts
451	113328	113344	CTTTAGTGGAC AGAATG	ASO- 0578	OxyMCs OxyTs OxyTs DNAts DNAs DNAs DNAts DNAts DNAts DNAts DNAs DNAs DNAs
452	113553	113570	TCATCATTTCTG TCTATGG	ASO- 0579	OxyTs OxyMCs OxyAs DNAts DNAts DNAs DNAs DNAts DNAts DNAts DNAts DNAts DNAts
453	113769	113786	GTTGGATTATT	ASO-	OxyGs OxyTs OxyTs OxyGs DNAs DNAs DNAs DNAts DNAts DNAts DNAs DNAs 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
			AATATCT	0700	DNAas DNAas DNAts OxyAs OxyTs OxyMCs OxyT
565	145328	145344	AGTGGAGATA TGATCA	ASO- 0701	OxyAs OxyGs OxyTs DNAGs DNAGs DNAGs DNAas DNAGs DNAts
566	145632	145649	AAAGAAAGTTA CTGGATC	ASO- 0702	OxyAs OxyAs OxyGs DNAas DNAas DNAGs DNAts DNAts DNAas
567	146064	146081	TGGGAGTTTGA TTAGCTG	ASO- 0703	OxyTs OxyGs DNAGs DNAGs DNAGs DNAts DNAts DNAts DNAGs DNAas
568	146200	146217	GAATAGAAATA TAGACAG	ASO- 0704	OxyGs OxyAs OxyTs DNAas DNAGs DNAas DNAas DNAas DNAts DNAas
569	146424	146443	AAAGCACTGAA AACTAAGTT	ASO- 0705	OxyAs OxyAs OxyGs DNAGs DNAas DNAGs DNAts DNAGs DNAas DNAas
570	146833	146849	GTAGTTGGATT TGGTTC	ASO- 0706	OxyGs DNAts DNAas DNAGs DNAts DNAts DNAGs DNAGs DNAts DNAts
571	146843	146860	CAAAGATTGAG GTAGTTG	ASO- 0042	OxyMCs OxyAs OxyAs DNAGs DNAas DNAts DNAts DNAts DNAGs DNAas
572	146922	146938	AATCAATTGTTT GTCAGC	ASO- 0707	OxyAs OxyAs OxyTs OxyMCs DNAas DNAts DNAts DNAts DNAts DNAts
573	147960	147978	GAGTAGGAAAA TTAAACTC	ASO- 0708	OxyGs OxyAs OxyGs OxyTs DNAas DNAGs DNAGs DNAas DNAas DNAas
574	148347	148364	GCTATAATTTT GAGGGTA	ASO- 0709	OxyGs OxyMCs DNAts DNAas DNAts DNAas DNAts DNAts DNAts DNAts
575	148501	148518	TTTGTCAGGGT AAAATAA	ASO- 0710	OxyTs OxyTs OxyTs OxyGs DNAts DNAGs DNAGs DNAts DNAGs DNAts
576	149240	149258	ATAATACATTTT GGCAGTC	ASO- 0711	OxyAs OxyTs OxyAs OxyAs DNAts DNAas DNAGs DNAts DNAts DNAts
577	149261	149279	AAACATTTGAG AAAAACAGG	ASO- 0712	OxyAs OxyAs OxyAs OxyMCs DNAas DNAts DNAts DNAts DNAGs DNAas
578	149892	149910	TTCCACTCTCT TATTTTAA	ASO- 0713	OxyTs OxyTs OxyMCs DNAGs DNAas DNAGs DNAts DNAts DNAts DNAts
579	150255	150272	TCCATTCACTT ATTAATA	ASO- 0714	OxyTs OxyMCs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts
580	150696	150713	AAAGAGTTTGG TTTGATG	ASO- 0715	OxyAs OxyAs OxyAs OxyGs DNAGs DNAGs DNAts DNAts DNAts DNAGs
581	151007	151026	ATATTTTATAAG TCTTGCAT	ASO- 0716	OxyAs OxyTs OxyAs OxyTs DNAts DNAts DNAts DNAts DNAts DNAas
582	151090	151109	ATATTTTATCTT TATTTACT	ASO- 0717	OxyAs OxyTs OxyAs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts
583	151379	151398	CTTTATCATCTA	ASO-	OxyMCs 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
			ATCCATC	0043	DNAas DNAas DNAts DNAts DNacs OxyMCs OxyTs OxyMC
584	151387	151404	TCTGTGCTTTA TCATCTA	ASO-0718	OxyTs OxyMCs DNAts DNags DNats DNacs DNats DNats DNats DNats DNAs
585	151841	151859	TTTTAGCTTCA GGTGACA	ASO-0719	OxyTs OxyTs DNats DNats DNAas DNags DNacs DNats DNats DNacs DNAs
586	151842	151860	ATTTAGCTTCA GGTGATC	ASO-0720	OxyAs DNats DNats DNats DNats DNAas DNags DNacs DNats DNats DNacs
587	152436	152455	TGGTTGAGATT AAATGAGAT	ASO-0721	OxyTs OxyGs DNags DNats DNats DNags DNAas DNags DNAs DNats DNats
588	152678	152697	ATTGTGTTATA CCTATTCCA	ASO-0722	OxyAs DNats DNats DNags DNats DNats DNats DNats DNats DNats DNAs
589	152683	152700	AAAAATTGTGTT ATACCTA	ASO-0723	OxyAs OxyAs OxyAs DNats DNats DNags DNats DNats DNats DNats DNats
590	152708	152726	TGCGACTAGAA AAAAATAA	ASO-0724	OxyTs OxyMCs OxyGs OxyMCs DNAas DNacs DNats DNats DNAs DNags DNAs
591	152709	152726	TCGCACTAGAA AAAAATA	ASO-0725	OxyTs OxyMCs OxyGs OxyMCs DNAas DNacs DNats DNats DNAs DNags DNAs
592	152709	152727	GTCGCAC TAGA AAAAATA	ASO-0726	OxyGs OxyTs OxyMCs OxyGs DNacs DNAas DNAs DNats DNats DNAs DNags
593	152709	152728	AGTCGCAC TAG AAAAATA	ASO-0727	OxyAs OxyGs OxyTs OxyMCs DNags DNacs DNAs DNAs DNacs DNats DNAs
594	152712	152731	TGAAGTCGCAC TAGAAAAA	ASO-0728	OxyTs OxyGs OxyAs OxyAs DNags DNats DNats DNats DNAs DNacs DNAs
595	152713	152731	TGAAGTCGCAC TAGAAAAA	ASO-0729	OxyTs OxyGs OxyAs OxyAs DNags DNats DNats DNats DNAs DNacs DNAs
596	152713	152732	ATGAAGTCGCA CTAGAAAA	ASO-0730	OxyAs OxyTs OxyGs OxyAs DNAas DNags DNats DNats DNAmcs DNags DNacs
597	152714	152731	TGAAGTCGCAC TAGAAAA	ASO-0731	OxyTs OxyGs OxyAs OxyAs DNags DNats DNats DNats DNAs DNacs DNAs
598	152714	152732	ATGAAGTCGCA CTAGAAAA	ASO-0732	OxyAs OxyTs OxyGs OxyAs DNAas DNags DNats DNats DNAmcs DNags DNacs
599	152714	152733	CATGAAGTCGC ACTAGAAAA	ASO-0733	OxyMCs OxyAs OxyTs OxyGs DNAas DNags DNats DNats DNAmcs DNags
600	152715	152730	GAAGTCGCACT AGAAA	ASO-0734	OxyGs OxyAs OxyAs OxyGs DNats DNats DNAmcs DNags DNacs DNAs
601	152715	152731	TGAAGTCGCAC TAGAAA	ASO-0735	OxyTs OxyGs OxyAs OxyAs DNags DNats DNats DNats DNAmcs DNags DNAs
602	152715	152732	ATGAAGTCGCA	ASO-	OxyAs OxyTs OxyGs OxyAs DNAas DNags DNats DNats DNAmcs DNags DNacs

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 DNAAcs DNAts DNAmcs DNAGs DNAcs DNAas DNAAcs 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 DNAAcs DNAts DNAas OxyGs OxyAs OxyA
606	152716	152733	CATGAAGTCGC ACTAGAA	ASO-0740	OxyMCs OxyAs OxyTs DNAGs DNAas DNAAcs DNAts DNAmcs DNAGs DNAcs DNAas DNAAcs DNAts DNAas OxyGs OxyAs OxyA
607	152760	152777	CAAA TCAAACA CCAAGTA	ASO-0741	OxyMCs OxyAs OxyAs DNAts DNAAcs DNAas DNAAcs DNAAcs DNAas DNAAcs DNAAcs OxyAs OxyGs OxyTs OxyA
608	152760	152778	CAAAA TCAAAC ACCAAGTA	ASO-0742	OxyAs OxyMCs OxyAs OxyAs DNAts DNAAcs DNAas DNAAcs DNAAcs DNAcs DNAas DNAAcs DNAAcs DNAAcs OxyGs OxyTs OxyA
609	152761	152779	TACAAA TCAAA CACCAAGT	ASO-0743	OxyTs OxyAs OxyMCs OxyAs DNAAcs DNAAcs DNAts DNAAcs DNAAcs DNAas DNAAcs DNAAcs DNAAcs DNAAcs OxyAs OxyGs OxyT
610	152761	152780	TTACAAA TCAA ACACCAAGT	ASO-0744	OxyTs OxyAs OxyAs OxyMCs DNAAcs DNAAcs DNAAcs DNAts DNAAcs DNAAcs DNAas DNAAcs DNAAcs DNAAcs DNAAcs OxyAs OxyAs OxyGs OxyT
611	152763	152782	ACTTACAAA TC AAACACCAC	ASO-0745	OxyAs OxyMCs DNAts DNAAcs DNAAcs DNAAcs DNAAcs DNAAcs DNAts DNAas DNAAcs DNAAcs DNAAcs DNAAcs OxyMCs OxyAs OxyA
612	152764	152782	ACTTACAAA TC AAACACCAC	ASO-0746	OxyAs OxyMCs DNAts DNAAcs DNAAcs DNAAcs DNAAcs DNAAcs DNAts DNAcs DNAAcs DNAAcs DNAAcs DNAAcs OxyAs OxyMCs OxyA
613	152764	152783	TACTTACAAA T CAACACCAC	ASO-0747	OxyTs OxyAs OxyMCs DNAts DNAAcs DNAAcs DNAAcs DNAAcs DNAAcs DNAts DNAAcs DNAAcs DNAAcs DNAAcs OxyAs OxyMCs OxyA
614	152765	152782	ACTTACAAA TC AAACACCAC	ASO-0748	OxyAs OxyMCs OxyTs OxyTs DNAAcs DNAAcs DNAAcs DNAAcs DNAAcs DNAts DNAcs DNAAcs DNAAcs DNAAcs DNAAcs OxyAs OxyMCs OxyMC
615	152765	152783	TACTTACAAA T CAACACCAC	ASO-0749	OxyTs OxyAs OxyMCs DNAts DNAAcs DNAAcs DNAAcs DNAAcs DNAAcs DNAts DNAAcs DNAAcs DNAAcs DNAAcs OxyMCs OxyAs OxyMCs OxyMC
616	152765	152784	ATACTTACAAA T CAACACCAC	ASO-0750	OxyAs OxyTs OxyAs OxyMCs DNAts DNAAcs DNAAcs DNAAcs DNAAcs DNAAcs DNAas DNAts DNAAcs DNAAcs DNAAcs DNAAcs OxyAs OxyMCs OxyMC
617	152766	152783	TACTTACAAA T CAACACCAC	ASO-0751	OxyTs OxyAs OxyMCs OxyTs DNAAcs DNAAcs DNAAcs DNAAcs DNAAcs DNAAcs DNAts DNAAcs DNAAcs DNAAcs DNAAcs OxyAs OxyMCs OxyA
618	152766	152784	ATACTTACAAA T CAACACCAC	ASO-0752	OxyAs OxyTs OxyAs OxyMCs DNAts DNAAcs DNAAcs DNAAcs DNAAcs DNAAcs DNAas DNAts DNAAcs DNAAcs DNAAcs DNAAcs OxyAs OxyMCs OxyA
619	152766	152785	TATACTTACAAA TCAACACCAC	ASO-0753	OxyTs OxyAs OxyTs OxyAs DNAAcs DNAAcs DNAAcs DNAAcs DNAAcs DNAAcs DNAas DNAts DNAAcs DNAAcs DNAAcs DNAAcs OxyAs OxyMCs OxyA
620	152767	152785	TATACTTACAAA TCAACACA	ASO-0754	OxyTs OxyAs OxyTs OxyAs DNAAcs DNAAcs DNAAcs DNAAcs DNAAcs DNAAcs DNAas DNAts DNAAcs DNAAcs DNAAcs DNAAcs OxyAs OxyMCs OxyA
621	152767	152786	ATATACTTACAAA	ASO-	OxyAs OxyTs OxyAs OxyTs DNAAcs DNAAcs DNAAcs DNAts DNAAcs DNAAcs DNAas DNAAcs DNAAcs DNAAcs DNAAcs

