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(54) Title: COMPOSITIONS AND METHODS FOR SILENCING CARBONIC ANHYDRASE 2 EXPRESSION

(57) Abstract: Carbonic anhydrase inhibitors have been shown to reduce aqueous humor production and thereby reduce intraocular pressure in the eye. Accordingly, there is a need for agents that can selectively and efficiently inhibit expression of the CA2 gene such that subjects having a CA2-associated disorder, such as glaucoma, can be effectively treated. The disclosure relates to double-stranded ribonucleic acid (dsRNA) compositions targeting carbonic anhydrase 2 (CA2), and methods of using such dsRNA compositions to alter (e.g., inhibit) expression of carbonic anhydrase 2.

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COMPOSITIONS AND METHODS FOR SILENCING CARBONIC ANHYDRASE 2 EXPRESSION

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of priority to U.S. Provisional Application No. 63/194,073, filed on May 27, 2021, and claims the benefit of priority to U.S. Provisional Application No. 63/289,319, filed on December 14, 2021. The entire contents of the foregoing applications are hereby incorporated herein by reference.

FIELD OF THE DISCLOSURE

The disclosure relates to the specific inhibition of the expression of carbonic anhydrase 2.

BACKGROUND OF THE INVENTION

Glaucoma is a leading cause of vision loss. Risk factors for glaucoma include increased intraocular pressure, age, race and vascular disease. The increased intraocular pressure may cause damage to the optic nerve and loss of never fibers. Lowering intraocular pressure can reduce development and progression of vision loss.

Carbonic anhydrase 2 (CA2) is a member of the carbonic anhydrase (CA) family of metalloenzymes. CA2 catalyzes the reversible conversion of carbon dioxide to bicarbonate. Carbonic anhydrases are expressed in the eye and CA2 appears to be the main CA form present in human ciliary epithelium which is responsible for producing aqueous humor. Carbonic anhydrase inhibitors have been shown to reduce aqueous humor production and thereby reduce intraocular pressure in the eye.

Accordingly, there is a need for agents that can selectively and efficiently inhibit expression of the CA2 gene such that subjects having a CA2-associated disorder, such as glaucoma, can be effectively treated.

BRIEF SUMMARY OF THE INVENTION

The present disclosure describes methods and iRNA compositions for modulating the expression of carbonic anhydrase 2 (CA2). In certain embodiments, expression of CA2 is reduced or inhibited using a CA2-specific iRNA. Such inhibition can be useful in treating

disorders related to CA2 expression, such as ocular disorders (*e.g.*, glaucoma or conditions associated with glaucoma).

Accordingly, described herein are compositions and methods that effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of CA2, such as in a cell or in a subject (*e.g.*, in a mammal, such as a human subject). Also described are compositions and methods for treating a disorder related to expression of CA2, such as glaucoma or conditions associated with glaucoma.

The iRNAs (*e.g.*, dsRNAs) included in the compositions featured herein include an RNA strand (the antisense strand) having a region, *e.g.*, a region that is 30 nucleotides or less, generally 19-24 nucleotides in length, that is substantially complementary to at least part of an mRNA transcript of CA2 (*e.g.*, a human CA2) (also referred to herein as a "CA2-specific iRNA"). In some embodiments, the CA2 mRNA transcript is a human CA2 mRNA transcript, *e.g.*, SEQ ID NO: 1 herein.

In some embodiments, the iRNA (*e.g.*, dsRNA) described herein comprises an antisense strand having a region that is substantially complementary to a region of a human CA2 mRNA. In some embodiments, the human CA2 mRNA has the sequence NM_000067.3 (SEQ ID NO: 1). The sequence of NM_000067.3is also herein incorporated by reference in its entirety. The reverse complement of SEQ ID NO: 1 is provided as SEQ ID NO: 2 herein.

In some aspects, the present disclosure provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of carbonic anhydrase 2 (CA2), wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, of a portion of a coding strand of human CA2 and the antisense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, of the corresponding portion of a non-coding strand of human CA2 such that the sense strand is complementary to the at least 15 contiguous nucleotides in the antisense strand.

In some aspects, the present disclosure provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of CA2, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides, with 0, 1, 2, or 3

mismatches, of a portion of nucleotide sequence of SEQ ID NO: 2 such that the sense strand is complementary to the at least 15 contiguous nucleotides in the antisense strand.

In some aspects, the present disclosure provides a human cell or tissue comprising a reduced level of CA2 mRNA or a level of CA2 protein as compared to an otherwise similar untreated cell or tissue, wherein optionally the cell or tissue is not genetically engineered (*e.g.*, wherein the cell or tissue comprises one or more naturally arising mutations, *e.g.*, CA2), wherein optionally the level is reduced by at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%. In some embodiments, the human cell or tissue is a ciliary epithelium cell, an optic nerve cell, a trabecular meshwork cell, a Schlemm's canal cell (e.g., including an endothelial cell), a juxtacanalicular tissue cell, a ciliary muscle cell, a retinal cell, an astrocyte, a pericyte, a Müller cell, a ganglion cell (e.g., including a retinal ganglion cell), an endothelial cell, a photoreceptor cell, a retinal blood vessel (e.g., including endothelial cells and vascular smooth muscle cells), episcleral veins or choroid tissue, e.g., a choroid vessel.

The present disclosure also provides, in some aspects, a cell containing the dsRNA agent described herein.

In another aspect, provided herein is a human ocular cell, *e.g.*, (a ciliary epithelium cell, an optic nerve cell, a trabecular meshwork cell, a Schlemm's canal cell (e.g., including an endothelial cell), a juxtacanalicular tissue cell, a ciliary muscle cell, a retinal cell, an astrocyte, a pericyte, a Müller cell, a ganglion cell (e.g., including a retinal ganglion cell), an endothelial cell, a photoreceptor cell, a retinal blood vessel (e.g., including endothelial cells and vascular smooth muscle cells), episcleral veins or choroid tissue, e.g., a choroid vessel) comprising a reduced level of CA2 mRNA or a level of CA2 protein as compared to an otherwise similar untreated cell. In some embodiments, the level is reduced by at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%.

In some aspects, the present disclosure also provides a pharmaceutical composition for inhibiting expression of a gene encoding CA2, comprising a dsRNA agent described herein.

The present disclosure also provides, in some aspects, a method of inhibiting expression of CA2 in a cell, the method comprising:

(a) contacting the cell with the dsRNA agent described herein, or a pharmaceutical composition described herein; and

(b) maintaining the cell produced in step (a) for a time sufficient to obtain degradation of the mRNA transcript of CA2, thereby inhibiting expression of the CA2 in the cell.

The present disclosure also provides, in some aspects, a method of inhibiting expression of CA2 in a cell, the method comprising:

(a) contacting the cell with the dsRNA agent described herein, or a pharmaceutical composition described herein; and

(b) maintaining the cell produced in step (a) for a time sufficient to reduce levels of CA2 mRNA, CA2 protein, or both of CA2 mRNA and protein, thereby inhibiting expression of the CA2 in the cell.

The present disclosure also provides, in some aspects, a method of inhibiting expression of CA2 in an ocular cell or tissue, the method comprising:

(a) contacting the cell or tissue with a dsRNA agent that binds CA2; and

(b) maintaining the cell or tissue produced in step (a) for a time sufficient to reduce levels of CA2 mRNA, CA2 protein, or both of CA2 mRNA and protein, thereby inhibiting expression of CA2 in the cell or tissue.

The present disclosure also provides, in some aspects, a method of treating a subject diagnosed with a CA2-associated disorder comprising administering to the subject a therapeutically effective amount of the dsRNA agent described herein or a pharmaceutical composition described herein, thereby treating the disorder.

In any of the aspects herein, *e.g.*, the compositions and methods above, any of the embodiments herein (*e.g.*, below) may apply.

In some embodiments, the coding strand of human CA2 has the sequence of SEQ ID NO: 1. In some embodiments, the non-coding strand of human CA2 has the sequence of SEQ ID NO: 2.

In some embodiments, the sense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides, with 0, or 1, 2, or 3 mismatches, of the corresponding portion of the nucleotide sequence of SEQ ID NO: 1.

In some embodiments, the dsRNA agent comprises a sense strand and an antisense strand, wherein the antisense strand comprises a nucleotide sequence comprising at least 17 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, of a portion of nucleotide sequence of SEQ ID NO: 2 such that the sense strand is complementary to the at least 17 contiguous

nucleotides in the antisense strand. In some embodiments, the sense strand comprises a nucleotide sequence comprising at least 17 contiguous nucleotides, with 0, or 1, 2, or 3 mismatches, of the corresponding portion of the nucleotide sequence of SEQ ID NO: 1.