FIG. 1A (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
			GTTCTTT	0773	DNAas DNAGs DNATs DNATs OxyMCs OxyTs OxyTs OxyT
641	159871	159887	CTCAGCTATGT TCTATA	ASO- 0774	OxyMCs OxyTs DNACs DNAas DNAGs DNACs DNATs DNAas DNATs DNAGs DNATs DNATs DNACs OxyTs OxyAs OxyTs OxyA
642	160252	160269	TTTTATGTAGAT TAACTG	ASO- 0775	OxyTs OxyTs OxyTs OxyTs DNAas DNATs DNAGs DNATs DNAas DNAGs DNAas DNATs DNATs DNAas OxyAs OxyMCs OxyTs OxyG
643	160665	160684	TAATCGTGTAT TTTTGCCTTC	ASO- 0776	OxyTs OxyAs OxyAs DNATs DNAmcs DNAGs DNATs DNAGs DNATs DNAas DNATs DNATs DNATs DNATs DNAGs DNACs DNACs DNATs OxyTs OxyMC
644	160668	160685	TTAATCGTGTA TTTTGCC	ASO- 0045	OxyTs DNATs DNAas DNAas DNATs DNAmcs DNAGs DNATs DNAGs DNATs DNAas DNATs DNATs DNATs OxyTs OxyGs OxyMCs OxyMC
645	160671	160687	AGTTAATCGTGT TATTTT	ASO- 0777	OxyAs OxyGs OxyTs OxyTs DNAas DNAas DNATs DNAmcs DNAGs DNATs DNAGs DNATs DNAas OxyTs OxyTs OxyTs OxyT
646	161777	161794	TAAGGAGGACA GAACAGG	ASO- 0778	OxyTs OxyAs OxyAs DNAGs DNAGs DNAas DNAGs DNAGs DNATs DNAas DNACs DNAas DNAGs DNAas DNAas DNACs OxyAs OxyGs OxyG
647	161877	161895	ATCTAAAAGGT TATATACT	ASO- 0779	OxyAs OxyTs OxyMCs OxyTs DNAas DNAas DNAas DNATs DNAGs DNAGs DNAGs DNATs DNATs DNAas DNATs DNAas OxyTs OxyAs OxyMCs OxyT
648	162407	162424	AGGAAATAAGC TATAAGG	ASO- 0780	OxyAs OxyGs OxyGs OxyAs DNAas DNAas DNATs DNATs DNAas DNAGs DNAGs DNATs DNAas DNATs OxyAs OxyAs OxyGs OxyG
649	162720	162737	GCTATGGAGAC AGTATGG	ASO- 0781	OxyGs OxyMCs DNATs DNAas DNATs DNAGs DNAGs DNAGs DNATs DNAas DNACs DNAas DNAGs DNATs DNAas DNATs OxyGs OxyG
650	162730	162747	CAAAGGTAAAG CTATGGA	ASO- 0782	OxyMCs OxyAs OxyAs OxyAs DNAGs DNAGs DNATs DNAas DNAas DNAas DNAGs DNACs DNATs DNAas OxyTs OxyGs OxyGs OxyA
651	163806	163825	TAGAAGACTGA CACTACTCA	ASO- 0783	OxyTs OxyAs DNAGs DNAas DNAas DNAGs DNAas DNACs DNATs DNATs DNAas DNACs DNAas DNACs DNATs DNAas DNAGs DNATs OxyMCs OxyA
652	163809	163827	GATAGAAGACT GACACTAC	ASO- 0046	OxyGs OxyAs DNATs DNAas DNAGs DNAas DNAGs DNATs DNAas DNACs DNATs DNAGs DNAas DNACs DNAas OxyMCs OxyTs OxyAs OxyMC
653	163811	163827	GATAGAAGACT GACACT	ASO- 0784	OxyGs OxyAs DNATs DNAas DNAGs DNAas DNAGs DNATs DNAas DNACs DNATs DNAGs DNAas OxyMCs OxyAs OxyMCs OxyT
654	164061	164078	AGTTATTTTATTG GTTTTAA	ASO- 0785	OxyAs OxyGs OxyTs OxyTs DNAas DNATs DNATs DNATs DNAas DNATs DNATs DNAGs DNAGs DNATs OxyTs OxyTs OxyAs OxyA
655	164362	164380	CTTAAGGAAAT GTTATAAC	ASO- 0786	OxyMCs OxyTs OxyTs OxyAs DNAas DNAGs DNAGs DNAas DNAas DNATs DNATs DNAGs DNATs DNATs DNAas OxyTs OxyAs OxyAs OxyMC
656	165139	165156	ATTGAGTACAG GCAGAGT	ASO- 0787	OxyAs DNATs DNATs DNAGs DNAas DNAGs DNATs DNAas DNACs DNAGs DNAGs DNACs DNAas DNAGs OxyAs OxyGs OxyT
657	165142	165160	ATTTATTGAGTA CAGGCAG	ASO- 0788	OxyAs OxyTs OxyTs DNATs DNAas DNATs DNATs DNATs DNAGs DNATs DNAas DNACs DNAas DNAGs DNAGs OxyMCs OxyAs OxyG
658	165664	165682	GTCTTCATGCT ATTTTCAC	ASO- 0789	OxyGs OxyTs OxyMCs DNATs DNATs DNATs DNACs DNAas DNATs DNAGs DNATs DNAas DNATs DNATs DNATs DNATs DNACs OxyAs OxyMC
659	166220	166239	ATGGTCTATTA	ASO-	OxyAs OxyTs OxyGs DNAGs DNATs DNACs 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
660	166409	166426	AATGTGCAA AGCAGTGATAC AAGGGAC	0790 ASO-0791	DNAas DNAas DNAts DNAGs DNAts DNAGs OxyMCs OxyAs OxyA OxyAs OxyGs OxyMCs DNAas DNAGs DNAts DNAGs DNAas DNAts DNAas DNAcs DNAas DNAas DNAGs DNAGs DNAGs OxyAs OxyMC
661	166738	166754	GAGATTATCCT TCAAAT	ASO-0792	OxyGs OxyAs OxyGs OxyAs DNAts DNAts DNAts DNAas DNAts DNAts DNAts DNAcs OxyAs OxyAs OxyT
662	167073	167090	TGGGAATAGTG GAAGGAG	ASO-0793	OxyTs DNAGs DNAGs DNAGs DNAas DNAts DNAts DNAas DNAGs DNAts DNAGs DNAGs DNAas DNAas OxyGs OxyGs OxyAs OxyG
663	167365	167382	GATGATGTAAA CAGAGAG	ASO-0794	OxyGs OxyAs OxyTs DNAGs DNAas DNAts DNAGs DNAts DNAas DNAas DNAcs DNAas DNAGs OxyAs OxyGs OxyAs OxyG
664	167371	167388	CAGGTGGATGA TGTAAC	ASO-0795	OxyMCs OxyAs OxyGs OxyTs DNAts DNAGs DNAGs DNAas DNAts DNAGs DNAas DNAts DNAGs DNAts DNAas OxyAs OxyAs OxyMC
665	168021	168040	TATTGAAGGCT TATTTACCA	ASO-0796	OxyTs DNAas DNAts DNAts DNAGs DNAas DNAts DNAGs DNAts DNAts DNAts DNAas DNAts DNAts DNAts DNAas OxyMCs OxyMCs OxyA
666	168023	168040	TATTGAAGGCT TATTTAC	ASO-0797	OxyTs OxyAs OxyTs OxyTs DNAGs DNAas DNAts DNAGs DNAts DNAts DNAts DNAas DNAts OxyTs OxyTs OxyAs OxyMC
667	168468	168487	TTTTAACTGATG AATTGCTGA	ASO-0798	OxyTs DNAts DNAts DNAas DNAas DNAts DNAts DNAGs DNAas DNAts DNAGs DNAas DNAas DNAts DNAts DNAGs OxyMCs OxyTs OxyGs OxyA
668	169122	169141	CCTTGC TTGTA TTTTCAAAT	ASO-0799	OxyMCs OxyMCs DNAts DNAts DNAGs DNAts DNAts DNAts DNAts DNAts DNAas DNAts DNAts DNAts DNAts DNAts DNAas DNAas OxyAs OxyT
669	169402	169420	TTTACATTTAAT TAAC TTT	ASO-0800	OxyTs OxyTs OxyTs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAas DNAas OxyMCs OxyTs OxyTs OxyT
670	169409	169427	CCATGATTTTA CATTTAAT	ASO-0047	OxyMCs OxyMCs OxyAs OxyTs DNAGs DNAas DNAts DNAts DNAts DNAts DNAas DNAts DNAas DNAts DNAts OxyTs OxyAs OxyAs OxyT
671	169672	169689	CTGGGAGATGA AATGGAT	ASO-0801	OxyMCs OxyTs DNAGs DNAGs DNAGs DNAas DNAGs DNAas DNAts DNAGs DNAas DNAas DNAts DNAts DNAGs OxyGs OxyAs OxyT
672	169826	169843	AGAGAAATGTCT AAAGTAC	ASO-0802	OxyAs OxyGs OxyAs DNAGs DNAas DNAts DNAts DNAGs DNAts DNAts DNAas DNAas DNAts OxyGs OxyTs OxyAs OxyMC
673	170374	170391	GATTTCTCTAA ATGTGTA	ASO-0803	OxyGs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAas DNAts DNAGs OxyTs OxyGs OxyTs OxyA
674	170483	170501	TTAA TTA CTCTC TAAACTT	ASO-0804	OxyTs OxyTs OxyAs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAas DNAas OxyAs OxyMCs OxyTs OxyT
675	170826	170843	AAATCTGCTTG TTTG TCA	ASO-0805	OxyAs OxyAs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAGs DNAts DNAts DNAts DNAts DNAts OxyMCs OxyA
676	170995	171012	GCTCAA TAA TT GCTTCTA	ASO-0806	OxyGs OxyMCs DNAts DNAts DNAts DNAas DNAts DNAts DNAas DNAts DNAts DNAGs DNAts DNAts DNAts DNAts OxyTs OxyA
677	171616	171632	TGATAGTATAT GGTTT	ASO-0807	OxyTs OxyGs OxyAs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAGs OxyGs OxyTs OxyTs OxyT
678	171755	171774	TAAATGAATGT	ASO-	OxyTs OxyAs OxyAs OxyAs DNAts DNAts DNAGs DNAas 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
			GTAAGAAG	0860	DNAas DNAGs DNATs DNAas OxyAs OxyAs OxyG
726	180769	180785	TTAATATAAGG AGGTAG	ASO- 0861	OxyTs OxyAs OxyAs DNATs DNAas DNATs DNAas DNAGs DNAGs
727	180774	180793	TAATTTTATTAA TATAAGGA	ASO- 0862	OxyTs OxyAs OxyAs OxyTs DNATs DNATs DNAas DNATs DNATs DNAas
728	181169	181188	AGATTATCAGG ATTAAATGA	ASO- 0863	DNAas DNATs DNAas DNATs DNAas DNATs DNATs DNATs DNATs DNATs
729	181170	181188	AGATTATCAGG ATTAAATG	ASO- 0864	OxyAs OxyGs OxyAs OxyTs DNATs DNAas DNATs DNATs DNATs DNATs
730	181774	181791	CCATGACCTTA TTAATGA	ASO- 0865	DNAas DNATs DNATs DNAas DNATs DNATs DNATs DNATs DNATs
731	181775	181791	CCATGACCTTA TTAATG	ASO- 0866	OxyMCs OxyMCs OxyAs OxyTs DNAGs DNAas DNATs DNATs DNATs
732	182679	182696	AAATTGTTGCT TCTCATC	ASO- 0867	OxyAs OxyAs OxyAs DNATs DNATs DNATs DNATs DNATs DNATs
733	182764	182780	TTTTGGAGACT AAGCTA	ASO- 0868	OxyTs OxyTs OxyTs DNATs DNATs DNATs DNAas DNATs DNATs DNATs
734	183386	183405	TTCATATCAGTT CAAAATGA	ASO- 0053	DNAas DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNATs
735	183560	183576	ATTGTCAGGAT TGGGTC	ASO- 0869	OxyAs OxyTs DNATs DNATs DNATs DNATs DNATs DNATs DNATs
736	183578	183595	TATTTGGTTATT TGTGAG	ASO- 0870	OxyTs OxyAs OxyTs DNATs DNATs DNATs DNATs DNATs DNATs
737	184119	184136	ATTTGCATAAAT GTTGTG	ASO- 0871	OxyAs OxyTs OxyTs OxyTs DNATs DNATs DNATs DNATs DNATs
738	184370	184387	CCTTGTATTTT GTCTGTT	ASO- 0872	OxyMCs OxyMCs DNATs DNATs DNATs DNATs DNATs DNATs DNATs
739	184697	184714	TTAAAAGTTTAT CAGCTT	ASO- 0873	OxyTs OxyTs OxyAs DNATs DNATs DNATs DNATs DNATs DNATs
740	184958	184975	TTGTTTAGTATT CATTTTC	ASO- 0874	OxyTs OxyTs OxyGs OxyTs DNATs DNATs DNATs DNATs DNATs
741	185161	185177	GAGGCTAGAAT AATTTTG	ASO- 0875	OxyGs OxyAs OxyGs OxyGs DNATs DNATs DNATs DNATs DNATs
742	185516	185533	ACAATGAAGAA TAGTATA	ASO- 0876	DNAas DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNATs
743	186088	186104	TGTGGAAATAA GTGCAT	ASO- 0877	OxyTs OxyGs OxyTs DNATs DNATs DNATs DNATs DNATs DNATs
744	186089	186105	TTGTGGAATAA	ASO-	OxyTs OxyTs OxyGs OxyTs 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
			GGGCAGA	0975	DNAas DNAgs DNAGs DNAGs OxyMCs OxyAs OxyGs OxyA
859	213182	213199	ACTGCAAGAT ACAAGGG	ASO-0976	OxyAs OxyMCs DNAts DNAGs DNACs DNAas DNAAas DNAGs DNAas DNAts DNAas DNACs DNAas OxyAs OxyGs OxyTs OxyG
860	213182	213200	GACTGCAAGA TACAAGGG	ASO-0977	OxyGs DNAas DNACs DNAts DNAGs DNACs DNAas DNAAas DNAGs DNAGs DNAts DNAas DNACs DNAas OxyGs OxyTs OxyG
861	213183	213200	GACTGCAAGA TACAAGG	ASO-0978	OxyGs OxyAs OxyMCs DNAts DNAGs DNACs DNAas DNAAas DNAGs DNAGs DNAts DNAas DNACs OxyAs OxyTs OxyG
862	213183	213201	TGACTGCAAG ATACAAGG	ASO-0979	OxyTs OxyGs OxyAs DNACs DNAts DNAGs DNACs DNAas DNAAas DNAGs DNAGs DNAts DNAas DNACs DNAas OxyGs OxyG
863	213183	213202	ATGACTGCAAA GATACAAGG	ASO-0980	OxyAs OxyTs DNAGs DNAas DNACs DNAts DNAGs DNACs DNAas DNAAas DNAGs DNAGs DNAts DNAas DNACs OxyAs OxyTs OxyG
864	213184	213201	TGACTGCAAG ATACAAG	ASO-0981	OxyTs OxyGs OxyAs OxyMCs DNAts DNAGs DNACs DNAas DNAAas DNAGs DNAGs DNAts DNAas DNACs OxyAs OxyTs OxyG
865	213184	213202	ATGACTGCAAA GATACAAG	ASO-0982	OxyAs OxyTs OxyGs DNAas DNACs DNAts DNAGs DNACs DNAas DNAAas DNAGs DNAGs DNAts DNAas DNACs OxyAs OxyTs OxyG
866	213184	213203	AATGACTGCAA AGATACAAG	ASO-0983	OxyAs OxyAs OxyTs OxyGs DNAas DNACs DNAts DNAGs DNACs DNAas DNAAas DNAGs DNAGs DNAts DNAas DNACs OxyAs OxyTs OxyG
867	213185	213204	CAATGACTGCA AAGATACAA	ASO-0984	OxyMCs OxyAs OxyTs DNAGs DNAas DNACs DNAts DNAGs DNAGs DNAts DNAas DNACs OxyAs OxyTs OxyG
868	213186	213204	CAATGACTGCA AAGATACA	ASO-0985	OxyMCs OxyAs OxyTs DNAGs DNAas DNACs DNAts DNAGs DNAGs DNAts DNAas DNACs OxyAs OxyTs OxyG
869	213186	213205	ACAATGACTGC AAAGATACA	ASO-0986	OxyAs OxyMCs OxyAs OxyTs DNAGs DNAas DNACs DNAts DNAGs DNAGs DNAts DNAas DNACs OxyAs OxyTs OxyG
870	213187	213205	ACAATGACTGC AAAGATAC	ASO-0987	OxyAs OxyMCs OxyAs OxyTs DNAGs DNAas DNACs DNAts DNAGs DNAGs DNAts DNAas DNACs OxyAs OxyTs OxyG
871	213188	213206	TACAATGACTG CAAAGATA	ASO-0988	OxyTs OxyAs OxyMCs OxyAs DNAas DNACs DNAts DNAGs DNACs DNAts DNAGs DNACs DNAas DNAAas DNAGs OxyTs OxyA
872	213189	213208	TATACAATGAC TGCAAAGAT	ASO-0989	OxyTs OxyAs DNAts DNAGs DNACs DNAas DNAAas DNAGs DNAGs DNAts DNAas DNACs OxyAs OxyTs OxyG
873	213191	213208	TATACAATGAC TGCAAAG	ASO-0990	OxyTs OxyAs OxyTs OxyAs DNACs DNAas DNAAas DNAGs DNAGs DNAts DNAas DNACs OxyAs OxyTs OxyG
874	213240	213256	AACATGCCAT TTAGGT	ASO-0991	OxyAs OxyAs DNACs DNAts DNAGs DNACs DNAts DNAGs DNACs DNAts DNAGs DNACs OxyAs OxyTs OxyG
875	213240	213257	GAACATGCCA TTTAGGT	ASO-0992	OxyGs OxyAs OxyAs DNACs DNAts DNAGs DNACs DNAts DNAGs DNACs DNAts DNAGs DNACs DNAts DNAGs OxyGs OxyT
876	213240	213259	GTGAACATGTC CATTTAGGT	ASO-0993	OxyGs DNAts DNAGs DNAas DNAAas DNAGs DNACs DNAts DNAGs DNAGs DNAts DNAas DNACs DNAts DNAGs OxyTs OxyG
877	213241	213257	GAACATGCCA	ASO-	OxyGs OxyAs OxyAs OxyMCs DNAts DNAGs DNACs DNAts DNAGs DNACs DNAts DNAGs DNACs DNAts DNAGs DNACs DNAts DNAGs DNACs

FIG. 1A (cont.)

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 DNAts DNAas OxyGs OxyG
878	213241	213258	TGAACTATGCC ATTTAGG	ASO-0995	OxyTs DNAGs DNAas DNACs DNAts DNAas DNAts DNAGs DNACs DNACs DNAas DNAts DNAts OxyAs OxyGs OxyG
879	213241	213259	GTGAACATATGC CATTTAGG	ASO-0996	OxyGs DNAts DNAGs DNAas DNACs DNAts DNAts DNAas DNAts DNAGs DNACs DNACs DNAas DNAts DNAts OxyAs OxyGs OxyG
880	213242	213259	GTGAACATATGC CATTTAG	ASO-0997	OxyGs OxyTs DNAGs DNAas DNAas DNACs DNAts DNAts DNAas DNAts DNAGs DNACs DNACs DNAts OxyTs OxyAs OxyG
881	213242	213260	TGTGAACATATG CCATTTAG	ASO-0998	OxyTs DNAGs DNAts DNAGs DNAas DNAas DNACs DNAts DNAts DNAas DNAts DNAGs DNACs DNACs DNAts OxyTs OxyAs OxyG
882	213242	213261	CTGTGAACATAT GCCATTTAG	ASO-0999	OxyMCs DNAts DNAGs DNAts DNAGs DNAas DNAas DNACs DNAts DNAts DNAas DNAts DNAGs DNACs DNACs DNAts OxyAs OxyG
883	213243	213259	GTGAACATATGC CATTTA	ASO-1000	OxyGs OxyTs DNAGs DNAas DNAas DNACs DNAts DNAts DNAas DNAts DNAGs DNACs DNACs DNAas OxyTs OxyAs OxyG
884	213243	213260	TGTGAACATATG CCATTTA	ASO-1001	OxyTs OxyGs OxyTs DNAGs DNAas DNAas DNACs DNAts DNAts DNAas DNAts DNAGs DNACs DNACs DNAas DNAts DNAts OxyTs OxyA
885	213243	213261	CTGTGAACATAT GCCATTTA	ASO-1002	OxyMCs DNAts DNAGs DNAts DNAGs DNAas DNAas DNACs DNAts DNAts DNAas DNAts DNAGs DNACs DNACs DNAts OxyTs OxyA
886	213246	213262	CCTGTGAACATA TGCCAT	ASO-1003	OxyMCs OxyMCs DNAts DNAGs DNAts DNAGs DNAas DNAas DNACs DNAts DNAts DNAGs DNACs DNACs DNAts OxyAs OxyT
887	213248	213263	CCCTGTGAACT ATGCC	ASO-1004	OxyMCs DNACs DNACs DNAts DNAGs DNAts DNAGs DNAas DNAas DNACs DNACs DNAts DNAs DNAs DNAts DNAGs OxyMCs OxyMC
888	213267	213283	CCATATACTGA CCTTCA	ASO-1005	OxyMCs OxyMCs OxyAs DNAts DNAs DNAts DNAs DNAts DNAs DNAts DNAGs DNAs DNAs DNAts DNAGs DNAs DNACs DNACs DNAts OxyMCs OxyA
889	213267	213284	TCCATATACTG ACCTTCA	ASO-1006	OxyTs OxyMCs DNACs DNAs DNAts DNAts DNAs DNAts DNAs DNAts DNAs DNAts DNAGs DNAs DNAs DNACs DNACs DNAts OxyTs OxyMCs OxyA
890	213268	213284	TCCATATACTG ACCTTC	ASO-1007	OxyTs OxyMCs DNACs DNAs DNAts DNAts DNAs DNAts DNAs DNAts DNAs DNAts DNAGs DNAs DNAs DNACs DNACs DNAts DNAGs DNAs DNAs DNAts OxyTs OxyMC
891	213269	213285	CTCCATATACT GACCTT	ASO-1008	OxyMCs DNAts DNACs DNACs DNAas DNAts DNAts DNAas DNAts DNAs DNAs DNAts DNAGs DNAs DNAs DNAts DNAGs DNAts OxyT
892	213269	213286	ACTCCATATACT TGACCTT	ASO-1009	OxyAs OxyMCs DNAts DNACs DNACs DNAs DNAs DNAts DNAs DNAts DNAs DNAts DNAGs DNAs DNAs DNAts DNAGs DNAts OxyT
893	213270	213286	ACTCCATATACT TGACCT	ASO-1010	OxyAs OxyMCs OxyTs OxyMCs DNACs DNAs DNAts DNAts DNAas DNAts DNAs DNAs DNAts DNAGs DNAs DNAs DNAts DNAGs DNAts OxyT
894	213271	213287	GACTCCATATA CTGACC	ASO-1011	OxyGs OxyAs OxyMCs DNAts DNACs DNACs DNAs DNAs DNAts DNAs DNAts DNAs DNAts DNAGs DNAs DNAs DNAts DNAGs DNAts OxyMC
895	213450	213467	TTTTGCTATGAT GTATAT	ASO-1012	OxyTs OxyTs OxyTs OxyTs DNAGs DNACs DNAts DNAts DNAas DNAts DNAs DNAts DNAGs DNAs DNAts DNAGs DNAts OxyAs OxyT
896	213587	213605	AGGCGGACATA	ASO-	OxyAs DNAGs DNAGs DNAmcs DNAGs DNAGs DNAs DNAs DNAts DNAGs DNAs DNAs 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 OxyAs OxyG
897	213587	213606	CAGGCGGACAT ACATCACAG	ASO-1014	OxyMCs DNAas DNAcs DNAGs DNAmcs DNAGs DNAGs DNAas DNAGs DNAas DNAts DNAas DNAGs DNAmcs DNAts DNAGs DNAas DNAGs OxyG
898	213588	213605	AGGCGGACATA CATCACA	ASO-1015	OxyAs OxyGs DNAGs DNAmcs DNAGs DNAGs DNAas DNAGs DNAGs DNAts DNAas DNAGs DNAmcs DNAts DNAGs DNAas OxyMCs OxyA
899	213588	213606	CAGGCGGACAT ACATCACA	ASO-1016	OxyMCs DNAas DNAGs DNAGs DNAmcs DNAGs DNAGs DNAGs DNAas DNAGs DNAGs DNAts DNAas DNAGs DNAmcs DNAts DNAGs DNAas OxyMCs OxyA
900	213589	213605	AGGCGGACATA CATCAC	ASO-1017	OxyAs OxyGs DNAGs DNAmcs DNAGs DNAGs DNAas DNAGs DNAGs DNAts DNAas DNAGs DNAmcs DNAts OxyMCs OxyAs OxyMC
901	213589	213606	CAGGCGGACAT ACATCAC	ASO-1018	OxyMCs DNAas DNAGs DNAGs DNAmcs DNAGs DNAGs DNAas DNAGs DNAGs DNAts DNAas DNAGs DNAmcs OxyTs OxyMCs OxyAs OxyMC
902	213589	213607	ACAGCGGAC ATACATCAC	ASO-1019	OxyAs DNAGs DNAas DNAGs DNAGs DNAmcs DNAGs DNAGs DNAas DNAGs DNAGs DNAts DNAas DNAGs DNAmcs DNAts OxyMCs OxyAs OxyMC
903	213589	213608	TACAGCGGAC ATACATCAC	ASO-1020	OxyTs OxyAs DNAGs DNAas DNAGs DNAGs DNAmcs DNAGs DNAGs DNAas DNAGs DNAGs DNAts DNAas DNAGs DNAmcs DNAts DNAGs OxyAs OxyMC
904	213590	213605	AGGCGGACATA CATCA	ASO-1021	OxyAs OxyGs DNAGs DNAmcs DNAGs DNAGs DNAas DNAGs DNAGs DNAts DNAas DNAGs DNAmcs OxyTs OxyMCs OxyA
905	213590	213606	CAGGCGGACAT ACATCA	ASO-1022	OxyMCs OxyAs DNAGs DNAGs DNAmcs DNAGs DNAGs DNAas DNAGs DNAGs DNAts DNAas DNAGs DNAmcs OxyTs OxyMCs OxyA
906	213590	213607	ACAGCGGAC ATACATCA	ASO-1023	OxyAs OxyMCs DNAas DNAGs DNAGs DNAmcs DNAGs DNAGs DNAas DNAGs DNAGs DNAts DNAas DNAGs DNAmcs DNAts OxyTs OxyMCs OxyA
907	213590	213608	TACAGCGGAC ATACATCA	ASO-1024	OxyTs DNAas DNAGs DNAas DNAGs DNAGs DNAmcs DNAGs DNAGs DNAts DNAas DNAGs DNAmcs DNAts DNAGs DNAas OxyTs OxyMCs OxyA
908	213591	213606	CAGGCGGACAT ACATC	ASO-1025	OxyMCs OxyAs DNAGs DNAGs DNAmcs DNAGs DNAGs DNAas DNAGs DNAGs DNAts DNAas OxyMCs OxyAs OxyTs OxyMC
909	213591	213607	ACAGCGGAC ATACATC	ASO-1026	OxyAs OxyMCs DNAas DNAGs DNAGs DNAmcs DNAGs DNAGs DNAas DNAGs DNAGs DNAts DNAas DNAGs DNAmcs OxyAs OxyTs OxyMC
910	213591	213608	TACAGCGGAC ATACATC	ASO-1027	OxyTs DNAas DNAGs DNAas DNAGs DNAGs DNAmcs DNAGs DNAGs DNAts DNAas DNAGs DNAmcs DNAts DNAGs DNAas OxyTs OxyMC
911	213591	213609	CTACAGCGGGA CATAATC	ASO-1028	OxyMCs DNAts DNAas DNAGs DNAGs DNAmcs DNAGs DNAGs DNAGs DNAts DNAas DNAGs DNAmcs DNAts DNAGs DNAas OxyTs OxyMC
912	213592	213608	TACAGCGGAC ATACAT	ASO-1029	OxyTs OxyAs OxyMCs DNAas DNAGs DNAGs DNAmcs DNAGs DNAGs DNAGs DNAts DNAas DNAGs DNAmcs OxyAs OxyT
913	213592	213609	CTACAGCGGGA CATAAT	ASO-1030	OxyMCs DNAts DNAas DNAGs DNAGs DNAmcs DNAGs DNAGs DNAGs DNAts DNAas DNAGs DNAmcs DNAts OxyAs OxyT
914	213592	213610	TCTACAGCGGG ACATAAT	ASO-1031	OxyTs DNAGs DNAts DNAas DNAGs DNAGs DNAmcs DNAGs DNAGs DNAts DNAas DNAGs DNAmcs DNAts DNAGs OxyAs OxyT
915	213593	213608	TACAGCGGAC	ASO-	OxyTs OxyAs OxyMCs OxyAs DNAGs DNAGs DNAmcs DNAGs DNAGs DNAas DNAGs DNAGs 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
			AAATTCCTC	1051	DNAas DNAas DNAas DNAats DNAats DNacs OxyTs OxyTs OxyMC
935	213930	213947	TCCTGGTTATA AATTCCT	ASO- 1052	OxyTs OxyMCs OxyMCs DNAats DNacs DNags DNats DNats DNats DNAas DNats DNAas DNAas DNAas DNAats DNAats DNats OxyMCs OxyTs OxyT
936	213930	213948	TTCCCTGGTTAT AAATTCCT	ASO- 1053	OxyTs OxyTs OxyMCs DNacs DNats DNags DNags DNats DNats DNAas DNats DNAas DNAas DNAas DNAats OxyTs OxyMCs OxyTs OxyT
937	213930	213949	TTTTCCCTGGTTA TAAATTCCT	ASO- 1054	OxyTs OxyTs OxyTs OxyMCs DNacs DNats DNags DNags DNats DNats DNAas DNats DNAas DNAas DNAas DNats DNats OxyMCs OxyTs OxyT
938	213931	213948	TTCCCTGGTTAT AAATTCCT	ASO- 1055	OxyTs OxyTs OxyMCs OxyMCs DNats DNags DNags DNats DNats DNAas DNats DNAas DNAas DNAas DNats DNats OxyMCs OxyT
939	213931	213949	TTTTCCCTGGTTA TAAATTCCT	ASO- 1056	OxyTs OxyTs OxyTs OxyMCs DNacs DNats DNags DNags DNats DNats DNAas DNats DNAas DNAas DNAas DNats OxyTs OxyMCs OxyT
940	213931	213950	ATTTCCCTGGTT ATAAATTCCT	ASO- 1057	OxyAs OxyTs OxyTs OxyTs DNacs DNacs DNats DNats DNags DNags DNats DNats DNAas DNats DNAas DNAas DNAas DNats DNats OxyTs OxyMCs OxyT
941	213932	213948	TTCCCTGGTTAT AAATTCCT	ASO- 1058	OxyTs OxyTs OxyMCs OxyMCs DNats DNags DNags DNats DNats DNAas DNats DNAas DNAas DNAas OxyAs OxyTs OxyTs OxyMC
942	213932	213949	TTTTCCCTGGTTA TAAATTCCT	ASO- 1059	OxyTs OxyTs OxyTs OxyMCs DNacs DNats DNags DNags DNats DNats DNAas DNats DNAas DNAas DNAas OxyAs OxyTs OxyTs OxyMC
943	213932	213950	ATTTCCCTGGTT ATAAATTCCT	ASO- 1060	OxyAs OxyTs OxyTs OxyTs DNacs DNacs DNats DNats DNags DNags DNats DNats DNAas DNats DNAas DNAas DNAas OxyAs OxyTs OxyTs OxyMC
944	213932	213951	CATTTCCTGGTT TATAAATTC	ASO- 1061	OxyMCs OxyAs OxyTs OxyTs DNats DNacs DNacs DNats DNags DNags DNats DNats DNats DNAas DNats DNAas DNAas DNats DNats OxyTs OxyTs OxyMC
945	213933	213951	CATTTCCTGGTT TATAAATTC	ASO- 1062	OxyMCs OxyAs OxyTs OxyTs DNats DNacs DNacs DNats DNags DNags DNats DNats DNats DNAas DNats DNAas DNAas OxyAs OxyAs OxyTs OxyT
946	213933	213952	TCATTTCCCTGG TTATAAATTC	ASO- 1063	OxyTs OxyMCs OxyAs DNats DNats DNats DNacs DNacs DNats DNats DNags DNags DNats DNats DNAas DNats DNAas OxyAs OxyAs OxyTs OxyT
947	213934	213951	CATTTCCTGGTT TATAAATTC	ASO- 1064	OxyMCs OxyAs OxyTs OxyTs DNats DNacs DNacs DNats DNags DNags DNats DNats DNats DNAas DNats OxyAs OxyAs OxyTs OxyT
948	213934	213952	TCATTTCCCTGG TTATAAATTC	ASO- 1065	OxyTs OxyMCs OxyAs OxyTs DNats DNats DNats DNacs DNacs DNats DNats DNags DNags DNats DNats DNAas DNats OxyAs OxyAs OxyTs OxyT
949	214149	214165	CACTGCTCTGTA TACCCTCT	ASO- 1066	OxyMCs DNAas DNacs DNats DNags DNats DNats DNats DNats DNags DNats DNAas DNats DNAas DNacs DNacs DNacs OxyMCs OxyT
950	214152	214169	CACTCACTGTC TGATACT	ASO- 1067	OxyMCs OxyAs OxyMCs DNats DNacs DNacs DNats DNats DNats DNats DNags DNats DNacs DNats DNags DNats DNAas DNats OxyAs OxyMC
951	214152	214170	ACACTCACTGTC CTGTATAC	ASO- 1068	OxyAs OxyMCs OxyAs DNacs DNats DNats DNats DNacs DNacs DNats DNats DNags DNats DNacs DNats DNags DNags DNats DNats DNAas DNats OxyAs OxyMC
952	214153	214169	CACTCACTGTC TGATACT	ASO- 1069	OxyMCs OxyAs OxyMCs DNats DNacs DNacs DNats DNats DNats DNats DNags DNats DNacs DNats DNags DNats DNAas DNats OxyTs OxyA
953	214159	214175	AGCTTACACTC	ASO-	OxyAs DNags DNacs DNats DNats DNats DNats DNacs DNacs DNats DNats DNags DNats DNacs DNats DNags 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
			ACTAGG	1219	DNAas DNAas DNACs OxyTs OxyAs OxyGs OxyG
1107	233828	233844	GAATTTGGTAT TCAGGT	ASO-1220	OxyGs OxyAs OxyTs DNATs DNATs DNAGs DNAGs DNAas DNATs DNATs DNACs DNAas OxyGs OxyTs OxyT
1108	234122	234141	CATTTATGGGG TATAATATG	ASO-1221	OxyMCs OxyAs OxyTs DNATs DNATs DNATs DNATs DNAGs DNAGs DNAGs DNATs DNAas DNATs DNAas DNATs OxyTs OxyAs OxyTs OxyG
1109	234373	234390	TGATATTTGTTT TATTGT	ASO-1222	OxyTs OxyGs OxyAs DNATs DNATs DNATs DNATs DNAGs DNATs DNACs DNATs DNAas OxyTs OxyTs OxyGs OxyT
1110	234379	234397	TTTTATTTTGATA TTTGTTC	ASO-1223	OxyTs OxyTs OxyTs OxyAs DNATs DNATs DNATs DNATs DNAGs DNAas DNATs DNAas DNATs DNATs DNATs OxyGs OxyTs OxyT OxyMC
1111	235164	235183	ATAGTGTGTTT TGTGAGTCT	ASO-1224	OxyAs DNATs DNAas DNAGs DNATs DNAGs DNATs DNATs DNATs DNATs DNATs DNAGs DNATs DNAGs DNAas DNAGs OxyTs OxyMCs OxyT
1112	235255	235271	AAAGGTTAGAT ATATGA	ASO-1225	OxyAs OxyAs OxyAs OxyGs DNAGs DNATs DNATs DNATs DNATs DNAGs DNATs DNAas DNATs OxyAs OxyTs OxyGs OxyA
1113	235523	235540	TATAAGTTTCTA AGGAGT	ASO-1226	OxyTs OxyAs OxyTs DNAAas DNAAas DNAGs DNATs DNATs DNATs DNATs DNAas DNAAas DNAGs OxyGs OxyAs OxyGs OxyT