In some embodiments, the dsRNA agent comprises a sense strand and an antisense strand, wherein the antisense strand comprises a nucleotide sequence comprising at least 19 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, of a portion of nucleotide sequence of SEQ ID NO: 2 such that the sense strand is complementary to the at least 19 contiguous nucleotides in the antisense strand. In some embodiments, the sense strand comprises a nucleotide sequence comprising at least 19 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, of the corresponding portion of the nucleotide sequence of SEQ ID NO: 1.

In some embodiments, the dsRNA agent comprises a sense strand and an antisense strand, wherein the antisense strand comprises a nucleotide sequence comprising at least 21 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, of a portion of nucleotide sequence of SEQ ID NO: 2 such that the sense strand is complementary to the at least 21 contiguous nucleotides in the antisense strand. In some embodiments, the sense strand comprises a nucleotide sequence comprising at least 21 contiguous nucleotides, with 0, or 1, 2, or 3 mismatches, of the corresponding portion of the nucleotide sequence of SEQ ID NO: 1.

In some embodiments, the portion of the sense strand is a portion within a sense strand in any one of Tables 3-10.

In some embodiments, the portion of the antisense strand is a portion within an antisense strand in any one of Tables 3-10.

In some embodiments, the antisense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, from one of the antisense sequences listed in any one of Tables 3-10. In some embodiments, the sense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, from a sense sequence listed in any one of Tables 3-10 that corresponds to the antisense sequence.

In some embodiments, the antisense strand comprises a nucleotide sequence comprising at least 17 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, from one of the antisense sequences listed in any one of Tables 3-10. In some embodiments, the sense strand comprises a nucleotide sequence comprising at least 17 contiguous nucleotides, with 0, 1, 2, or 3 mismatches,

from a sense sequence listed in any one of Tables 3-10 that corresponds to the antisense sequence.

In some embodiments, the antisense strand comprises a nucleotide sequence comprising at least 19 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, from one of the antisense sequences listed in any one of Tables 3-10. In some embodiments, the sense strand comprises a nucleotide sequence comprising at least 19 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, from a sense sequence listed in any one of Tables 3-10 that corresponds to the antisense sequence.

In some embodiments, the antisense strand comprises a nucleotide sequence comprising at least 21 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, from one of the antisense sequences listed in any one of Tables 3-10. In some embodiments, the sense strand comprises a nucleotide sequence comprising at least 21 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, from a sense sequence listed in any one of Tables 3-10 that corresponds to the antisense sequence.

In some embodiments, the sense strand of the dsRNA agent is at least 23 nucleotides in length, *e.g.*, 23-30 nucleotides in length.

In some embodiments, at least one of the sense strand and the antisense strand is conjugated to one or more lipophilic moieties. In some embodiments, the lipophilic moiety is conjugated to one or more positions in the double stranded region of the dsRNA agent. In some embodiments, the lipophilic moiety is conjugated via a linker or carrier. In some embodiments, lipophilicity of the lipophilic moiety, measured by logKow, exceeds 0. In some embodiments, In some embodiments, the hydrophobicity of the double-stranded RNAi agent, measured by the unbound fraction in a plasma protein binding assay of the double-stranded RNAi agent, exceeds 0.2. In some embodiments, the plasma protein binding assay is an electrophoretic mobility shift assay using human serum albumin protein.

In some embodiments, the dsRNA agent comprises at least one modified nucleotide. In some embodiments, no more than five of the sense strand nucleotides and not more than five of the nucleotides of the antisense strand are unmodified nucleotides. In some embodiments, all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand comprise a modification.

In some embodiments, at least one of the modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 3'-terminal deoxythimidine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5'-phosphate, a nucleotide comprising a 5'-phosphate mimic, a glycol modified nucleotide, and a 2-O-(N-methylacetamide) modified nucleotide; and combinations thereof. In some embodiments, no more than five of the sense strand nucleotides and not more than five of the nucleotides of the antisense strand include modifications other than 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, unlocked nucleic acids (UNA) or glycerol nucleic acid (GNA).

In some embodiments, the dsRNA comprises a non-nucleotide spacer (wherein optionally the non-nucleotide spacer comprises a C3-C6 alkyl) between two of the contiguous nucleotides of the sense strand or between two of the contiguous nucleotides of the antisense strand.

In some embodiments, each strand is no more than 30 nucleotides in length. In some embodiments, at least one strand comprises a 3' overhang of at least 1 nucleotide. In some embodiments, at least one strand comprises a 3' overhang of at least 2 nucleotides. In some embodiments, at least one strand comprises a 3' overhang of 2 nucleotides.