1114	235870	235888	GATATATAATAA AATGGTA	ASO-1227	OxyGs OxyAs OxyTs OxyAs DNATs DNAAas DNATs DNATs DNAAas DNATs DNAas DNAAas DNATs DNATs OxyGs OxyTs OxyTs OxyA
1115	236126	236143	TTTGTTTCTGA GTAGTG	ASO-1228	OxyTs OxyTs OxyTs OxyGs DNATs DNATs DNATs DNATs DNATs DNATs DNAas DNAGs DNATs DNAas DNAGs OxyTs OxyG
1116	236409	236427	ATTAATGTTTAT TATTTGC	ASO-1229	OxyAs OxyTs OxyTs OxyAs DNAAas DNATs DNAGs DNATs DNATs DNATs DNATs DNATs DNAAas DNATs OxyTs OxyTs OxyGs OxyMC
1117	236658	236675	AGAAAAGTAGC AAGACAA	ASO-1230	OxyAs OxyGs OxyAs OxyAs DNAAas DNAAas DNAGs DNATs DNATs DNATs DNAas DNAAas DNAGs OxyAs OxyMCs OxyAs OxyA
1118	237019	237035	TGAACTGAAAGA CTGTTG	ASO-1231	OxyTs OxyGs OxyAs OxyAs DNACs DNATs DNAGs DNAAas DNAAas DNAGs DNACs DNATs DNAGs DNATs OxyTs OxyG
1119	237093	237112	GTAGAGAAAATT TAAGACAGT	ASO-0076	OxyGs OxyTs OxyAs OxyGs DNAAas DNAGs DNAAas DNAAas DNATs DNATs DNATs DNAAas DNAGs DNAGs DNACs OxyAs OxyGs OxyT
1120	237101	237119	AGTAAATGTAG AGAAATTT	ASO-1232	OxyAs OxyGs OxyTs OxyAs DNAAas DNAAas DNATs DNATs DNATs DNATs DNAas DNAGs DNAAas DNAAas OxyAs OxyTs OxyTs OxyT
1121	237723	237742	TAAGTGAACAG TTTTGTAGT	ASO-1233	OxyTs OxyAs OxyAs OxyGs DNATs DNAGs DNAAas DNAAas DNACs DNAGs DNATs DNATs DNATs DNATs DNAGs DNATs DNAAas OxyGs OxyT
1122	237726	237744	TTTAAAGTGAAC AGTTTTGT	ASO-1234	OxyTs OxyTs OxyTs OxyAs DNAAas DNAGs DNATs DNATs DNATs DNATs DNAas DNAGs DNATs DNATs OxyTs OxyTs OxyGs OxyT
1123	238473	238492	CACATGACATT AAATTGTAC	ASO-1235	OxyMCs OxyAs OxyMCs OxyAs DNATs DNATs DNAGs DNAAas DNATs DNATs DNATs DNAAas DNAAas DNATs DNATs OxyTs OxyTs OxyAs OxyMC
1124	238476	238493	ACACATGACAT TAAATTG	ASO-1236	OxyAs OxyMCs OxyAs OxyMCs DNAAas DNATs DNAGs DNAAas DNATs DNATs DNATs DNAAas DNAAas OxyAs OxyTs OxyTs OxyG
1125	238988	239004	GTATTTGGTGT	ASO-	OxyGs DNATs DNAAas DNATs DNATs DNATs DNAGs 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
			GGTGGG	1237	DNAGs DNAGs DNATs OxyGs OxyGs OxyG
1126	238992	239008	GATGGTATTGG GTGTGG	ASO- 1238	OxyGs OxyAs OxyTs DNAGs DNAGs DNATs DNAs DNATs DNATs DNATs DNAGs DNAGs DNATs DNAGs DNATs OxyGs OxyG
1127	239707	239725	AGGAGAGATGA AGAAAGGAA	ASO- 1239	OxyAs OxyGs OxyGs DNAs DNAGs DNAs DNAGs DNAs DNATs DNAGs DNAs DNAs DNAGs DNAs DNAs OxyGs OxyGs OxyAs OxyA
1128	240013	240032	AGTATTCTCTC CATTTTATG	ASO- 1240	OxyAs DNAGs DNATs DNAs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNACs DNAs DNATs DNATs DNATs OxyAs OxyTs OxyG
1129	240243	240260	GAGAGGATAAA TAGGAAA	ASO- 1241	OxyGs OxyAs OxyGs OxyAs DNAGs DNAGs DNAs DNATs DNATs DNAs DNAs DNATs DNAs DNAGs OxyGs OxyAs OxyAs OxyA
1130	240554	240570	CCTGCATCTGT TAATAT	ASO- 1242	OxyMCs OxyMCs DNATs DNAGs DNACs DNAs DNATs DNATs DNATs DNAGs DNATs DNATs DNAs DNAs OxyTs OxyAs OxyT
1131	240766	240785	ATTATTTATTTA TTTTCTC	ASO- 1243	OxyAs OxyTs OxyTs OxyAs DNATs DNATs DNATs DNAs DNAs DNATs DNATs DNAs DNATs DNATs DNATs DNATs DNACs OxyMCs OxyTs OxyMC
1132	241923	241941	GTGTTGCTCAA CTGAGAGA	ASO- 1244	OxyGs DNATs DNAGs DNATs DNATs DNAGs DNATs DNATs DNATs DNAs DNAs DNACs DNATs DNAGs DNAs DNAGs OxyAs OxyGs OxyA
1133	241976	241994	TTTTCTTTATCT ATGAACT	ASO- 1245	OxyTs OxyTs OxyTs DNACs DNATs DNATs DNATs DNAs DNAs DNATs DNATs DNATs DNAs DNATs DNAGs DNAs OxyAs OxyMCs OxyT
1134	242356	242373	CCTGATGTGAA ATTGTCA	ASO- 1246	OxyMCs OxyMCs DNATs DNAGs DNAs DNATs DNATs DNAGs DNATs DNAGs DNAs DNAs DNAs DNATs DNATs DNAGs OxyTs OxyMCs OxyA
1135	242729	242748	GTAATAGTGAT AGTTTCCAT	ASO- 0077	OxyGs DNATs DNAs DNAs DNATs DNAs DNAGs DNATs DNAGs DNAs DNATs DNAs DNAGs DNATs DNATs DNATs OxyMCs OxyMCs OxyAs OxyT
1136	242869	242887	ATGAAAATGAT GATAGTAA	ASO- 1247	OxyAs OxyTs OxyGs OxyAs DNAs DNAs DNAs DNATs DNATs DNAGs DNAs DNAGs DNAs DNATs DNAs OxyGs OxyTs OxyAs OxyA
1137	243066	243083	GTTTAATCATCT TAGAAT	ASO- 1248	OxyGs OxyTs OxyTs DNAs DNAs DNAs DNATs DNATs DNACs DNAs DNATs DNATs DNATs DNAs OxyGs OxyAs OxyAs OxyT
1138	243824	243842	TTTGTTGAGTG ATGGTGTC	ASO- 1249	OxyTs OxyTs DNATs DNAGs DNATs DNATs DNAGs DNAs DNAGs DNATs DNAGs DNAs DNATs DNAGs DNATs DNATs DNAGs OxyTs OxyMC
1139	244141	244159	ATTGTAGGAAA ACTTCAGA	ASO- 1250	OxyAs OxyTs OxyTs DNAGs DNATs DNAs DNAGs DNAGs DNATs DNAs DNAs DNAs DNATs DNATs DNATs OxyMCs OxyAs OxyGs OxyA
1140	244265	244284	ATAGAGAAATGA CACCTGGAG	ASO- 1251	OxyAs DNATs DNAs DNAGs DNAs DNAGs DNAs DNAs DNATs DNATs DNAGs DNAs DNACs DNAs DNATs DNATs DNATs OxyGs OxyGs OxyAs OxyG
1141	244266	244284	ATAGAGAAATGA CACCTGGA	ASO- 1252	OxyAs DNATs DNAs DNAGs DNAs DNAGs DNAs DNAs DNATs DNATs DNAGs DNAs DNACs DNAs DNATs DNATs DNATs OxyTs OxyGs OxyGs OxyA
1142	244266	244285	TATAGAGAAATG ACACCTGGA	ASO- 1253	OxyTs OxyAs DNATs DNAs DNAGs DNAs DNAGs DNAs DNAs DNATs DNATs DNAs DNAs DNATs DNATs DNATs DNATs OxyGs OxyGs OxyA
1143	244267	244286	ATATAGAGAAT GACACCTGG	ASO- 1254	OxyAs DNATs DNAs DNATs DNAs DNAGs DNAs DNATs DNATs DNAGs DNAs DNAGs DNAs DNATs DNAs DNATs DNATs OxyMCs OxyTs OxyGs OxyG
1144	244268	244286	ATATAGAGAAT	ASO-	OxyAs OxyTs DNAs DNATs DNAs DNAGs DNAs DNATs DNATs DNAGs DNAs 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
			GACACCTG	1255	DNAGs DNAAAs DNAAcs DNAAcs OxyMCs OxyTs OxyG
1145	244268	244287	AATATAGAGAA TGACACCTG	ASO-1256	OxyAs OxyTs DNAAAs DNAAcs DNAAcs DNAAcs OxyMCs OxyTs OxyG DNAAAs DNAAAs
1146	244269	244286	ATATAGAGAAT GACACCT	ASO-1257	OxyAs OxyTs OxyAs DNAAAs DNAAcs DNAAcs DNAAcs DNAAcs DNAAAs DNAAAs DNAAAs DNAAAs
1147	244269	244287	AATATAGAGAA TGACACCT	ASO-1258	OxyAs OxyTs OxyAs DNAAAs DNAAcs DNAAcs DNAAcs DNAAcs DNAAAs DNAAAs DNAAAs DNAAAs
1148	244269	244288	GAATATAGAGA ATGACACCT	ASO-1259	OxyGs OxyAs OxyTs DNAAAs DNAAcs DNAAcs DNAAcs DNAAcs DNAAAs DNAAAs DNAAAs DNAAAs
1149	244270	244286	ATATAGAGAAT GACACC	ASO-1260	OxyAs OxyTs OxyAs OxyTs DNAAAs DNAAcs DNAAcs DNAAcs DNAAcs DNAAAs DNAAAs DNAAAs DNAAAs
1150	244270	244287	AATATAGAGAA TGACACC	ASO-1261	OxyAs OxyTs OxyAs DNAAAs DNAAcs DNAAcs DNAAcs DNAAcs DNAAAs DNAAAs DNAAAs DNAAAs
1151	244270	244288	GAATATAGAGA ATGACACC	ASO-1262	OxyGs OxyAs OxyTs DNAAAs DNAAcs DNAAcs DNAAcs DNAAcs DNAAAs DNAAAs DNAAAs DNAAAs
1152	244270	244289	AGAAATATAGAG AATGACACC	ASO-1263	OxyAs OxyGs DNAAAs DNAAcs DNAAcs DNAAcs DNAAcs DNAAAs DNAAAs DNAAAs DNAAAs
1153	244271	244288	GAATATAGAGA ATGACAC	ASO-1264	OxyGs OxyAs OxyTs DNAAAs DNAAcs DNAAcs DNAAcs DNAAcs DNAAAs DNAAAs DNAAAs DNAAAs
1154	244271	244290	TAGAAATATAGA GAATGACAC	ASO-1265	OxyTs OxyAs OxyGs OxyAs DNAAAs DNAAcs DNAAcs DNAAcs DNAAcs DNAAAs DNAAAs DNAAAs DNAAAs
1155	244274	244291	GTAGAAATATAG AGAAATGA	ASO-1266	OxyGs OxyTs OxyAs OxyGs DNAAAs DNAAcs DNAAcs DNAAcs DNAAcs DNAAAs DNAAAs DNAAAs DNAAAs
1156	244351	244367	ACATCATAAGC TCCAGC	ASO-1267	OxyAs OxyMCs OxyAs DNAAAs DNAAcs DNAAcs DNAAcs DNAAcs DNAAAs DNAAAs DNAAAs DNAAAs
1157	244351	244368	TACATCATAAG CTCCAGC	ASO-1268	OxyTs DNAAAs DNAAcs DNAAcs DNAAcs DNAAcs DNAAcs DNAAcs DNAAcs DNAAAs DNAAAs DNAAAs DNAAAs
1158	244351	244369	ATACATCATAA GCTCCAGC	ASO-1269	OxyAs DNAAAs DNAAcs DNAAcs DNAAcs DNAAcs DNAAcs DNAAcs DNAAcs DNAAAs DNAAAs DNAAAs DNAAAs
1159	244352	244369	ATACATCATAA GCTCCAG	ASO-1270	OxyAs OxyTs OxyAs DNAAAs DNAAcs DNAAcs DNAAcs DNAAcs DNAAAs DNAAAs DNAAAs DNAAAs
1160	244352	244370	CATACATCATA AGCTCCAG	ASO-1271	OxyMCs OxyAs DNAAAs DNAAcs DNAAcs DNAAcs DNAAcs DNAAAs DNAAAs DNAAAs DNAAAs
1161	244352	244371	ACATACATCAT AAGCTCCAG	ASO-1272	OxyAs OxyMCs OxyAs DNAAAs DNAAcs DNAAcs DNAAcs DNAAcs DNAAAs DNAAAs DNAAAs DNAAAs
1162	244353	244369	ATACATCATAA GCTCCA	ASO-1273	OxyAs OxyTs DNAAAs DNAAcs DNAAcs DNAAcs DNAAcs DNAAAs DNAAAs DNAAAs DNAAAs
1163	244353	244370	CATACATCATA	ASO-	OxyMCs OxyAs DNAAAs DNAAcs DNAAcs DNAAcs DNAAcs 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
			AGTCCA	1274	DNAas DNAas DNAGs DNACs DNAts DNAts OxyMCs OxyA
1164	244353	244371	ACATACATCAT AAGCTCCA	ASO- 1275	OxyAs OxyMCs OxyAs DNAts DNAts DNACs DNAts DNAts DNACs DNAas DNAts DNAas DNAs DNAGs DNACs DNAts DNAts DNACs OxyMCs OxyA
1165	244353	244372	TACATACATCA TAAGCTCCA	ASO- 1276	OxyTs OxyAs DNACs DNAts DNAts DNAs DNACs DNAts DNAts DNACs DNAas DNAts DNAas DNAs DNAGs DNACs DNAts DNAts DNACs OxyMCs OxyA
1166	244354	244370	CATACATCATA AGCTCC	ASO- 1277	OxyMCs OxyAs DNAts DNAs DNACs DNAs DNAts DNAts DNACs DNAas DNAts DNAas DNAs DNAGs OxyMCs OxyTs OxyMCs OxyMC
1167	244354	244371	ACATACATCAT AAGCTCC	ASO- 1278	OxyAs OxyMCs OxyAs DNAts DNAs DNACs DNAs DNAts DNAts DNACs DNAas DNAts DNAas DNAs DNAGs DNACs OxyTs OxyMCs OxyMC
1168	244354	244372	TACATACATCA TAAGCTCC	ASO- 1279	OxyTs OxyAs DNACs DNAts DNAts DNAs DNACs DNAts DNAts DNACs DNAas DNAts DNAas DNAs DNAGs DNACs DNAts OxyMCs OxyMC
1169	244354	244373	TTACATACATC ATAAGCTCC	ASO- 1280	OxyTs DNAts DNAs DNACs DNAts DNAts DNAs DNACs DNAts DNAts DNACs DNAas DNAts DNAs DNAGs DNACs OxyTs OxyMCs OxyMC
1170	244355	244371	ACATACATCAT AAGCTC	ASO- 1281	OxyAs OxyMCs OxyAs DNAts DNAs DNACs DNAs DNAts DNAts DNACs DNAas DNAts DNAas DNAs OxyGs OxyMCs OxyTs OxyMC
1171	244355	244372	TACATACATCA TAAGCTC	ASO- 1282	OxyTs OxyAs OxyMCs OxyAs DNAts DNAs DNACs DNAs DNAts DNAts DNACs DNAas DNAts DNAs DNAGs OxyMCs OxyTs OxyMC
1172	244355	244373	TTACATACATC ATAAGCTC	ASO- 1283	OxyTs OxyTs OxyAs OxyMCs DNAs DNAts DNAts DNAs DNACs DNAts DNAs DNAts DNACs DNAs DNAts DNAs DNAs DNAGs DNACs OxyTs OxyMC
1173	244355	244374	ATTACATACAT CATAAGCTC	ASO- 1284	OxyAs DNAts DNAts DNAs DNACs DNAs DNAts DNAs DNAts DNAs DNAs DNAts DNACs DNAs DNAts DNAs DNAs OxyGs OxyMCs OxyTs OxyMC
1174	244356	244373	TTACATACATC ATAAGCT	ASO- 1285	OxyTs OxyTs DNAs DNACs DNAs DNAts DNAts DNAs DNACs DNAs DNAts DNACs DNAas DNAts DNAs OxyAs OxyGs OxyMCs OxyT
1175	244356	244374	ATTACATACAT CATAAGCT	ASO- 1286	OxyAs DNAts DNAts DNAs DNACs DNAs DNAts DNAts DNAs DNAs DNAts DNAts DNACs DNAs DNAts DNAs OxyAs OxyGs OxyMCs OxyT
1176	244356	244375	TATTACATACAT CATAAGCT	ASO- 1287	OxyTs OxyAs DNAts DNAts DNAs DNACs DNAs DNAts DNAts DNAs DNAs DNAts DNAts DNACs DNAs DNAts DNAs OxyAs OxyGs OxyMCs OxyT
1177	244357	244373	TTACATACATC ATAAGC	ASO- 1288	OxyTs OxyTs OxyAs OxyMCs DNAs DNAts DNAts DNAs DNACs DNAs DNAts DNACs DNAs DNAts OxyAs OxyAs OxyGs OxyMC
1178	244357	244374	ATTACATACAT CATAAGC	ASO- 1289	OxyAs OxyTs OxyTs OxyAs DNAts DNAs DNAts DNAts DNAs DNACs DNAs DNAts DNACs DNAs DNAts OxyAs OxyAs OxyGs OxyMC
1179	244357	244375	TATTACATACAT CATAAGC	ASO- 1290	OxyTs OxyAs OxyTs OxyTs DNAs DNACs DNAs DNAts DNAts DNAs DNAs DNAts DNAts DNACs DNAs DNAts OxyAs OxyAs OxyGs OxyMC
1180	244357	244376	TTATTACATACA TCATAAGC	ASO- 1291	OxyTs OxyTs OxyAs OxyTs DNAts DNAs DNACs DNAs DNAts DNAts DNAs DNACs DNAas DNAts DNAs DNAts DNAs DNAts DNAs OxyAs OxyGs OxyMC
1181	244358	244375	TATTACATACAT CATAAG	ASO- 1292	OxyTs OxyAs OxyTs OxyTs DNAs DNACs DNAs DNAts DNAts DNAs DNAs DNAts DNAts DNACs DNAs OxyTs OxyAs OxyAs OxyG
1182	244358	244376	TTATTACATACA	ASO-	OxyTs OxyTs OxyAs OxyTs DNAts DNAs DNACs DNAs DNAts DNAs DNAts DNAs DNACs