In some embodiments, the double stranded region is 15-30 nucleotide pairs in length. In some embodiments, the double stranded region is 17-23 nucleotide pairs in length. In some embodiments, the double stranded region is 17-25 nucleotide pairs in length. In some embodiments, the double stranded region is 23-27 nucleotide pairs in length. In some embodiments, the double stranded region is 19-21 nucleotide pairs in length. In some embodiments, the double stranded region is 21-23 nucleotide pairs in length. In some embodiments, each strand has 19-30 nucleotides. In some embodiments, each strand has 19-23 nucleotides. In some embodiments, each strand has 21-23 nucleotides.

In some embodiments, the agent comprises at least one phosphorothioate or methylphosphonate internucleotide linkage. In some embodiments, the phosphorothioate or methylphosphonate internucleotide linkage is at the 3'-terminus of one strand. In some embodiments, the strand is the antisense strand. In some embodiments, the strand is the sense strand.

In some embodiments, the phosphorothioate or methylphosphonate internucleotide linkage is at the 5'-terminus of one strand. In some embodiments, the strand is the antisense strand. In some embodiments, the strand is the sense strand.

In some embodiments, each of the 5'- and 3'-terminus of one strand comprises a phosphorothioate or methylphosphonate internucleotide linkage. In some embodiments, the strand is the antisense strand.

In some embodiments, the base pair at the 1 position of the 5'-end of the antisense strand of the duplex is an AU base pair.

In some embodiments, the sense strand has a total of 21 nucleotides and the antisense strand has a total of 23 nucleotides. In some embodiments, one or more lipophilic moieties are conjugated to one or more internal positions on at least one strand. In some embodiments, the one or more lipophilic moieties are conjugated to one or more internal positions on at least one strand via a linker or carrier.

In some embodiments conjugating a lipophilic moiety to one or more internal positions on at least one strand of the double-stranded iRNA agent provides surprisingly good results for in vivo intravitreal delivery of the double-stranded iRNAs, resulting in efficient entry into ocular tissues. Examples and synthesis of lipophilic moieties are listed in PCT application number PCT/US2019/031170 which is hereby incorporated by reference in its entirety.

In some embodiments, the internal positions include all positions except the terminal two positions from each end of the at least one strand. In some embodiments, the internal positions include all positions except the terminal three positions from each end of the at least one strand. In some embodiments, the internal positions exclude a cleavage site region of the sense strand. In some embodiments, the internal positions include all positions except positions 9-12, counting from the 5'-end of the sense strand. In some embodiments, the internal positions include all positions except positions 11-13, counting from the 3'-end of the sense strand. In some embodiments, the internal positions exclude a cleavage site region of the antisense strand. In

some embodiments, the internal positions include all positions except positions 12-14, counting from the 5'-end of the antisense strand. In some embodiments, the internal positions include all positions except positions 11-13 on the sense strand, counting from the 3'-end, and positions 12-14 on the antisense strand, counting from the 5'-end.

In some embodiments, the one or more lipophilic moieties are conjugated to one or more of the internal positions selected from the group consisting of positions 4-8 and 13-18 on the sense strand, and positions 6-10 and 15-18 on the antisense strand, counting from the 5'end of each strand. In some embodiments, the one or more lipophilic moieties are conjugated to one or more of the internal positions selected from the group consisting of positions 5, 6, 7, 15, and 17 on the sense strand, and positions 15 and 17 on the antisense strand, counting from the 5'-end of each strand.

In some embodiments, the positions in the double stranded region exclude a cleavage site region of the sense strand.