FIG. 1A (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
1202	245669	245686	TGTGCTAG TTTAAATTCCTG AAGCTT	1312 ASO-1313	DNAAs DNATs DNAGs DNATs DNAGs OxyMCs OxyTs OxyAs OxyG OxyTs OxyTs DNATs DNATs DNAAs DNAAs DNATs DNATs DNATs DNATs DNATs DNATs DNAGs DNAAs DNAAs OxyGs OxyMCs OxyTs OxyT
1203	246287	246305	CAAAATGAGGT ATTATATA	ASO-1314	OxyMCs OxyAs OxyAs OxyAs DNATs DNATs DNATs DNAGs DNAAs DNAGs DNAGs DNATs DNAs DNATs DNATs DNATs OxyTs OxyAs OxyTs OxyA
1204	246518	246536	GAGTATCTGAT AAGGGACC	ASO-1315	OxyGs OxyAs DNAGs DNATs DNAs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNAAs DNAAs DNAGs DNAGs DNAGs DNAAs OxyMCs OxyMC
1205	246523	246542	ATTAAGAGTA TCTGATAAG	ASO-0078	OxyAs OxyTs OxyTs OxyAs DNAAs DNAAs DNAGs DNAGs DNAAs DNATs DNATs DNATs DNATs DNATs DNAGs DNAs OxyTs OxyAs OxyAs OxyG
1206	246727	246746	GTGATGGAAAC TTCAAAAAT	ASO-1316	OxyGs OxyTs OxyGs OxyAs DNATs DNATs DNAGs DNAGs DNAAs DNAAs DNATs DNATs DNATs DNATs DNATs DNATs OxyAs OxyAs OxyAs OxyT
1207	246773	246789	TTGATGAGGTC TTTTGCC	ASO-1317	OxyTs DNATs DNAGs DNAAs DNATs DNAGs DNAGs DNATs DNATs DNATs DNATs DNATs DNATs DNATs OxyGs OxyGs OxyMC
1208	246773	246790	ATTGATGAGGT CTTTGGC	ASO-1318	OxyAs DNATs DNATs DNAGs DNAAs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNATs OxyGs OxyGs OxyMC
1209	246849	246865	ACTTACACAGA TCCATG	ASO-1319	OxyAs OxyMCs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNAAs DNATs DNATs OxyMCs OxyAs OxyTs OxyG
1210	246849	246866	TACTTACACAG ATCCATG	ASO-1320	OxyTs OxyAs OxyMCs OxyTs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNAGs DNAAs DNATs DNATs DNATs DNATs DNATs OxyAs OxyTs OxyG
1211	246849	246867	TTACTTACACA GATCCATG	ASO-1321	OxyTs OxyTs OxyAs OxyMCs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNAAs DNAGs DNAAs DNATs DNATs DNATs DNATs DNATs DNAAs DNATs OxyTs OxyG
1212	246849	246868	TTTACTTACACA GATCCATG	ASO-1322	OxyTs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNAAs DNAGs DNAAs DNATs DNATs DNATs OxyMCs OxyAs OxyTs OxyG
1213	246850	246866	TACTTACACAG ATCCAT	ASO-1323	OxyTs OxyAs OxyMCs OxyTs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNAGs DNAAs DNATs DNATs DNATs DNATs OxyAs OxyT
1214	246850	246867	TTACTTACACA GATCCAT	ASO-1324	OxyTs OxyTs DNAs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNAGs DNAAs DNATs OxyMCs OxyMCs OxyAs OxyT
1215	246850	246868	TTTACTTACACA GATCCAT	ASO-1325	OxyTs OxyTs OxyTs OxyAs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNAAs DNAGs DNAAs DNATs DNATs DNATs OxyMCs OxyAs OxyT
1216	246850	246869	TTTTACTTACAC AGATCCAT	ASO-1326	OxyTs OxyTs OxyTs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNAGs DNAAs DNATs DNATs DNATs DNATs OxyMCs OxyAs OxyT
1217	246851	246867	TTACTTACACA GATCCA	ASO-1327	OxyTs OxyTs OxyAs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNAGs DNAAs DNATs OxyMCs OxyMCs OxyA
1218	246851	246868	TTTACTTACACA GATCCA	ASO-1328	OxyTs OxyTs OxyTs DNAs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNAAs DNAGs DNAAs DNATs DNATs OxyMCs OxyMCs OxyA
1219	246851	246869	TTTTACTTACAC AGATCCA	ASO-1329	OxyTs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNAGs DNAAs OxyTs OxyMCs OxyMCs OxyA
1220	246851	246870	GTTTACTTACA	ASO-	OxyGs OxyTs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNATs 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
			CAGATCCA	1330	DNAas DNAcs DNAas DNAcs DNAas DNAcs DNAcs OxyAs OxyAs
1221	246852	246868	TTTACTTACACA GATCC	ASO-1331	OxyTs OxyTs OxyTs DNAas DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs
1222	246852	246869	TTTTACTTACAC AGATCC	ASO-1332	OxyTs OxyTs OxyTs DNAas DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs
1223	246852	246870	GTTTTACTTACA CAGATCC	ASO-1333	OxyGs OxyTs DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs
1224	246852	246871	AGTTTTACTTAC ACAGATCC	ASO-1334	OxyAs DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs
1225	246853	246870	GTTTTACTTACA CAGATC	ASO-1335	OxyGs OxyTs OxyTs DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs
1226	246853	246871	AGTTTTACTTAC ACAGATC	ASO-1336	OxyAs OxyGs OxyTs OxyTs DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs
1227	246853	246872	AAGTTTTACTTA CACAGATC	ASO-1337	OxyAs OxyAs OxyGs OxyTs DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs
1228	246854	246871	AGTTTTACTTAC ACAGAT	ASO-1338	OxyAs OxyGs OxyTs OxyTs DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs
1229	246854	246872	AAGTTTTACTTA CACAGAT	ASO-1339	OxyAs OxyAs OxyGs OxyTs DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs
1230	246854	246873	GAAGTTTACT TACACAGAT	ASO-1340	OxyGs OxyAs OxyAs DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs
1231	246855	246874	AGAAGTTTAC TTACACAGA	ASO-1341	OxyAs DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs
1232	246856	246874	AGAAGTTTAC TTACACAG	ASO-1342	OxyAs OxyGs OxyAs DNAas DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs
1233	246856	246875	GAGAAAGTTTAA CTTACACAG	ASO-1343	OxyGs OxyAs DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs
1234	246857	246875	GAGAAAGTTTAA CTTACACA	ASO-1344	OxyGs OxyAs DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs
1235	246858	246875	GAGAAAGTTTAA CTTACAC	ASO-1345	OxyGs OxyAs OxyGs OxyAs DNAas DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs
1236	247171	247188	AAATCTTTTCTT CTGGGA	ASO-1346	OxyAs OxyAs OxyAs DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs
1237	247399	247415	GCCTTTGATTT ACTTAG	ASO-1347	DNAas DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs
1238	247440	247459	AATTACTTTTAT TTTTAATGT	ASO-1348	OxyAs OxyAs OxyTs OxyTs DNAas DNAcs DNAcs DNAcs DNAcs DNAcs DNAcs
1239	247882	247899	TTCTAAGTATTC	ASO-	OxyTs OxyTs OxyTs OxyTs DNAas DNAas DNAas DNAas DNAas DNAas 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
			AATTGC	1349	DNAcs DNAas DNAas DNAts OxyTs OxyGs OxyMC
1240	248013	248028	ACAGTAGAACG TTGCT	ASO- 1350	OxyAs OxyMCs OxyAs DNags DNAts DNAas DNags DNAas DNAmcs DNags DNAts DNAts OxyGs OxyMCs OxyT
1241	248013	248029	AACAGTAGAAC GTTGCT	ASO- 1351	OxyAs OxyAs OxyMCs OxyAs DNags DNAts DNAas DNags DNAas DNAas DNAmcs DNags DNAts DNAts OxyGs OxyMCs OxyT
1242	248014	248029	AACAGTAGAAC GTTGC	ASO- 1352	OxyAs OxyAs OxyMCs OxyAs DNags DNAts DNAas DNags DNAas DNAas DNAmcs DNags OxyTs OxyTs OxyGs OxyMC
1243	248014	248030	CAACAGTAGAA CGTTGC	ASO- 1353	OxyMCs OxyAs OxyAs DNacs DNAas DNags DNAts DNAas DNags DNAas DNAas DNAmcs DNags OxyTs OxyTs OxyGs OxyMC
1244	248015	248030	CAACAGTAGAA CGTTG	ASO- 1354	OxyMCs OxyAs OxyAs OxyMCs DNAas DNags DNAts DNAas DNags DNAas DNAas DNacs OxyGs OxyTs OxyTs OxyG
1245	248015	248031	GCAACAGTAGA ACGTTG	ASO- 1355	OxyGs OxyMCs OxyAs OxyAs DNacs DNAas DNags DNAts DNAas DNags DNAas DNAas DNAmcs DNags OxyTs OxyTs OxyG
1246	248051	248068	CAAGCAGTCTA CAGTCTC	ASO- 1356	OxyMCs OxyAs DNAas DNags DNacs DNAas DNags DNAts DNacs DNAts DNAas DNacs DNAas DNags DNAts DNacs OxyTs OxyMC
1247	248053	248069	TCAAGCAGTCT ACAGTC	ASO- 1357	OxyTs OxyMCs DNAas DNAas DNags DNacs DNAas DNags DNAts DNacs DNAts DNAas DNacs DNAas OxyGs OxyTs OxyMC
1248	248053	248070	TTCAAGCAGTC TACAGTC	ASO- 1358	OxyTs DNAts DNacs DNAas DNags DNacs DNAas DNags DNAts DNacs DNAts DNAas DNacs DNAas OxyGs OxyTs OxyMC
1249	248054	248070	TTCAAGCAGTC TACAGT	ASO- 1359	OxyTs OxyTs OxyMCs DNAas DNAas DNags DNacs DNAas DNags DNAts DNacs DNAts DNAas DNacs OxyAs OxyGs OxyT
1250	248054	248071	CTTCAAGCAGT CTACAGT	ASO- 1360	OxyMCs DNAts DNAts DNacs DNAas DNags DNacs DNAas DNags DNacs DNAts DNacs DNAts DNAas DNacs OxyAs OxyGs OxyT
1251	248055	248072	TCTTCAAGCAG TCTACAG	ASO- 1361	OxyTs OxyMCs DNAts DNAts DNacs DNAas DNags DNacs DNAas DNacs DNags DNAts DNacs DNAts DNAas DNacs OxyAs OxyG
1252	248055	248074	TTTCTTCAAGC AGTCTACAG	ASO- 1362	OxyTs DNAts DNAts DNacs DNAts DNAts DNacs DNAas DNags DNacs DNAas DNags DNAts DNacs DNAts DNacs DNacs OxyAs OxyG
1253	248056	248072	TCTTCAAGCAG TCTACA	ASO- 1363	OxyTs OxyMCs DNAts DNAts DNacs DNAas DNags DNacs DNacs DNAas DNags DNAts DNacs DNAts DNAas OxyMCs OxyA
1254	248056	248073	TTCTTCAAGCA GTCTACA	ASO- 1364	OxyTs OxyTs OxyMCs DNAts DNAts DNacs DNAas DNags DNacs DNacs DNAas DNags DNAts DNacs DNAts DNAas OxyMCs OxyA
1255	248056	248074	TTTCTTCAAGC AGTCTACA	ASO- 1365	OxyTs OxyTs DNAts DNacs DNAts DNAts DNacs DNAas DNags DNacs DNAas DNags DNAts DNacs DNAts DNAas OxyMCs OxyA
1256	248056	248075	ATTTCTTCAAG CAGTCTACA	ASO- 1366	OxyAs DNAts DNAts DNacs DNAts DNAts DNacs DNacs DNacs DNags DNacs DNAas DNags DNAts DNacs DNAts DNAas OxyMCs OxyA
1257	248057	248075	ATTTCTTCAAG CAGTCTAC	ASO- 1367	OxyAs DNAts DNAts DNacs DNAts DNAts DNacs DNacs DNacs DNags DNacs DNAas DNags DNAts DNacs OxyTs OxyAs OxyMC
1258	248057	248076	AATTTCTTCAA	ASO-	OxyAs OxyAs DNAts DNAts DNacs DNAts DNAts DNacs DNacs DNAas 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
1278	248079	248098	CTTCAA CTTTAGTTTTCT TCTAGCAT	1387 ASO-1388	DNAts DNACs DNAts OxyTs OxyMCs OxyAs OxyA OxyMCs DNAts DNAts DNAts DNAs DNAGs DNAts DNAts DNAts DNAts DNACs DNAts DNAts DNACs DNAts DNAs DNAGs DNAs DNAs OxyT
1279	248080	248098	CTTTAGTTTTCT TCTAGCA	ASO-1389	OxyMCs OxyTs DNAts DNAts DNAs DNAGs DNAts DNAts DNAts DNAts DNACs DNAts DNAts DNACs DNAts DNAs DNAGs OxyMCs OxyA
1280	248081	248098	CTTTAGTTTTCT TCTAGC	ASO-1390	OxyMCs OxyTs OxyTs DNAts DNAts DNAs DNAGs DNAts DNAts DNAts DNAts DNACs DNAts DNAts DNACs DNAts DNAs OxyGs OxyMC
1281	248082	248099	CCTTTAGTTTTCT TTCTAG	ASO-1391	OxyMCs OxyMCs DNAts DNAts DNAts DNAs DNAs DNAGs DNAts DNAts DNAts DNAts DNACs DNAts DNAts DNACs DNAts OxyAs OxyG
1282	248083	248100	ACCTTTAGTTTTCT CTTCTA	ASO-1392	OxyAs OxyMCs DNACs DNAts DNAts DNAts DNAs DNAs DNAGs DNAts DNAts DNAts DNACs DNAts DNAts OxyMCs OxyTs OxyA
1283	248085	248102	TTACCTTTAGTTT TTCTTC	ASO-1393	OxyTs OxyTs OxyAs OxyMCs DNACs DNAts DNAts DNAts DNAs DNAs DNAGs DNAts DNAts DNAts DNACs OxyTs OxyTs OxyMC
1284	248086	248103	CCTTACCTTTAG TTTTCTT	ASO-1394	OxyMCs OxyTs OxyTs DNAs DNACs DNACs DNAts DNAts DNAts DNAts DNAs DNAGs DNAts DNAts DNAts DNAts OxyMCs OxyTs OxyT
1285	248092	248111	TAAAATTTCTTA CCTTTAGT	ASO-1395	OxyTs OxyAs OxyAs DNAs DNAs DNAts DNAts DNAts DNAts DNACs DNAts DNAts DNAs DNACs DNACs DNAts DNAts OxyTs OxyAs OxyGs OxyT
1286	248093	248111	TAAAATTTCTTA CCTTTAG	ASO-1396	OxyTs OxyAs OxyAs DNAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAs DNACs DNACs DNAts OxyTs OxyTs OxyAs OxyG
1287	248093	248112	GTAAAAATTTCTT ACCTTTAG	ASO-1397	OxyGs OxyTs OxyAs OxyAs DNAs DNAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAs DNACs DNACs DNAts OxyTs OxyTs OxyAs OxyG
1288	248094	248112	GTAAAAATTTCTT ACCTTTA	ASO-1398	OxyGs OxyTs OxyAs OxyAs DNAs DNAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAs DNACs DNACs OxyTs OxyTs OxyTs OxyA
1289	248094	248113	TGTAAAAATTTCTT TACCTTTA	ASO-1399	OxyTs OxyGs OxyTs DNAs DNAs DNAs DNAs DNAs DNAts DNAts DNAts DNACs DNAts DNAts DNAs DNACs DNACs OxyTs OxyTs OxyTs OxyA
1290	248095	248113	TGTAAAAATTTCTT TACCTTT	ASO-1400	OxyTs OxyGs OxyTs DNAs DNAs DNAs DNAs DNAs DNAts DNAts DNAts DNACs DNAts DNAts DNAs DNACs OxyMCs OxyTs OxyTs OxyT
1291	248095	248114	ATGTAAAAATTTCT TTACCTTT	ASO-1401	OxyAs OxyTs OxyGs OxyTs DNAs DNAs DNAs DNAs DNAs DNAts DNAts DNAts DNACs DNAts DNAts DNAs DNACs DNACs OxyTs OxyTs OxyT
1292	248096	248114	ATGTAAAAATTTCT TTACCTT	ASO-1402	OxyAs OxyTs OxyGs OxyTs DNAs DNAs DNAs DNAs DNAs DNAts DNAts DNAts DNACs DNAts DNAts DNAs DNACs OxyMCs OxyTs OxyT
1293	248096	248115	AAATGTAAAAATTT CTTACCTT	ASO-1403	OxyAs OxyAs OxyTs DNAGs DNAts DNAs DNAs DNAs DNAs DNAs DNAts DNAts DNAts DNACs DNAts DNAts DNAs DNAs DNAs DNAs DNAs OxyT
1294	248097	248115	AAATGTAAAAATTT CTTACCT	ASO-1404	OxyAs OxyAs OxyTs DNAts DNAts DNAs DNAs DNAs DNAs DNAs DNAts DNAts DNAts DNACs DNAts DNAts OxyAs OxyMCs OxyMCs OxyT
1295	248097	248116	AAATGTAAAAATTT TCTTACCT	ASO-1405	OxyAs OxyAs OxyAs OxyTs DNAGs DNAts DNAts DNAs DNAs DNAs DNAs DNAts DNAts DNAts DNACs DNAts DNAts OxyAs OxyMCs OxyMCs OxyT
1296	248098	248115	AATGTAAAAATTT	ASO-	OxyAs OxyAs OxyTs OxyGs DNAts DNAts DNAs DNAs DNAs DNAts DNAts DNAts DNAts DNAts DNAts 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
			AGCAT	1425	DNAas DNags OxyMCs OxyAs OxyTs OxyT
1316	250211	250228	GTTTATGAAAC AGGTAAC	ASO- 1426	OxyGs OxyTs OxyTs DNAas DNats DNags DNAas DNAas DNags DNAas DNags DNAas DNags DNAas DNags DNags OxyTs OxyAs OxyAs OxyAs OxyMC
1317	250538	250555	TTTTAGTTTACA TGATGA	ASO- 1427	OxyTs OxyTs OxyTs DNAas DNags DNats DNats DNats DNats DNats DNags DNAas DNags DNAas DNats DNags OxyAs OxyTs OxyGs OxyA
1318	250877	250895	ATGATTCAGGG TAAGCAGG	ASO- 1428	OxyAs DNats DNags DNAas DNats DNats DNats DNags DNAas DNags DNags DNags DNags DNats DNAas DNAas DNags DNags DNags DNags OxyAs OxyGs OxyG
1319	251031	251050	TTATTTAATTAAT GAGATTGT	ASO- 0079	OxyTs OxyTs OxyAs OxyTs DNats DNAas DNats DNats DNats DNats DNags DNags DNags DNats DNags DNAas DNags DNAas OxyTs OxyTs OxyGs OxyT
1320	251036	251054	TAATTTAATTAAT AATTGAG	ASO- 1429	OxyTs OxyAs OxyTs DNats DNats DNags DNats DNats DNats DNats DNats DNats DNats DNats DNAas DNAas DNats OxyTs OxyGs OxyAs OxyG
1321	251421	251438	TGTTACTAAAC TTCTTGA	ASO- 1430	OxyTs OxyGs DNats DNats DNags DNags DNats DNats DNags DNAas DNAas DNags DNags DNats DNats DNags OxyTs OxyTs OxyGs OxyA
1322	251728	251745	CAGACAAATTG GTTTTAC	ASO- 1431	OxyMCs OxyAs DNags DNAas DNags DNAas DNAas DNags DNats DNats DNats DNats DNags DNags DNats DNats OxyTs OxyTs OxyAs OxyMC
1323	251947	251964	AAAGGATACTG GAACTTT	ASO- 1432	OxyAs OxyAs OxyAs OxyGs DNags DNAas DNats DNats DNags DNags DNats DNats DNags DNags DNAas DNAas OxyMCs OxyTs OxyTs OxyT
1324	251947	251966	GAAAAGGATAC TGGAACCTT	ASO- 1433	OxyGs OxyAs OxyAs OxyAs DNAas DNags DNags DNags DNags DNags DNats DNags DNags DNats DNags DNags DNAas DNAas OxyMCs OxyTs OxyTs OxyT
1325	251948	251966	GAAAAGGATAC TGGAACCTT	ASO- 1434	OxyGs OxyAs OxyAs OxyAs DNAas DNags DNags DNags DNags DNags DNats DNags DNags DNats DNags DNags DNAas DNAas OxyAs OxyMCs OxyTs OxyT
1326	251988	252004	CAGTTGTGTTT ATTGGA	ASO- 1435	OxyMCs OxyAs OxyGs DNats DNats DNags DNats DNags DNats DNats DNats DNats DNats DNAas DNats DNats OxyGs OxyGs OxyA
1327	252038	252055	AGCAAATTTAG AACTAAA	ASO- 1436	OxyAs OxyGs OxyMCs OxyAs DNAas DNags DNats DNats DNats DNats DNats DNags DNags DNAas DNAas DNags DNags OxyTs OxyAs OxyAs OxyA
1328	252038	252056	CAGCAAATTTA GAACTAAA	ASO- 1437	OxyMCs OxyAs OxyGs OxyMCs DNAas DNAas DNags DNats DNats DNats DNats DNats DNAas DNags DNAas DNAas DNags DNats OxyTs OxyAs OxyAs OxyA
1329	252039	252056	CAGCAAATTTA GAACTAA	ASO- 1438	OxyMCs OxyAs OxyGs OxyMCs DNAas DNAas DNags DNats DNats DNats DNats DNats DNAas DNags DNAas DNAas OxyMCs OxyTs OxyAs OxyA
1330	252238	252256	GCTGCTGTAAA ATGAGAGT	ASO- 1439	OxyGs DNags DNats DNags DNags DNats DNats DNags DNats DNags DNags DNags DNags DNAas DNats DNags DNAas DNags DNags DNags OxyAs OxyGs OxyT
1331	252239	252256	GCTGCTGTAAA ATGAGAG	ASO- 1440	OxyGs DNags DNats DNags DNags DNats DNats DNags DNats DNags DNags DNags DNags DNAas DNats DNags DNAas DNags DNags DNags OxyAs OxyGs OxyA
1332	252280	252298	TAACTTACCTTT ACTCCA	ASO- 1441	OxyTs DNAas DNags DNags DNats DNats DNats DNags DNags DNags DNags DNags DNags DNats DNags DNags DNats DNags DNags OxyMCs OxyAs OxyT
1333	252281	252298	TAACTTACCTTT ACTCCA	ASO- 1442	OxyTs DNAas DNags DNags DNats DNats DNats DNags DNags DNags DNags DNags DNags DNats DNags DNags DNats DNags DNags OxyMCs OxyA
1334	252281	252299	TTAACTTACCTT	ASO-	OxyTs OxyTs DNAas DNAas DNags DNats DNats DNats DNats DNags DNags DNags 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
			TACTCCA	1443	DNAts DNAts DNAAas DNAAcs DNAts DNAts DNAAcs OxyMCs OxyA
1335	252281	252300	TTTAACTTACCT TTACTCCA	ASO- 1444	OxyTs OxyTs DNAts DNAAas DNAAcs DNAts DNAts DNAAas DNAAcs DNAAcs DNAAcs OxyA
1336	252282	252299	TTAACTTACCTT TACTCC	ASO- 1445	OxyTs OxyTs OxyAs OxyAs DNAAcs DNAts DNAts DNAAas DNAAcs DNAAcs DNAts DNAts DNAAcs DNAAcs OxyMC
1337	252282	252300	TTTAACTTACCT TTACTCC	ASO- 1446	OxyTs OxyTs OxyTs DNAAas DNAAas DNAAcs DNAts DNAts DNAAas DNAAcs DNAAcs DNAAcs DNAAcs OxyMC
1338	252283	252299	TTAACTTACCTT TACTC	ASO- 1447	OxyTs OxyTs OxyAs DNAAas DNAAcs DNAts DNAts DNAAas DNAAcs DNAAcs DNAts DNAts DNAAcs DNAAcs OxyMCs OxyTs OxyMC
1339	252284	252301	GTTTAACTTAC CTTTACT	ASO- 1448	OxyGs OxyTs OxyTs DNAAas DNAAas DNAAcs DNAts DNAts DNAAas DNAAcs DNAAcs DNAts DNAts DNAAas DNAAcs
1340	252285	252301	GTTTAACTTAC CTTTAC	ASO- 1449	OxyGs OxyTs OxyTs DNAAas DNAAas DNAAcs DNAts DNAts DNAAas DNAAcs DNAAcs DNAts DNAts DNAAas DNAAcs
1341	252285	252302	TGTTTAACTTAC CTTTAC	ASO- 1450	OxyTs OxyGs OxyTs DNAts DNAts DNAAas DNAAas DNAAcs DNAts DNAts DNAAas DNAAcs DNAAcs DNAts DNAts DNAAas
1342	252285	252303	CTGTTTAACTTA CCTTTAC	ASO- 1451	OxyMCs DNAts DNAAcs DNAts DNAts DNAAas DNAAas DNAAcs DNAAas DNAAcs DNAts DNAts DNAAas DNAAcs DNAts DNAts
1343	252285	252304	CTGTGTTTAACTT ACCTTTAC	ASO- 1452	OxyTs OxyMCs DNAts DNAAcs DNAts DNAts DNAAas DNAAas DNAAcs DNAAas DNAAcs DNAts DNAts DNAAas DNAAcs DNAts DNAts
1344	252286	252303	CTGTGTTTAACTTA CCTTTA	ASO- 1453	OxyMCs OxyTs DNAAcs DNAts DNAts DNAAas DNAAas DNAAcs DNAAas DNAAcs DNAts DNAts DNAAas DNAAcs DNAts DNAts
1345	252286	252304	TCTGTGTTTAACTT ACCTTTA	ASO- 1454	OxyTs OxyMCs DNAts DNAAcs DNAts DNAts DNAAas DNAAas DNAAcs DNAAas DNAAcs DNAts DNAts DNAAas DNAAcs DNAts DNAts
1346	252286	252305	ATCTGTGTTTAACT TACCTTTA	ASO- 1455	OxyAs OxyTs OxyMCs DNAts DNAAcs DNAts DNAts DNAAas DNAAas DNAAcs DNAAas DNAAcs DNAts DNAts DNAAas DNAAcs DNAts DNAts
1347	252287	252305	ATCTGTGTTTAACT TACCTTT	ASO- 1456	OxyAs OxyTs OxyMCs DNAts DNAAcs DNAts DNAts DNAAas DNAAas DNAAcs DNAAas DNAAcs DNAts DNAts DNAAas DNAAcs DNAts DNAts
1348	252287	252306	CATCTGTTTAA CTTACCCTT	ASO- 1457	OxyMCs OxyAs OxyTs DNAAcs DNAts DNAAcs DNAts DNAts DNAAas DNAAas DNAAcs DNAAas DNAAcs DNAts DNAts DNAAas DNAAas
1349	252288	252305	ATCTGTGTTTAACT TACCTT	ASO- 1458	OxyAs OxyTs OxyMCs DNAts DNAAcs DNAts DNAts DNAAas DNAAas DNAAcs DNAAas DNAAcs DNAts DNAts DNAAas DNAAas DNAts DNAts
1350	252288	252306	CATCTGTTTAA CTTACCCTT	ASO- 1459	OxyMCs OxyAs DNAts DNAAcs DNAts DNAAcs DNAts DNAts DNAAas DNAAas DNAAcs DNAAas DNAAcs DNAts DNAts DNAAas DNAAas
1351	252289	252305	ATCTGTGTTTAACT TACCT	ASO- 1460	OxyAs DNAts DNAAcs DNAts DNAAcs DNAts DNAts DNAAas DNAAas DNAAcs DNAAas DNAAcs DNAts DNAts DNAAas DNAAas DNAts DNAts
1352	252289	252306	CATCTGTTTAA CTTACCCT	ASO- 1461	OxyMCs DNAAas DNAts DNAAcs DNAts DNAAcs DNAts DNAts DNAAas DNAAas DNAAcs DNAAas DNAAcs DNAts DNAts DNAAas DNAAas
1353	252290	252306	CATCTGTTTAA	ASO-	OxyMCs OxyAs OxyTs OxyMCs DNAts DNAAcs DNAts DNAts DNAAas DNAAas DNAAcs DNAAas DNAAcs DNAts DNAts 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
			CTTACC	1462	DNAas DNAcs DNAts DNAs OxyAs OxyMCs OxyMC
1354	252290	252307	GCATCTGTTTA ACTTACC	ASO-1463	OxyGs DNAcs DNAas DNAts DNAcs DNAts DNAs DNAts DNAts DNAs DNAas
1355	252336	252355	TAACATTTAAA GATTATCCA	ASO-1464	OxyTs OxyAs OxyMCs DNAas DNAts DNAts DNAts DNAs DNAas DNAs
1356	252624	252643	TTATTTGGAAA AGCATTTGG	ASO-1465	OxyTs DNAts DNAas DNAts DNAts DNAts DNAs DNAs DNAs DNAas DNAs
1357	252879	252897	TATTAATTTGTT TAGAAAAG	ASO-1466	OxyTs OxyAs OxyTs DNAs DNAs DNAts DNAts DNAts DNAts DNAs DNAs
1358	253054	253071	GTGTTGATGAA GAATGTA	ASO-1467	OxyGs OxyTs OxyGs DNAts DNAts DNAs DNAas DNAts DNAs DNAs DNAas
1359	253080	253097	ATTAATTAATTC CCAAGA	ASO-1468	OxyAs OxyTs OxyAs DNAas DNAts DNAts DNAts DNAs DNAas DNAs DNAts
1360	253537	253553	TATAAGTTGAA TGAAG	ASO-1469	OxyTs OxyAs OxyTs DNAs DNAs DNAts DNAts DNAts DNAs DNAs DNAas
1361	253645	253661	TTCTGAATTGA CCAGTC	ASO-1470	OxyTs OxyTs OxyMCs DNAts DNAs DNAs DNAas DNAs DNAts DNAts DNAs
1362	253645	253662	TTTCTGAATTG ACCAGTC	ASO-1471	OxyTs OxyTs OxyTs OxyMCs DNAts DNAs DNAs DNAas DNAs DNAts DNAs
1363	253647	253664	CTTTTCTGAATT GACCAG	ASO-1472	OxyMCs DNAts DNAts DNAts DNAts DNAts DNAs DNAs DNAs DNAas DNAs
1364	253648	253665	CTTTTCTGAA TTGACCA	ASO-1473	OxyMCs DNAts DNAts DNAts DNAts DNAts DNAs DNAs DNAs DNAs
1365	253649	253666	TCCTTTTCTGA ATTGACC	ASO-1474	OxyTs OxyMCs DNAts DNAts DNAts DNAts DNAts DNAs DNAs DNAs DNAs
1366	253649	253667	TTCCTTTTCTGA ATTGACC	ASO-1475	OxyTs OxyTs OxyMCs DNAts DNAts DNAts DNAts DNAts DNAs DNAs DNAs
1367	253673	253689	CATCTGAACAC TCGAAC	ASO-1476	OxyMCs OxyAs OxyTs OxyMCs DNAts DNAs DNAs DNAas DNAs DNAs
1368	253673	253690	TCATCTGAACA CTCGAAC	ASO-1477	OxyTs OxyMCs OxyAs DNAts DNAs DNAs DNAs DNAs DNAs DNAs DNAs
1369	253673	253691	ATCATCTGAAC ACTCGAAC	ASO-1478	OxyAs OxyTs OxyMCs OxyAs DNAts DNAs DNAs DNAs DNAs DNAs DNAs
1370	253673	253692	CATCATCTGAA CACTCGAAC	ASO-1479	OxyMCs OxyAs DNAts DNAs DNAs DNAts DNAts DNAts DNAs DNAs
1371	253676	253691	ATCATCTGAAC ACTCG	ASO-1480	OxyAs OxyTs OxyMCs OxyAs DNAts DNAts DNAts DNAs DNAs DNAs
1372	253676	253692	CATCATCTGAA	ASO-	OxyMCs OxyAs DNAts DNAs DNAs DNAts DNAts DNAts 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
			CACTCG	1481	DNAas DNAcs DNAas DNAs OxyTs OxyMCs OxyG
1373	253861	253879	CAAATTCAAATTT CAGAGAA	ASO-1482	OxyMCs OxyAs OxyAs DNAs DNats DNacs DNAs DNAas DNAs DNats DNats DNats DNacs DNAas DNags OxyAs OxyGs OxyAs OxyA
1374	254164	254183	AGGTGTAAAT TTATTGTTT	ASO-1483	OxyAs OxyGs OxyGs DNats DNags DNats DNats DNAs DNAs DNAs DNAs DNats DNats DNAas DNats OxyGs OxyTs OxyTs OxyT
1375	254301	254319	GTGTGATATAA TTATTTTA	ASO-1484	OxyGs OxyTs OxyGs OxyTs DNags DNAs DNats DNAs DNats DNAs DNAs DNats DNats DNAas DNats OxyTs OxyTs OxyTs OxyA
1376	254884	254903	TAAATGAATAT GTGCTCA	ASO-1485	OxyTs OxyTs OxyAs OxyAs DNAas DNats DNags DNAs DNAs DNAs DNAs DNats DNags DNats DNags DNacs DNacs OxyTs OxyMCs OxyA
1377	254916	254933	TTCTTTATTGTT AGGTAT	ASO-1486	OxyTs OxyTs OxyMCs DNats DNats DNAs DNAs DNats DNats DNags DNats DNats DNAas DNags OxyGs OxyTs OxyAs OxyT
1378	255212	255231	TATTTAATATGC TATATTTA	ASO-1487	OxyTs OxyAs OxyTs OxyTs DNats DNAs DNAs DNats DNats DNats DNags DNacs DNats DNAas DNats DNAs OxyTs OxyTs OxyA
1379	255431	255448	AGAAATTAACA TGATATT	ASO-1488	OxyAs OxyGs OxyAs OxyAs DNats DNats DNats DNAs DNAs DNAs DNAs DNats DNags DNAs OxyTs OxyAs OxyTs OxyT
1380	255686	255703	TAGTATTGAGA GGAAGAT	ASO-1808	OxyTs OxyAs OxyGs OxyTs DNAs DNats DNats DNags DNAs DNAs DNAs DNags DNags DNAas DNAs OxyGs OxyAs OxyT
1381	255869	255888	TATTTATTATTT TCTAAAGG	ASO-1489	OxyTs OxyAs OxyTs OxyTs DNats DNAs DNats DNats DNats DNats DNats DNats DNats DNacs DNats DNAs OxyAs OxyAs OxyGs OxyG
1382	256137	256155	TAAAGAATATAT CATTACC	ASO-1490	OxyTs OxyAs OxyAs OxyAs DNags DNAs DNAs DNAs DNats DNats DNAs DNats DNacs DNAs DNats OxyTs OxyAs OxyMCs OxyMC
1383	256310	256326	TTCAAATATTAG TGGGG	ASO-1491	OxyTs OxyTs OxyMCs OxyAs DNAs DNats DNats DNats DNats DNats DNAs DNags DNats DNags OxyGs OxyGs OxyG
1384	256760	256778	GATGAACGTGA AAGACATG	ASO-1492	OxyGs OxyAs OxyTs OxyGs DNAs DNAs DNAs DNAmcs DNags DNats DNags DNAas DNAas DNAs DNags DNAs DNAs DNacs OxyAs OxyTs OxyG
1385	256864	256883	TGCAGAAAATA GAAACAGAG	ASO-1493	OxyTs OxyGs OxyMCs DNAs DNags DNAs DNAs DNAs DNAs DNAs DNats DNAas DNags DNAas DNAs DNAs DNacs OxyAs OxyGs OxyAs OxyG
1386	256865	256884	ATGCAGAAAAT AGAAACAGA	ASO-1494	OxyAs OxyTs OxyGs OxyMCs DNAs DNags DNAs DNAs DNAs DNAs DNAs DNats DNAs DNags DNAs DNAs DNAs DNAs OxyMCs OxyAs OxyGs OxyA
1387	256887	256904	TTTGTTGTTTAT CTGTGG	ASO-1495	OxyTs DNats DNats DNags DNats DNats DNags DNats DNats DNats DNAs DNats DNacs DNats OxyGs OxyTs OxyGs OxyG
1388	256887	256905	CTTTGTTGTTTA TCTGTGG	ASO-1496	OxyMCs OxyTs DNats DNats DNags DNats DNats DNats DNags DNats DNats DNAas DNats DNacs DNats DNags DNats DNats OxyGs OxyG
1389	256888	256905	CTTTGTTGTTTA TCTGTG	ASO-1497	OxyMCs DNats DNats DNats DNats DNats DNats DNats DNags DNats DNats DNAas DNats DNacs OxyTs OxyGs OxyTs OxyG
1390	256889	256906	GCTTTGTTGTT TATCTGT	ASO-1498	OxyGs OxyMCs DNats DNats DNats DNats DNags DNats DNats DNats DNats DNats DNAs DNats DNacs DNats OxyGs OxyT
1391	256890	256908	TGGCTTTGTTG	ASO-	OxyTs DNags DNags DNacs DNats DNats DNats DNags DNats DNats 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
			TTCAGGT	1627	DNats DNats DNats DNacs DNAs OxyGs OxyGs OxyT
1525	282239	282258	TATGTAGTTTG GGTATTAT	ASO-0085	OxyTs OxyAs OxyTs OxyGs DNats DNAs DNags DNats DNats DNats DNats DNags
1526	282245	282261	CTTTATGTAGTT TGGGT	ASO-1628	OxyMCs OxyTs OxyTs DNats DNAs DNats DNags DNats DNAs DNags DNats DNats
1527	282662	282681	TTAAATTCACAT TTTACTTT	ASO-1629	OxyTs OxyTs OxyAs OxyAs DNAs DNats DNats DNats DNacs DNAs DNAs DNacs DNAs
1528	282946	282964	CTCCATAACAT TTACCATC	ASO-1630	OxyMCs OxyTs OxyMCs DNacs DNAs DNats DNats DNAs DNAs DNAs DNAs DNacs
1529	282952	282969	ATTCTCTCCAT AACATTT	ASO-1631	OxyAs OxyTs OxyTs OxyMCs DNats DNacs DNats DNats DNacs DNacs DNAs DNats
1530	283532	283549	TGTTAGTTTTAT TCTCAG	ASO-1632	OxyTs OxyGs OxyTs DNats DNAs DNags DNats DNats DNats DNats DNats DNAs
1531	283823	283841	GACAATAGTAA GAATTTTA	ASO-1633	OxyGs OxyAs OxyMCs OxyAs DNAs DNAs DNats DNAs DNAs DNags DNats DNAs
1532	284117	284136	TAAAGGTGTTT TTAGTTTAA	ASO-1634	OxyTs OxyAs OxyAs OxyAs DNags DNags DNats DNats DNags DNats DNats DNacs
1533	284473	284490	TCTTGTGAAA TATTGGG	ASO-1635	OxyTs OxyMCs OxyTs OxyTs DNags DNats DNats DNats DNags DNAs DNAs
1534	284474	284491	TTCTTGTGAA ATATTGG	ASO-1636	OxyTs OxyTs OxyMCs OxyTs DNats DNags DNats DNats DNats DNags DNAs
1535	285623	285640	TTGCAAGACTT ATTTAGG	ASO-1637	OxyTs OxyTs OxyGs OxyMCs DNAs DNAs DNags DNAs DNAs DNacs DNats
1536	285794	285811	TATGTTGCATT CATCTAT	ASO-1638	OxyTs OxyAs DNats DNags DNats DNats DNags DNacs DNacs DNAs DNats DNats
1537	285985	286002	GCCAAATTTACA AAACATA	ASO-1639	OxyGs OxyMCs OxyMCs OxyAs DNAs DNAs DNats DNats DNats DNats DNAs DNacs
1538	286389	286405	GCTCTCAGTCA TATTTC	ASO-1640	OxyGs OxyMCs DNats DNacs DNats DNats DNAs DNAs DNags DNats DNats DNacs
1539	286862	286881	GTAGGTTTTAA TTTTCTTTCA	ASO-1641	OxyGs OxyTs OxyAs DNags DNags DNats DNats DNats DNats DNats DNAs DNAs
1540	286962	286979	GAGTTAAITTC AAAGTGT	ASO-1642	OxyGs OxyAs OxyGs DNats DNats DNAs DNAs DNats DNats DNats DNats DNacs
1541	287329	287348	TGTAATCAAT TTTATATTA	ASO-1643	OxyTs OxyGs OxyMCs OxyTs DNAs DNAs DNAs DNats DNats DNacs DNAs DNAs
1542	287332	287350	TCTGCTAA TCA ATTTTATA	ASO-0086	OxyTs OxyMCs OxyTs OxyGs DNacs DNats DNats DNats DNAs DNAs DNats DNacs
1543	287693	287712	TTAAGAGTTGA	ASO-	OxyTs DNats DNAs DNAs DNags DNags DNAs DNats DNats DNats DNags 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
			TATATAG	1662	DNAts DNAas DNAts OxyAs OxyTs OxyAs OxyG
1563	293844	293860	AGTTTATAGAG TGTGAA	ASO- 1663	OxyAs OxyGs OxyTs OxyTs DNAts DNAas DNAts DNAas DNAGs DNAas DNAGs
1564	294150	294166	CAGTTAGGCAA TAGGTG	ASO- 1664	OxyMCs DNAas DNAGs DNAts DNAts DNAas DNAGs DNAGs DNAGs DNAas
1565	294498	294513	TTACTTCATCG AGACT	ASO- 1665	DNAs DNAts DNAas OxyGs OxyTs OxyG
1566	294500	294516	ATTTTACTTCAT CGAGA	ASO- 1666	OxyTs OxyTs OxyAs OxyMCs DNAts DNAts DNACs DNACs DNAts DNAts DNACs
1567	294955	294973	TTTATTTTCTTG TATAGCC	ASO- 1667	OxyAs OxyTs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1568	295332	295350	AGAAGTGACAT ATGAATCA	ASO- 1668	DNAGs DNAts DNAas DNAts DNAas DNAGs OxyMCs OxyMC
1569	295458	295477	TATTGAACTTTA TATAATTA	ASO- 1669	OxyAs OxyGs OxyAs OxyAs DNAGs DNAts DNAts DNAts DNAts DNAts DNAts
1570	296319	296336	TCTTGCTTTTCG TGCTAAA	ASO- 1670	OxyTs OxyAs OxyTs DNAGs DNAas DNAas DNAts DNAts DNAts DNAts DNAts
1571	296320	296336	TCTTGCTTTTCG TGCTAA	ASO- 1671	DNAs DNAts DNAas DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1572	296320	296337	CTCTTGCTTTC GTGCTAA	ASO- 1672	OxyMCs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1573	296323	296341	TAATCTCTTTCG TTTTCGTGC	ASO- 1673	DNAMcs DNAGs DNAts DNAGs DNACs OxyTs OxyAs OxyA
1574	296323	296342	ATAATCTCTTTCG CTTTCGTGC	ASO- 1674	OxyTs OxyAs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1575	296324	296342	ATAATCTCTTTCG CTTTCGTGC	ASO- 1675	DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1576	296324	296343	GATAATCTCTTTC GCTTTCGTGC	ASO- 1676	OxyAs DNAts DNAas DNAas DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1577	297079	297098	GAAAACATTTTC TTAAGCTGA	ASO- 0088	DNACs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1578	297079	297097	AAAACATTTTCTT AAGCTGA	ASO- 1677	OxyAs OxyAs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1579	297198	297216	TACAAACATAT AAAAGAGA	ASO- 1678	OxyGs OxyAs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1580	297595	297612	CTTTTCAATCAT ATTACAC	ASO- 1679	DNAts DNAts DNAas DNAts DNAts DNAts DNAts DNAts DNAts DNAts
1581	297953	297971	AATTATAGTATT	ASO-	OxyAs OxyAs OxyTs 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
1582	298036	298053	ACAGTAA TGCTTCAGTAT ATATCTT	1680 1681	DNAs DNAas DNacs DNAcs OxyGs OxyTs OxyAs OxyA OxyTs OxyGs DNacs DNats DNats DNacs DNacs DNAas DNags DNats DNAas DNats DNAas DNats DNAas OxyTs OxyMCs OxyTs OxyT
1583	299320	299338	CAAAGATATTA GTGAACCTG	1682	OxyMCs OxyAs OxyAs OxyAs DNags DNAas DNats DNAas DNats DNats DNAas DNags DNats DNags DNAas OxyAs OxyMCs OxyTs OxyG
1584	299326	299342	TAGGCAAAGAT ATTAGT	1683	OxyTs OxyAs OxyGs OxyGs DNacs DNAas DNAas DNags DNAas DNats DNAas DNats DNats OxyAs OxyGs OxyT
1585	299788	299807	TCCTCTATAAAT ATGGTTTT	1684	OxyTs OxyMCs OxyMCs DNats DNacs DNats DNats DNats DNAas DNats DNAas DNAas DNats DNAas DNats DNags DNags DNats DNats OxyTs OxyT
1586	299887	299905	GCTTAAAATCA AATATATA	1685	OxyGs OxyMCs OxyTs OxyTs DNAas DNAas DNAas DNats DNats DNats DNAas DNAas DNats DNats DNags DNags OxyTs OxyAs OxyA
1587	300239	300255	AAGGTAGATCA AATGGA	1686	OxyAs OxyAs OxyGs OxyGs DNats DNAas DNags DNAas DNats DNacs DNAas DNAas OxyTs OxyGs OxyG
1588	300543	300560	AAGGTTAAGA GAGGAAG	1687	OxyAs OxyAs OxyGs OxyGs DNats DNats DNats DNAas DNAas DNags DNAas DNags DNAas DNags OxyGs OxyAs OxyG
1589	300798	300816	TATTGTGTTTAA GTTTAT	0089	OxyTs OxyAs OxyTs OxyTs DNags DNats DNags DNats DNats DNats DNAas DNAas DNags DNats DNats OxyTs OxyAs OxyT
1590	300801	300819	TATTATTGTGTT TAAGTTT	1688	OxyTs OxyAs OxyTs OxyTs DNAas DNats DNats DNags DNats DNats DNats DNats DNats DNAas DNAas OxyGs OxyTs OxyT
1591	301617	301636	TTTTGTTGTTTC ATGTGTAA	1689	OxyTs OxyTs OxyTs DNats DNags DNats DNats DNats DNats DNats DNats DNacs DNAas DNats DNags DNats DNags OxyTs OxyAs OxyA
1592	301676	301694	AGATTTTTCTGT AAAAGAA	1690	OxyAs OxyGs OxyAs OxyTs DNats DNats DNats DNats DNats DNats DNags DNats DNAas DNAas OxyAs OxyGs OxyA
1593	301775	301793	GAATAAATGTA CCATTTTC	1691	OxyGs OxyAs OxyAs OxyTs DNAas DNAas DNats DNats DNags DNats DNAas DNacs DNacs DNAas DNats OxyTs OxyTs OxyMC
1594	301776	301795	AGGAATAAATG TACCATTT	1692	OxyAs OxyGs OxyGs DNAas DNats DNats DNags DNAas DNAas DNats DNags DNats DNAas DNacs DNacs DNAas OxyTs OxyTs OxyT
1595	301777	301795	AGGAATAAATG TACCATTT	1693	OxyAs OxyGs OxyGs OxyAs DNats DNats DNags DNAas DNAas DNats DNags DNats DNAas DNacs DNacs OxyAs OxyTs OxyT
1596	301777	301796	TAGGAATAAAT GTACCAATTT	1694	OxyTs OxyAs OxyGs OxyGs DNAas DNats DNats DNags DNAas DNAas DNats DNags DNats DNAas DNacs DNacs DNAas OxyTs OxyTs OxyT
1597	301778	301795	AGGAATAAATG TACCATT	1695	OxyAs OxyGs OxyGs OxyAs DNats DNats DNags DNAas DNAas DNats DNags DNats DNAas DNacs OxyMCs OxyAs OxyT
1598	301778	301796	TAGGAATAAAT GTACCATT	1696	OxyTs OxyAs OxyGs DNags DNAas DNats DNats DNags DNAas DNAas DNats DNags DNats DNAas DNacs OxyMCs OxyAs OxyT
1599	301778	301797	TTAGGAAATAA TGTACCATT	1697	OxyTs OxyTs OxyAs OxyGs DNags DNAas DNats DNats DNags DNAas DNAas DNats DNags DNats DNAas DNacs OxyMCs OxyAs OxyT
1600	301779	301796	TAGGAATAAAT	1698	OxyTs OxyAs OxyGs DNags DNAas DNats DNats DNags DNAas DNAas DNats DNats DNats DNAas DNacs OxyMCs OxyAs OxyT