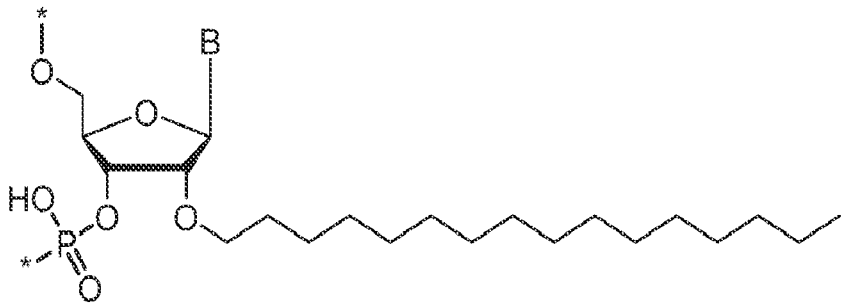
In some embodiments, the sense strand is 21 nucleotides in length, the antisense strand is 23 nucleotides in length, and the lipophilic moiety is conjugated to position 21, position 20, position 15, position 1, position 7, position 6, or position 2 of the sense strand or position 16 of the antisense strand. In some embodiments, the lipophilic moiety is conjugated to position 21, position 20, position 15, position 1, or position 7 of the sense strand. In some embodiments, the lipophilic moiety is conjugated to position 21, position 20, or position 15 of the sense strand. In some embodiments, the lipophilic moiety is conjugated to position 20 or position 15 of the sense strand. In some embodiments, the lipophilic moiety is conjugated to position 16 of the antisense strand. In some embodiments, the lipophilic moiety is conjugated to position 6, counting from the 5'-end of the sense strand. In one embodiment, the saturated or unsaturated C16 hydrocarbon chain is conjugated to position 6, counting from the 5'-end of the strand

In some embodiments, the lipophilic moiety is an aliphatic, alicyclic, or polyalicyclic compound. In some embodiments, the lipophilic moiety is selected from the group consisting of lipid, cholesterol, retinoic acid, cholic acid, adamantane acetic acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-bis-O(hexadecyl)glycerol, geranyloxyhexyanol, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl group, palmitic acid, myristic acid, O3-(oleoyl)lithocholic acid, O3-(oleoyl)cholenic acid, dimethoxytrityl, or phenoxazine. Suitable lipophilic moieties also include those containing a saturated or unsaturated C4-C30 hydrocarbon

chain (e.g., C4-C30 alkyl or alkenyl), and an optional functional group selected from the group consisting of hydroxyl, amine, carboxylic acid, sulfonate, phosphate, thiol, azide, and alkyne. The functional groups are useful to attach the lipophilic moiety to the iRNA agent. In some embodiments, the lipophilic moiety contains a saturated or unsaturated C6-C18 hydrocarbon chain (e.g., a linear C6-C18 alkyl or alkenyl). In one embodiment, the lipophilic moiety contains a saturated or unsaturated C16 hydrocarbon chain (e.g., a linear C16 alkyl or alkenyl).

In some embodiments, the lipophilic moiety is a C6-C30 acid (e.g., hexanoic acid, heptanoic acid, octanoic acid, nonanoic acid, decanoic acid, undecanoic acid, dodcanoic acid, tridecanoic acid, tetradecanoic acid, pentadecanoic acid, hexadecanoic acid, heptadecanoic acid, octadecanoic acid, oleic acid, linoleic acid, arachidonic acid, cis-4,7,10,13,16,19-docosahexanoic acid, vitamin A, vitamin E, cholesterol etc.) or a C6-C30 alcohol (e.g., hexanol, heptanol, octanol, nonanol, decanol, undecanol, dodcanol, tridecanol, tetradecanol, pentadecanol, hexadecanol, heptadecanol, octadecanol, oleyl alcohol, linoleyl alcohol, arachidonic alcohol, cis-4,7,10,13,16,19-docosahexanol, retinol, vitamin E, cholesterol etc.).

In one embodiment, the ligand is conjugated at the 2'-position of a nucleotide or modified nucleotide within the sense or antisense strand. For example, a C16 ligand may be conjugated as shown in the following structure:



where * denotes a bond to an adjacent nucleotide, and B is a nucleobase or a nucleobase analog, optionally where B is adenine, guanine, cytosine, thymine or uracil.

In some embodiments, the lipophilic moiety is conjugated via a carrier that replaces one or more nucleotide(s) in the internal position(s) or the double stranded region. In some embodiments, the carrier is a cyclic group selected from the group consisting of pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, [1,3]dioxolanyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl,

quinoxalinyl, pyridazinonyl, tetrahydrofuranyl, and decalinyl; or is an acyclic moiety based on a serinol backbone or a diethanolamine backbone.

In some embodiments, the lipophilic moiety is conjugated to the double-stranded iRNA agent via a linker containing an ether, thioether, urea, carbonate, amine, amide, maleimide-thioether, disulfide, phosphodiester, sulfonamide linkage, a product of a click reaction, or carbamate.

In some embodiments, the lipophilic moiety is conjugated to a nucleobase, sugar moiety, or internucleosidic linkage.

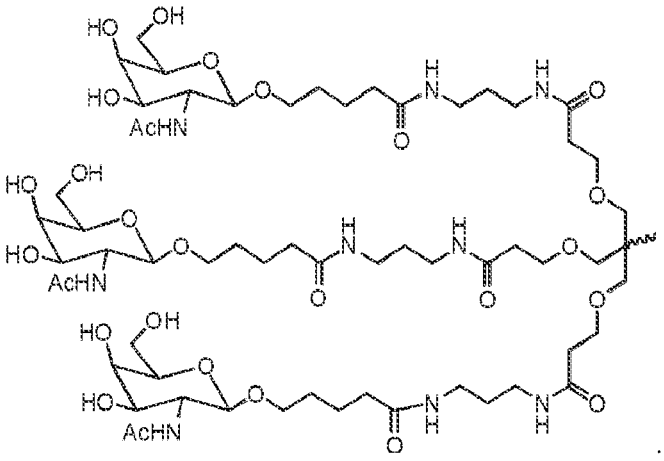
In some embodiments, the lipophilic moiety or targeting ligand is conjugated via a bio-cleavable linker selected from the group consisting of DNA, RNA, disulfide, amide, functionalized monosaccharides or oligosaccharides of galactosamine, glucosamine, glucose, galactose, mannose, and combinations thereof.

In some embodiments, the 3' end of the sense strand is protected via an end cap which is a cyclic group having an amine, said cyclic group being selected from the group consisting of pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, [1,3]dioxolanyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl, tetrahydrofuranyl, and decalinyl.

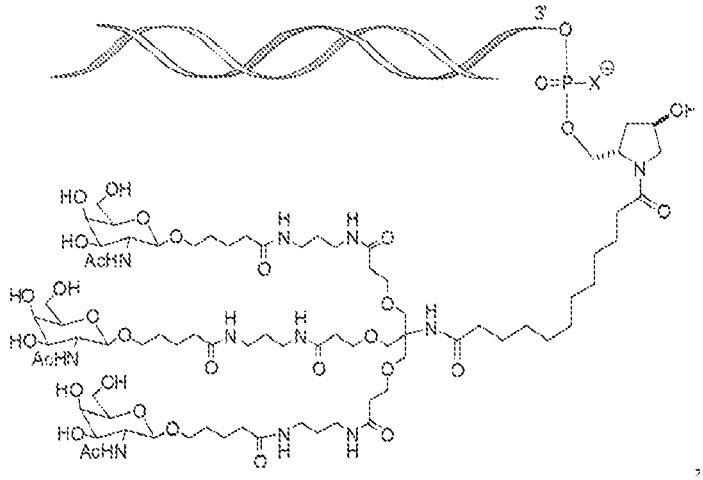
In some embodiments, the dsRNA agent further comprises a targeting ligand, *e.g.*, a ligand that targets an ocular tissue. In some embodiments, the ocular tissue is ciliary epithelium, an optic nerve, a trabecular meshwork, a juxtacanalicular tissue, a ganglion (e.g., including a retinal ganglion), episcleral veins or a Schlemm's canal (e.g., including an endothelial cell).

In some embodiments, the ligand is conjugated to the sense strand. In some embodiments, the ligand is conjugated to the 3' end or the 5' end of the sense strand. In some embodiments, the ligand is conjugated to the 3' end of the sense strand.

In some embodiments, the ligand comprises N-acetylgalactosamine (GalNAc). In some embodiments, the targeting ligand comprises one or more GalNAc conjugates or one or more GalNAc derivatives. In some embodiments, the ligand is one or more GalNAc conjugates or one or more GalNAc derivatives are attached through a monovalent linker, or a bivalent, trivalent, or tetravalent branched linker. In some embodiments, the ligand is



In some embodiments, the dsRNA agent is conjugated to the ligand as shown in the following schematic



wherein X is O or S. In some embodiments, the X is O.

In some embodiments, the dsRNA agent further comprises a terminal, chiral modification occurring at the first internucleotide linkage at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration, a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration, and a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp configuration or Sp configuration.

In some embodiments, the dsRNA agent further comprises a terminal, chiral modification occurring at the first and second internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration, a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the antisense strand, having the

linkage phosphorus atom in Rp configuration, and a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp or Sp configuration.

In some embodiments, the dsRNA agent further comprises a terminal, chiral modification occurring at the first, second and third internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration, a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration, and a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp or Sp configuration.