FIG. 1A (cont.)

SEQ ID No.	Start (SEQ ID NO: 1)	End (SEQ ID NO: 1)	ASO Sequence	ASO No.	ASO with Chemical Structure
			GTACCAT	1698	DNAGs DNATs DNAAs OxyMCs OxyAs OxyT
1601	301779	301797	TTAGGAATAAA TGTACCAT	ASO- 1699	OxyTs OxyAs DNAGs DNAGs DNAAs DNATs DNATs DNAAs DNAAs DNATs DNAGs DNATs DNAAs OxyMCs OxyAs OxyT
1602	301779	301798	ATTAGGAATAA ATGTACCAT	ASO- 1700	OxyAs OxyTs OxyTs DNAGs DNAGs DNAAs DNATs DNATs DNATs DNAAs DNAAs DNATs DNAGs DNATs DNAAs OxyMCs OxyAs OxyT
1603	301780	301797	TTAGGAATAAA TGTACCA	ASO- 1701	OxyTs OxyTs OxyAs DNAGs DNAGs DNAAs DNATs DNATs DNATs DNAAs DNATs DNAGs DNATs OxyAs OxyMCs OxyT
1604	301780	301798	ATTAGGAATAA ATGTACCA	ASO- 1702	OxyAs OxyTs OxyTs DNAGs DNAGs DNAAs DNATs DNATs DNATs DNAAs DNAAs DNATs DNAGs DNATs OxyAs OxyMCs OxyT
1605	301780	301799	AATTAGGAATA AATGTACCA	ASO- 1703	OxyAs OxyAs OxyTs DNAGs DNAGs DNAGs DNAAs DNATs DNATs DNATs DNAAs DNAAs DNATs DNAGs DNATs OxyAs OxyMCs OxyA
1606	301781	301798	ATTAGGAATAA ATGTACC	ASO- 1704	OxyAs OxyTs OxyAs DNAGs DNAGs DNAAs DNATs DNATs DNATs DNAAs DNAAs DNATs DNAGs OxyTs OxyAs OxyMCs OxyT
1607	301781	301799	AATTAGGAATA AATGTACC	ASO- 1705	OxyAs OxyAs OxyTs DNAGs DNAGs DNAGs DNAAs DNATs DNATs DNATs DNAAs DNAAs DNATs DNAGs OxyTs OxyAs OxyMCs OxyT
1608	301788	301807	TGTTATTAAAT AGGAATAA	ASO- 1706	OxyTs OxyGs OxyTs DNAGs DNATs DNATs DNATs DNAAs DNATs DNATs DNATs DNAGs DNAGs DNATs DNAAs OxyTs OxyAs OxyT
1609	301793	301810	GCATGTATTA AATTAGG	ASO- 1707	OxyGs OxyMCs OxyAs OxyTs DNAGs DNATs DNATs DNATs DNATs DNATs DNAAs DNAAs DNATs DNATs OxyAs OxyGs OxyT
1610	302323	302340	TATATTATACAT TAACTG	ASO- 1708	OxyTs OxyAs OxyTs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNAAs DNATs DNATs DNAAs OxyAs OxyMCs OxyTs OxyT
1611	302378	302396	TTATATATAGTT TTATGAA	ASO- 1709	OxyTs OxyAs OxyTs DNAGs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNAAs OxyTs OxyGs OxyAs OxyA
1612	302987	303005	TCATTAGGTGT AAGGAAAA	ASO- 1710	OxyTs OxyMCs OxyAs OxyTs DNATs DNATs DNAGs DNAGs DNATs DNAGs DNATs DNAAs DNAGs DNAGs DNAGs OxyAs OxyAs OxyA
1613	303219	303237	GTTTATTTGTTT GTAAATG	ASO- 1711	OxyGs OxyTs OxyTs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNAGs DNATs DNAAs OxyAs OxyT
1614	303388	303407	CTGAAATAGGT TAAAAATAT	ASO- 1712	OxyMCs OxyTs OxyGs OxyAs DNAGs DNATs DNATs DNATs DNATs DNATs DNAGs DNATs DNATs DNAAs DNATs DNATs DNATs DNATs DNATs DNATs OxyT
1615	303883	303900	ATATCAAGTTT CAGGTAT	ASO- 1713	OxyAs OxyTs OxyAs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNAGs OxyTs OxyAs OxyT
1616	304085	304101	GCTGGAGAGAT ATATTT	ASO- 1714	OxyGs OxyMCs OxyTs OxyGs DNAGs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNAAs OxyTs OxyT
1617	304347	304366	AGTGAAAGAG AAAAACATG	ASO- 1715	OxyAs OxyGs OxyMCs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNAAs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNATs
1618	304348	304366	AGTGAAAGAG AAAAACAT	ASO- 1716	OxyAs OxyGs OxyMCs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNAAs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNATs
1619	304348	304367	AAGCTGAAAGA	ASO- 1716	OxyAs OxyAs OxyGs OxyMCs DNATs DNATs DNATs DNATs DNATs DNATs DNATs DNAAs 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
1620	304374	304392	GAAAAACAT TGGATTGGTTT ATTGCTTT	1717 ASO-1718	DNAas DNAgs DNAas DNAas DNAas OxyAs OxyMCs OxyAs OxyT OxyTs OxyGs DNAas DNAas DNAts DNAts DNAgs DNAgs DNAts DNAts
1621	304458	304474	CATGCTACTGTG TGAGCC	ASO-1719	OxyMCs OxyAs DNAts DNAgs DNAts DNAas DNAcs DNAts DNAgs DNAts DNAgs DNAts DNAgs DNAas DNAgs OxyMCs OxyMC
1622	304459	304475	CCATGTACTGT GTGAGC	ASO-1720	OxyMCs DNAcs DNAas DNAts DNAgs DNAts DNAas DNAcs DNAts DNAgs DNAts DNAgs DNAts DNAgs DNAas OxyGs OxyMC
1623	304584	304600	TATTTACTTGAT GGGTA	ASO-1721	OxyTs OxyAs OxyTs DNAts DNAas DNAcs DNAts DNAts DNAgs DNAas DNAts DNAgs OxyGs OxyTs OxyA
1624	304584	304601	ATATTTACTTGA TGGTA	ASO-1722	OxyAs OxyTs OxyAs OxyTs DNAts DNAts DNAas DNAcs DNAts DNAgs DNAas DNAts DNAgs DNAgs OxyGs OxyTs OxyA
1625	304584	304602	AATATTTACTTG ATGGTA	ASO-1723	OxyAs OxyTs DNAas DNAts DNAts DNAas DNAcs DNAts DNAts DNAts DNAgs DNAas DNAts DNAgs OxyGs OxyTs OxyA
1626	304585	304602	AA TATTTACTTG ATGGGT	ASO-1724	OxyAs OxyTs DNAas DNAts DNAts DNAts DNAas DNAcs DNAts DNAts DNAgs DNAas DNAts OxyGs OxyTs OxyA
1627	304648	304665	AACAA TGGAAT AAGTAGA	ASO-1725	OxyAs OxyAs OxyMCs OxyAs DNAas DNAts DNAgs DNAgs DNAas DNAas DNAts DNAas DNAas DNAgs OxyTs OxyAs OxyGs OxyA
1628	304966	304984	CTCCTGATAAT ATATGGC	ASO-1726	OxyMCs OxyTs OxyMCs DNAcs DNAts DNAgs DNAas DNAts DNAas DNAas DNAts DNAas DNAts DNAas DNAts DNAts DNAgs OxyGs OxyMC
1629	305066	305082	TAGAGTGGTGA GGTGAG	ASO-1727	OxyTs DNAas DNAgs DNAas DNAgs DNAts DNAts DNAgs DNAgs DNAts DNAas DNAgs DNAgs OxyTs OxyGs OxyAs OxyG
1630	305517	305534	CCTATTTTCAAT TATTCC	ASO-1728	OxyMCs OxyMCs OxyTs DNAas DNAts DNAts DNAts DNAts DNAcs DNAas DNAas DNAts DNAts DNAas DNAts DNAts OxyMCs OxyMC
1631	305595	305613	AAGAGATCAAC AGTGGACC	ASO-0090	OxyAs OxyAs DNAgs DNAas DNAgs DNAas DNAts DNAcs DNAas DNAas DNAcs DNAas DNAgs DNAts DNAgs DNAgs OxyAs OxyMCs OxyMC
1632	305842	305859	TTGGGAATAAA TTTCAGC	ASO-1729	OxyTs OxyTs OxyGs DNAgs DNAgs DNAas DNAas DNAts DNAas DNAas DNAts DNAts DNAts OxyMCs OxyAs OxyGs OxyMC
1633	305982	305998	TACTGTATGAA TGTAAC	ASO-1730	OxyTs OxyAs OxyMCs OxyTs DNAgs DNAts DNAas DNAts DNAgs DNAas DNAas DNAts DNAgs OxyTs OxyAs OxyAs OxyMC
1634	306082	306098	AGAAGCCCCAT TTAAGC	ASO-1731	OxyAs DNAgs DNAas DNAas DNAgs DNAcs DNAcs DNAcs DNAcs DNAas DNAts DNAts DNAts DNAas DNAas DNAas OxyGs OxyMC
1635	306087	306104	ATTAAGAGAA CCCCAT	ASO-1732	OxyAs DNAts DNAts DNAas DNAas DNAgs DNAas DNAgs DNAas DNAas DNAgs DNAcs DNAcs DNAcs OxyMCs OxyAs OxyTs OxyT
1636	306087	306105	TATTAAGAGAA GCCCCAT	ASO-1733	OxyTs DNAas DNAts DNAts DNAas DNAas DNAgs DNAas DNAgs DNAas DNAas DNAgs DNAcs DNAcs DNAcs OxyMCs OxyAs OxyTs OxyT
1637	306088	306104	ATTAAGAGAA CCCCAT	ASO-1734	OxyAs DNAts DNAts DNAas DNAas DNAgs DNAas DNAgs DNAas DNAas DNAgs DNAcs DNAcs OxyMCs OxyMCs OxyAs OxyT
1638	306088	306105	TATTAAGAGAA	ASO-	OxyTs DNAas DNAts DNAts DNAas DNAas DNAgs DNAas DNAgs 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
			GCCCCAT	1735	DNAas DNAGs DNACs DNACs OxyMCs OxyMCs OxyAs OxyT
1639	306088	306106	CTATTAAGAGA AGCCCCAT	ASO- 1736	OxyMCs DNAts DNAas DNAts DNAts DNAas DNAGs DNACs DNAGs DNAas DNAGs DNAas DNAas DNAGs DNACs DNACs DNACs OxyMCs OxyAs OxyT
1640	306089	306105	TATTAAGAGAA GCCCCA	ASO- 1737	OxyTs OxyAs DNAts DNAts DNAas DNAts DNAGs DNAas DNAGs DNAas DNAas DNAGs DNACs DNACs OxyMCs OxyMCs OxyA
1641	306089	306106	CTATTAAGAGA AGCCCCA	ASO- 1738	OxyMCs DNAts DNAas DNAts DNAts DNAts DNAas DNAGs DNACs DNAGs DNAas DNAas DNAas DNAGs DNACs DNACs OxyMCs OxyMCs OxyA
1642	306090	306106	CTATTAAGAGA AGCCCC	ASO- 1739	OxyMCs OxyTs OxyAs DNAts DNAts DNAts DNAas DNAGs DNACs DNAGs DNAas DNAas DNAGs DNAGs DNACs DNACs OxyMCs OxyMC
1643	306090	306107	CCTATTAAGAG AAGCCCC	ASO- 1740	OxyMCs DNACs DNAts DNAas DNAts DNAts DNAts DNAas DNAGs DNACs DNAGs DNAGs DNAas DNAGs DNACs DNACs OxyMCs OxyMC
1644	306091	306107	CCTATTAAGAG AAGCCC	ASO- 1741	OxyMCs DNACs DNAts DNAas DNAts DNAts DNAts DNAas DNAGs DNACs DNAGs DNAGs DNAas DNAGs DNACs OxyMCs OxyMCs OxyA
1645	306091	306108	GCCTATTAAGA GAAGCCC	ASO- 1742	OxyGs DNACs DNACs DNAts DNAas DNAts DNAts DNAts DNAas DNAGs DNACs DNAGs DNAas DNAGs DNACs DNACs OxyMCs OxyMC
1646	306092	306108	GCCTATTAAGA GAAGCC	ASO- 1743	OxyGs DNACs DNACs DNAts DNAas DNAts DNAts DNAts DNAas DNAGs DNACs DNAGs DNAas OxyAs OxyGs OxyMCs OxyMC
1647	306109	306126	CATTGGAAATA CAGGGTG	ASO- 1744	OxyMCs OxyAs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAas DNAGs DNAas DNACs DNACs DNAGs DNAGs DNAGs OxyGs OxyTs OxyG
1648	306110	306126	CATTGGAAATA CAGGGT	ASO- 1745	OxyMCs OxyAs OxyTs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAas DNAas DNACs DNACs DNAGs DNAGs OxyGs OxyGs OxyT
1649	306471	306488	ATTACTTTTGA TGTGAA	ASO- 1746	OxyAs OxyTs OxyTs OxyTs DNAas DNACs DNAts DNAts DNAts DNAts DNAts DNAas DNAts DNAGs OxyTs OxyGs OxyAs OxyA
1650	306687	306704	TTTAAATTTTCAG CTTGAC	ASO- 1747	OxyTs OxyTs DNAts DNAas DNAas DNAts DNAts DNAts DNAts DNAts DNAts DNAGs DNACs DNAts OxyTs OxyGs OxyAs OxyMC
1651	306870	306887	ATTTGTTAAA GCTCTGA	ASO- 1748	OxyAs OxyTs OxyTs DNAts DNAts DNAts DNAts DNAts DNAts DNAas DNAGs DNAGs DNACs DNAts OxyMCs OxyTs OxyGs OxyA
1652	307270	307287	TATGTATAAGA GATGTTT	ASO- 1749	OxyTs OxyAs OxyTs OxyGs DNAts DNAas DNAts DNAts DNAts DNAts DNAts DNAGs DNAas DNAts OxyGs OxyTs OxyTs OxyT
1653	307498	307515	ATGCACTCAGA AACATGC	ASO- 1750	OxyAs DNAts DNAGs DNACs DNAas DNACs DNAts DNAts DNAts DNAts DNAts DNAas DNAas DNACs OxyAs OxyTs OxyGs OxyMC
1654	307499	307517	TCATGCACCTCA GAAACATG	ASO- 1751	OxyTs OxyMCs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAas DNAGs DNAas DNAas DNAGs DNACs DNACs OxyAs OxyTs OxyG
1655	307500	307517	TCATGCACCTCA GAAACAT	ASO- 1752	OxyTs OxyMCs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAas DNAGs DNAas DNAas DNAGs DNACs DNACs OxyAs OxyA
1656	307500	307518	TTCATGCACCTC AGAAACAT	ASO- 1753	OxyTs OxyTs OxyMCs OxyAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNACs DNAas DNAGs DNAas DNAas DNAGs DNACs DNACs OxyAs OxyT
1657	307584	307600	GTTGAAGTGTA	ASO-	OxyGs OxyTs OxyTs OxyGs DNAas DNAas DNAGs DNAts DNAts 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
			AAATTTATT	1792	DNacs DNAas DNAas DNAas DNAts DNAts DNAts DNAas OxyTs OxyT
1696	309491	309510	AGCAGAAATCA CAAAATTTAT	ASO-0091	OxyAs OxyGs OxyMCs DNAas DNags DNAas DNAas DNAts OxyTs OxyAs OxyT DNAas DNacs DNAas DNAas DNAts OxyTs OxyTs OxyAs OxyT
1697	309491	309509	GCAGAAATCAC AAATTTAT	ASO-0092	OxyGs OxyMCs OxyAs DNags DNAas DNAts OxyTs OxyAs OxyT DNacs DNAas DNAas DNAts OxyTs OxyTs OxyAs OxyT
1698	309492	309511	CAGCAGAAATC ACAAATTTA	ASO-0093	OxyAs OxyGs OxyMCs DNAas DNags DNAas DNAas DNAts DNacs DNAas DNacs DNAas DNAas DNAts OxyTs OxyTs OxyTs OxyA
1699	309492	309510	AGCAGAAATCA CAAAATTTA	ASO-1793	OxyMCs OxyAs OxyGs DNacs DNAas DNags DNAas DNAas DNAts DNacs DNAas DNacs DNAas DNAts OxyTs OxyTs OxyTs OxyA
1700	309493	309511	CAGCAGAAATC ACAAATTTT	ASO-1794	OxyMCs OxyAs OxyGs OxyMCs DNAas DNags DNAas DNAas DNAts DNacs DNAas DNacs DNAas DNAts OxyTs OxyTs OxyT
1701	309493	309512	TCAGCAGAAAT CACAAA TTT	ASO-1795	OxyTs OxyMCs OxyAs OxyGs DNacs DNAas DNags DNAas DNAas DNAts DNacs DNAas DNacs DNAas DNAts OxyTs OxyTs OxyT
1702	309494	309512	TCAGCAGAAAT CACAAAAT	ASO-1796	OxyTs OxyMCs OxyAs OxyGs DNacs DNAas DNags DNAas DNAas DNAts DNacs DNAas DNacs DNAas OxyAs OxyAs OxyTs OxyT
1703	309494	309513	GTCAGCAGAAA TCACAAAAT	ASO-1797	OxyGs OxyTs OxyMCs DNAas DNags DNacs DNAas DNags DNAas DNAas DNAts DNacs DNAas DNacs DNAas OxyAs OxyAs OxyTs OxyT
1704	309495	309513	GTCAGCAGAAA TCACAAAAT	ASO-1798	OxyGs OxyTs OxyMCs OxyAs DNags DNacs DNAas DNags DNAas DNAas DNAts DNacs DNAas DNacs OxyAs OxyAs OxyAs OxyT
1705	309495	309514	TGTCAGCAGAA ATCACAAAAT	ASO-1799	OxyTs OxyGs OxyTs OxyMCs DNAas DNags DNacs DNAas DNags DNAas DNAas DNAts DNacs DNAas DNacs OxyAs OxyAs OxyT
1706	309496	309513	GTCAGCAGAAA TCACAAA	ASO-1800	OxyGs OxyTs OxyMCs OxyAs DNags DNacs DNAas DNags DNAas DNAas DNAts DNacs DNAas OxyMCs OxyAs OxyAs OxyA
1707	309496	309514	TGTCAGCAGAA ATCACAAA	ASO-1801	OxyTs OxyGs OxyTs OxyMCs DNAas DNags DNacs DNAas DNags DNAas DNAas DNAts DNacs DNAas DNacs OxyAs OxyAs OxyA
1708	309497	309514	TGTCAGCAGAA ATCACAA	ASO-1802	OxyTs OxyGs OxyTs OxyMCs DNAas DNags DNacs DNAas DNags DNAas DNAas DNAts DNacs DNAas DNacs OxyAs OxyA
1709	310121	310138	GAGAGTAAAT ACAATCT	ASO-1803	OxyGs OxyAs OxyGs OxyAs DNags DNAts DNAts DNAas DNAts DNAas DNacs DNAas DNAts OxyTs OxyMCs OxyT
1710	310122	310140	AGGAGAGGTAA ATACAATC	ASO-0094	OxyAs OxyGs OxyGs OxyAs DNags DNAas DNags DNAts DNAts DNAas DNAts DNAas DNacs DNAas OxyAs OxyTs OxyMC
1711	310224	310241	TAGGAATGCAA TGATGAA	ASO-1804	OxyTs OxyAs OxyGs OxyGs DNAas DNAts DNAts DNags DNAas DNAts DNags DNAas DNAts DNags OxyAs OxyA
1712	310486	310503	ATCATTCTAGT CACTCTG	ASO-1805	OxyAs DNAts DNacs DNAas DNAts DNAts DNacs DNAts DNAts DNacs DNAas DNacs OxyTs OxyMCs OxyTs OxyG
1713	310832	310849	GTGTCATCTAT GTTTACC	ASO-1806	OxyTs OxyAs OxyGs OxyTs DNAas DNAts DNAts DNags DNAas DNags DNags DNAas DNAas OxyGs OxyAs OxyT