In some embodiments, the dsRNA agent further comprises a terminal, chiral modification occurring at the first, and second internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration, a terminal, chiral modification occurring at the third internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Rp configuration, a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration, and a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp or Sp configuration.

In some embodiments, the dsRNA agent further comprises a terminal, chiral modification occurring at the first, and second internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration, a terminal, chiral modification occurring at the first, and second internucleotide linkages at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration, and a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp or Sp configuration.

In some embodiments, the dsRNA agent further comprises a phosphate or phosphate mimic at the 5'-end of the antisense strand. In some embodiments, the phosphate mimic is a 5'-vinyl phosphonate (VP).

In various embodiments of the aforementioned dsRNA agents, the dsRNA agent targets a hotspot region of an mRNA encoding CA2.

In another aspect, the present invention provides a dsRNA agent that targets a hotspot region of a carbonic anhydrase 2 (CA2) mRNA.

In some embodiments, a cell described herein, *e.g.*, a human cell, was produced by a process comprising contacting a human cell with the dsRNA agent described herein.

In some embodiments, a pharmaceutical composition described herein comprises the dsRNA agent and a lipid formulation.

In some embodiments (*e.g.*, embodiments of the methods described herein), the cell is within a subject. In some embodiments, the subject is a human. In some embodiments, the level of CA2 mRNA is inhibited by at least 50%. In some embodiments, the level of CA2 protein is inhibited by at least 50%. In some embodiments, the expression of CA2 is inhibited by at least 50%. In some embodiments, inhibiting expression of CA2 decreases the CA2 protein level in a biological sample (*e.g.*, an optic nerve sample) from the subject by at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 95%. In some embodiments, inhibiting expression of CA2 gene decreases the CA2 mRNA level in a biological sample (*e.g.*, an optic nerve sample) from the subject by at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 95%.

In some embodiments, the subject has been diagnosed with a CA2-associated disorder. In some embodiments, the subject meets at least one diagnostic criterion for a CA2-associated disorder. In some embodiments, the CA2 associated disorder is glaucoma or conditions associated with glaucoma.

In some embodiments, the ocular cell or tissue is a ciliary epithelium cell, an optic nerve cell, a trabecular meshwork cell, a Schlemm's canal cell (e.g., including an endothelial cell), a juxtacanalicular tissue cell, a ciliary muscle cell, a retinal cell, an astrocyte, a pericyte, a Müller cell, a ganglion cell (e.g., including a retinal ganglion cell), an endothelial cell, a photoreceptor cell, a retinal blood vessel (e.g., including endothelial cells and vascular smooth muscle cells), episcleral veins or choroid tissue, e.g., a choroid vessel.

In some embodiments, the CA2-associated disorder is glaucoma and/or conditions associated with glaucoma.

In some embodiments, treating comprises amelioration of at least one sign or symptom of the disorder. In some embodiments, the at least one sign or symptom includes a measure of one or more of intraocular pressure, vision loss, optic nerve damage, ocular inflammation, visual acuity, or presence, level, or activity of CA2 (*e.g.*, CA2 gene, CA2 mRNA, or CA2 protein).

In some embodiments, a level of the CA2 that is higher than a reference level is indicative that the subject has glaucoma or a glaucoma associated condition. In some embodiments, treating comprises prevention of progression of the disorder. In some embodiments, the treating comprises one or more of (a) inhibiting or reducing intraocular pressure; (b) inhibiting or reducing the expression or activity of CA2; (c) decreasing the amount of aqueous humor; (d) inhibiting or reducing optic nerve damage; or (e) inhibiting or reducing retinal ganglion cell death.

In some embodiments, the treating results in at least a 30% mean reduction from baseline of CA2 mRNA in the cell or tissue. In some embodiments, the treating results in at least a 60% mean reduction from baseline of CA2 mRNA in the cell or tissue. In some embodiments, the treating results in at least a 90% mean reduction from baseline of CA2 mRNA in the cell or tissue.

In some embodiments, after treatment the subject experiences at least an 8-week duration of knockdown following a single dose of dsRNA as assessed by CA2 protein in, for example, the ciliary epithelium. In some embodiments, treating results in at least a 12-week duration of knockdown following a single dose of dsRNA as assessed by CA2 protein in, for example, the ciliary epithelium. In some embodiments, treating results in at least a 16-week duration of knockdown following a single dose of dsRNA as assessed by CA2 protein in, for example, the ciliary epithelium.