FIG. 1B

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
225	56869	56886	119837	119854	--	--	TAAAAAGTGG TAGATTCC	ASO-0293	OxyTs OxyAs OxyAs OxyAs DNAas DNAas DNags DNats DNags DNats DNAas DNAas OxyTs OxyTs OxyMCs OxyMC
226	56869	56887	119837	119855	--	--	TTAAAAAGTG GTAGATTCC	ASO-0295	OxyTs OxyTs OxyAs OxyAs DNAas DNAas DNags DNats DNags DNats DNAas DNAas OxyTs OxyTs OxyMCs OxyMC
265	69183	69202	69439	69458	--	--	ATATTCATACA TACATATTC	ASO-0333	OxyAs OxyTs OxyAs OxyTs DNats DNacs DNAas DNats DNags DNats OxyAs OxyTs OxyMC
287	76153	76170	77746	77763	--	--	AGAGAATGAA AGTCTACA	ASO-0354	OxyAs OxyGs OxyAs DNags DNAas DNags DNats DNags DNAas DNAas DNags DNats DNacs OxyTs OxyAs OxyMCs OxyA
288	76153	76171	77746	77764	--	--	CAGAGAATGA AAGTCTACA	ASO-0356	OxyMCs OxyAs OxyGs DNAas DNags DNAas DNags DNats DNats DNags DNags DNacs OxyTs OxyAs OxyMCs OxyA
289	76153	76172	77746	77765	--	--	CCAGAGAATG AAAGTCTACA	ASO-0358	OxyMCs OxyMCs OxyAs DNags DNAas DNags DNAas DNags DNats DNats DNags DNags DNacs DNats DNAas OxyMCs OxyA
290	76154	76171	77747	77764	--	--	CAGAGAATGA AAGTCTAC	ASO-0360	OxyMCs OxyAs OxyGs OxyAs DNags DNAas DNags DNats DNags DNAas DNags DNats DNacs OxyTs OxyAs OxyMC
291	76154	76172	77747	77765	--	--	CCAGAGAATG AAAGTCTAC	ASO-0362	OxyMCs OxyMCs OxyAs DNags DNAas DNags DNats DNags DNAas DNags DNats DNacs OxyTs OxyAs OxyMC
292	76154	76173	77747	77766	--	--	ACCAGAGAAT GAAAAGTCTAC	ASO-0364	OxyAs OxyMCs OxyMCs OxyAs DNags DNags DNags DNAas DNAas DNats DNags DNags DNacs DNags DNags DNats DNats DNats OxyAs OxyMC

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 AGAATGAAA	ASO-0386	OxyAs OxyTs OxyGs DNAas DNAas DNacs DNacs DNAas DNAs DNAs DNAs OxyAs OxyAs OxyA
385	102012	102028	103215	103231	--	--	AATGTAACCTTG TTGAGT	ASO-0463	OxyAs OxyAs OxyTs OxyGs DNats DNAs DNAs DNacs DNats DNats DNats OxyGs OxyAs OxyT
386	102012	102029	103215	103232	--	--	AAATGTAACCTT GTTGAGT	ASO-0465	OxyAs OxyAs OxyTs OxyTs DNags DNats DNAs DNacs DNats DNats DNats OxyGs OxyAs OxyGs OxyT
387	102012	102030	103215	103233	--	--	GAAATGTAACCT TGTTGAGT	ASO-0467	OxyGs OxyAs OxyAs OxyAs DNats DNags DNats DNAs DNacs DNats DNats DNats OxyGs OxyAs OxyTs OxyT
388	102012	102031	103215	103234	--	--	AGAAATGTAA CTTGTGAGT	ASO-0469	OxyAs OxyGs OxyAs OxyAs DNAas DNats DNags DNats DNAs DNacs DNats DNats DNags OxyT
389	102013	102029	103216	103232	--	--	AAATGTAACCTT GTTGAG	ASO-0471	OxyAs OxyAs OxyTs OxyTs DNags DNats DNats DNAs DNacs DNats DNats OxyTs OxyGs OxyAs OxyG
390	102013	102030	103216	103233	--	--	GAAATGTAACCT TGTTGAG	ASO-0473	OxyGs OxyAs OxyAs OxyAs DNats DNags DNats DNAs DNacs DNats DNats DNags DNats OxyTs OxyGs OxyAs OxyG
391	102013	102031	103216	103234	--	--	AGAAATGTAA CTTGTGAG	ASO-0475	OxyAs OxyGs OxyAs DNAas DNAs DNats DNags DNats DNAs DNacs DNats DNats DNags OxyTs OxyTs OxyGs OxyAs OxyG
392	102013	102032	103216	103235	--	--	TAGAAATGTAA CTTGTGAG	ASO-0477	OxyTs OxyAs OxyGs OxyAs DNAas DNAas DNats DNags DNats DNAs DNacs DNacs DNats DNats DNags OxyAs OxyG
393	102014	102031	103217	103234	--	--	AGAAATGTAA CTTGTGAG	ASO-0479	OxyAs OxyGs OxyAs OxyAs DNAas DNats DNats DNags DNats DNAs DNacs DNats DNats DNags OxyTs OxyTs OxyGs OxyA
394	102014	102032	103217	103235	--	--	TAGAAATGTAA	ASO-	OxyTs OxyAs OxyGs OxyAs DNAas DNAas

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 DNAts DNAts DNAts OxyTs OxyGs OxyA
395	102014	102033	103217	103236	--	--	CTAGAAAATGTA ACTTGTGTTGA	ASO-0483	OxyMCs OxyTs OxyAs DNAGs DNAAAs DNAAAs DNAAAs DNAts DNAts DNAAAs DNAAcs DNAAcs DNAts DNAts DNAts OxyTs OxyGs OxyA
396	102015	102032	103218	103235	--	--	TAGAAAATGTAA CTTGTGTTG	ASO-0485	OxyTs OxyAs OxyGs OxyAs DNAAAs DNAAAs DNAts DNAGs DNAts DNAAAs DNAAcs DNAAcs DNAts DNAts OxyTs OxyG
397	102015	102033	103218	103236	--	--	CTAGAAAATGTA ACTTGTGTTG	ASO-0487	OxyMCs OxyTs OxyAs OxyGs DNAAAs DNAAAs DNAAAs DNAts DNAts DNAAAs DNAAcs DNAAcs DNAts DNAts OxyTs OxyTs
398	102015	102034	103218	103237	--	--	CCTAGAAAATG TAACTTGTGTTG	ASO-0489	OxyMCs OxyMCs DNAts DNAAAs DNAGs DNAAAs DNAAAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts OxyGs OxyTs OxyTs OxyG
399	102016	102033	103219	103236	--	--	CTAGAAAATGTA ACTTGTGTT	ASO-0491	OxyMCs OxyTs OxyAs OxyGs DNAAAs DNAAAs DNAAAs DNAts DNAts DNAts DNAAAs DNAAcs DNAAcs DNAts DNAts OxyT
400	102016	102034	103219	103237	--	--	CCTAGAAAATG TAACTTGTGTT	ASO-0493	OxyMCs OxyMCs OxyTs OxyAs DNAGs DNAAAs DNAAAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts OxyTs OxyT
401	102016	102035	103219	103238	--	--	ACCTAGAAAAT GTAACCTTGTGTT	ASO-0495	OxyAs OxyMCs OxyMCs DNAts DNAAAs DNAGs DNAAAs DNAAAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts OxyTs OxyT
402	102017	102034	103220	103237	--	--	CCTAGAAAATG TAACTTGTGTT	ASO-0497	OxyMCs OxyMCs OxyTs DNAAAs DNAGs DNAAAs DNAAAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts OxyTs OxyGs OxyT
403	102017	102035	103220	103238	--	--	ACCTAGAAAAT GTAACCTTGTGTT	ASO-0499	OxyAs OxyMCs OxyMCs DNAts DNAAAs DNAGs DNAAAs DNAAAs DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts DNAts OxyTs 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
							CTATACA	0561	DNAts DNAcS DNAts DNAts DNAAAs DNAAAs DNAts DNAAAs OxyTs OxyAs OxyMCs OxyA
435	102035	102053	103238	103256	--	--	GTTTTGTTCCCT ACTATACA	ASO-0563	OxyGs OxyTs DNAts DNAts DNAts DNAAAs DNAAAs DNAts DNAAAs DNAts DNAAAs DNAAAs OxyMCs OxyA
512	131977	131994	135062	135079	--	--	TGGAGATTTA GGATATTG	ASO-0635	OxyTs OxyGs OxyGs DNAAAs DNAAAs DNAAAs DNAts DNAts DNAAAs DNAAAs DNAts DNAAAs DNAAAs OxyTs OxyG
513	131977	131995	135062	135080	--	--	GTGGAGATTT AGGATATTG	ASO-0637	OxyGs OxyTs OxyGs DNAAAs DNAAAs DNAAAs DNAts DNAts DNAAAs DNAAAs DNAts DNAAAs DNAAAs OxyTs OxyTs OxyG
514	131977	131996	135062	135081	--	--	AGTGGAGATT TAGGATATTG	ASO-0639	OxyAs OxyGs OxyTs DNAAAs DNAAAs DNAAAs DNAts DNAts DNAAAs DNAAAs DNAts DNAAAs DNAAAs OxyG
515	131978	131996	135063	135081	--	--	AGTGGAGATT TAGGATATT	ASO-0641	OxyAs OxyGs OxyTs OxyGs DNAAAs DNAAAs DNAAAs DNAts DNAts DNAAAs DNAAAs DNAts DNAAAs DNAAAs OxyTs OxyT
516	131978	131997	135063	135082	--	--	CAGTGGAGAT TTAGGATATT	ASO-0643	OxyMCs OxyAs OxyGs DNAts DNAAAs DNAAAs DNAAAs DNAts DNAts DNAAAs DNAAAs DNAts DNAAAs DNAAAs OxyTs OxyT
517	131979	131997	135064	135082	--	--	CAGTGGAGAT TTAGGATAT	ASO-0645	OxyMCs OxyAs DNAAAs DNAAAs DNAAAs DNAts DNAts DNAAAs DNAAAs DNAts DNAAAs DNAAAs OxyTs OxyT
518	131979	131998	135064	135083	--	--	TCAGTGGAGA TTTAGGATAT	ASO-0647	OxyTs OxyMCs DNAAAs DNAAAs DNAAAs DNAts DNAAAs DNAAAs DNAts DNAAAs DNAAAs DNAAAs OxyT
519	131980	131997	135065	135082	--	--	CAGTGGAGAT TTAGGATA	ASO-0649	OxyMCs OxyAs OxyGs DNAts DNAAAs DNAAAs DNAAAs DNAts DNAts DNAAAs DNAAAs DNAts DNAAAs DNAAAs OxyTs OxyA
520	131980	131998	135065	135083	--	--	TCAGTGGAGA	ASO-	OxyTs OxyMCs OxyAs DNAAAs DNAAAs DNAAAs DNAts DNAAAs DNAAAs DNAts DNAAAs DNAAAs OxyTs OxyA

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
									DNAts DNAts DNAAAs DNAAgs OxyTs OxyAs OxyT
697	176160	176179	176268	176287	--	--	AGTATAGTATA GATTAGTAT	ASO-0830	OxyAs OxyGs OxyTs DNAAAs DNAts DNAAgs DNAAAs DNAAgs DNAAAs DNAAgs DNAAAs DNAAgs DNAAAs DNAAgs OxyTs OxyAs OxyT
698	176161	176178	176269	176287	--	--	GTATAGTATAG ATTAGTA	ASO-0832	OxyGs OxyTs OxyAs OxyT DNAAAs DNAAgs DNAts DNAAAs DNAAgs DNAAAs DNAAgs DNAAAs DNAAgs OxyTs OxyA
699	176161	176179	176269	176288	--	--	AGTATAGTATA GATTAGTA	ASO-0834	OxyAs OxyGs OxyTs DNAAAs DNAts DNAAgs DNAAgs DNAts DNAAAs DNAAgs DNAAAs DNAAgs DNAAAs DNAAgs OxyAs OxyGs OxyTs OxyA
700	176162	176178	176270	176287	--	--	GTATAGTATAG ATTAGT	ASO-0836	OxyGs OxyTs OxyAs OxyT DNAAAs DNAAgs DNAts DNAAAs DNAAgs DNAAAs DNAAgs DNAAAs OxyTs OxyAs OxyGs OxyT
701	176162	176179	176270	176288	--	--	AGTATAGTATA GATTAGT	ASO-0838	OxyAs OxyGs OxyTs DNAAAs DNAts DNAAgs DNAAgs DNAts DNAAAs DNAAgs DNAAAs DNAAgs OxyTs OxyAs OxyGs OxyT
702	176163	176179	176271	176287	--	--	AGTATAGTATA GATTAG	ASO-0840	OxyAs OxyGs OxyTs OxyAs DNAts DNAAAs DNAAgs DNAts DNAAAs DNAAgs DNAAAs DNAAgs DNAAAs OxyTs OxyAs OxyG
996	221987	222003	235946	235962	--	--	GATGATGAGT TTAAGGG	ASO-1111	OxyGs OxyAs OxyTs DNAAgs DNAAAs DNAts DNAAgs DNAAAs DNAAgs DNAAAs DNAAgs DNAAAs OxyAs OxyGs OxyG

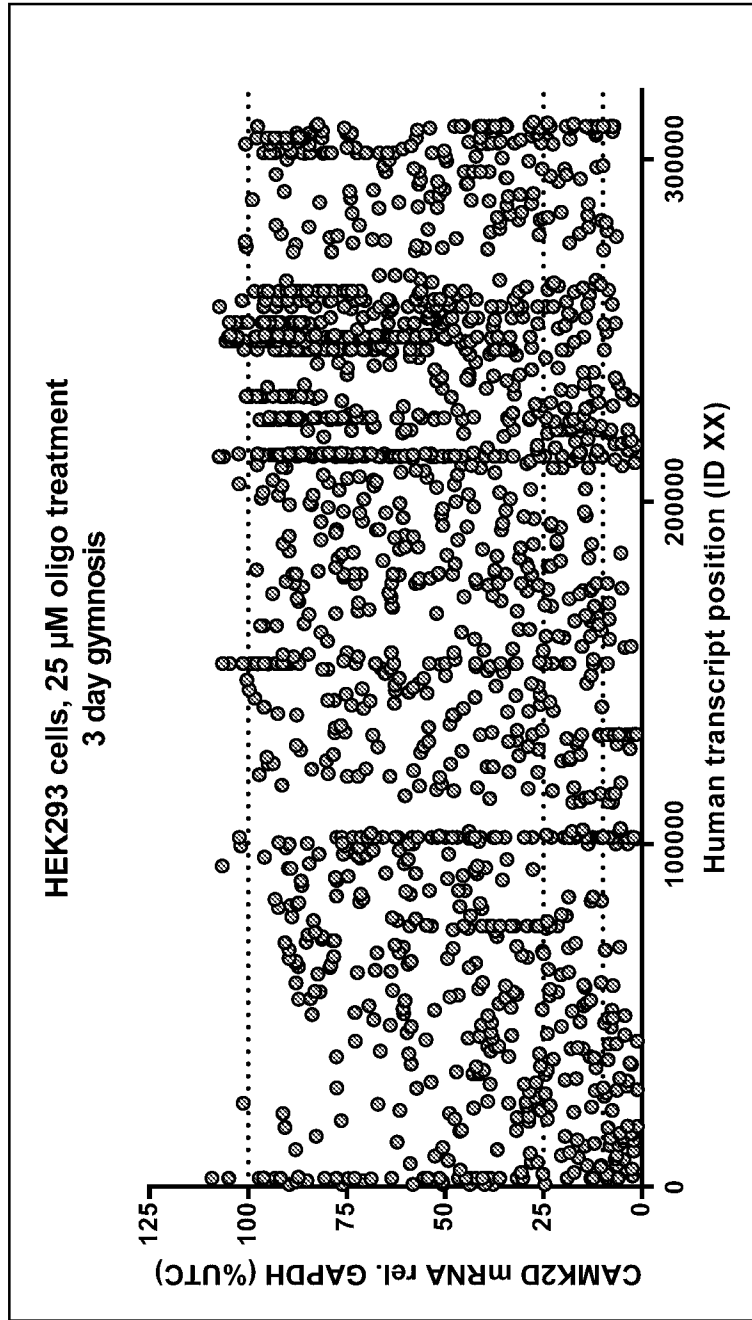


FIG. 2

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	ACAGttttatagataAAGA	ASO-0179
105	17708	17725	DES-0182	AGTCattaattcttTATC	ASO-0182
114	21808	21826	DES-0190	TCCttgtatttcttgAAT	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	TTCAtattatgctgTTTT	ASO-0251
186	44345	44361	DES-0257	AAAGtgagtgtaAGGT	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	CATTaaatatacttG TTC	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	TTTatgaagttctgTGG	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	TGTAtaattcacaTGTT	ASO-0657
524	132017	132035	DES-0659	ATGTataattcacaTGTT	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	TTTAacttactataTTGG	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	GTCAacaaccatttaTAG	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	ATTAattaattcccAAGA	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	TAAAtcactataatttgaGGC	ASO-1517
1415	258714	258732	DES-1523	GCAAaagaccttattctTG	ASO-1523
1420	258716	258732	DES-1528	GCAAaagaccttatTCT	ASO-1528
1429	258966	258982	DES-1537	TCaggggttggaTTAC	ASO-1537
1475	261720	261737	DES-1582	TCAAtattagttgtCATT	ASO-1582
1508	277421	277440	DES-1612	ATTGtatttcttgattTTAC	ASO-1612
1524	282021	282039	DES-1627	GTTattattatttcaGGT	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	TATatacagtgccCAT	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
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ASO-1357	88
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SEQUENCE LISTING

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