In some embodiments, the subject is human.

In some embodiments, the dsRNA agent is administered at a dose of about 0.01 mg/kg to about 50 mg/kg.

In some embodiments, the dsRNA agent is administered to the subject intraocularly. In some embodiments, the intraocular administration comprises intravitreal administration, e.g., intravitreal injection; transscleral administration, e.g., transscleral injection; subconjunctival administration, e.g., subconjunctival injection; retrobulbar administration, e.g., retrobulbar injection; intracameral administration, e.g., intracameral injection, or subretinal administration, e.g., subretinal injection.

In some embodiments, the dsRNA agent is administered to the subject intravenously. In some embodiments, the dsRNA agent is administered to the subject topically.

In some embodiments, a method described herein further comprises measuring a level of CA2 (*e.g.*, CA2 gene, CA2 mRNA, or CA2 protein) in the subject. In some embodiments, measuring the level of CA2 in the subject comprises measuring the level of CA2 protein in a biological sample from the subject (*e.g.*, a ciliary epithelium sample). In some embodiments, a method described herein further comprises performing a blood test, an imaging test, a tonometry test or a ciliary epithelium biopsy.

In some embodiments, a method described herein further comprises measuring a level of CA2 (*e.g.*, CA2 gene, CA2 mRNA, or CA2 protein) in the subject prior to treatment with the dsRNA agent or the pharmaceutical composition. In some embodiments, upon determination that a subject has a level of CA2 that is greater than a reference level, the dsRNA agent or the pharmaceutical composition is administered to the subject. In some embodiments, measuring a level of CA2 in the subject is performed after treatment with the dsRNA agent or the pharmaceutical composition.

In some embodiments, a method described herein further comprises treating the subject with a therapy suitable for treatment or prevention of a CA2-associated disorder, *e.g.*, glaucoma, wherein the therapy comprises medication to reduce intraocular pressure, laser treatment, surgery or trabeculectomy. In some embodiments, a method described herein further comprises administering to the subject an additional agent suitable for treatment or prevention of a CA2-associated disorder. In some embodiments, the additional agent comprises a prostaglandin analog, a beta blocker, an alpha-adrenergic agonist, a carbonic anhydrase inhibitor, or an anti-CA2 agent.

In some embodiments, the anti-CA2 agent comprises an anti-CA2 antibody or antigen-binding fragment thereof (e.g., an anti-CA2 antibody molecule).

All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety.

The details of various embodiments of the disclosure are set forth in the description below. Other features, objects, and advantages of the disclosure will be apparent from the description and the drawings, and from the claims.

DETAILED DESCRIPTION

iRNA directs the sequence-specific degradation of mRNA through a process known as RNA interference (RNAi). Described herein are iRNAs and methods of using them for modulating (*e.g.*, inhibiting) the expression of CA2. Also provided are compositions and methods for treatment of disorders related to CA2 expression, such as glaucoma or conditions associated with glaucoma.

Human CA2, also known as carbonic anhydrase 2, is a metalloenzyme encoded by the CA2 gene. CA2 catalyzes the interconversion between carbon dioxide and bicarbonate. CA2 is expressed by a variety of tissues including tissues of the eye, such as, ciliary epithelium, corneal epithelium, Müller cells, the lens, non-pigmented iris epithelium, retinal pigment epithelium, and pigmented and non-pigmented epithelium of the ciliary processes.

Without wishing to be bound by theory, CA2 may exacerbate the pathogenesis of glaucoma, e.g., by increasing intraocular pressure.CA2 appears to be the main CA form expressed in human ciliary epithelium which is responsible for producing aqueous humor. Carbonic anhydrase inhibitors have been shown to reduce aqueous humor production by up to 40% and thereby reduce intraocular pressure in the eye.

The following description discloses how to make and use compositions containing iRNAs to modulate (*e.g.*, inhibit) the expression of CA2, as well as compositions and methods for treating disorders related to expression of CA2.

In some aspects, pharmaceutical compositions containing CA2 iRNA and a pharmaceutically acceptable carrier, methods of using the compositions to inhibit expression of CA2, and methods of using the pharmaceutical compositions to treat disorders related to expression of CA2 (*e.g.*, glaucoma or conditions associated with glaucoma) are featured herein.

I. Definitions

For convenience, the meaning of certain terms and phrases used in the specification, examples, and appended claims, are provided below. If there is an apparent discrepancy between the usage of a term in other parts of this specification and its definition provided in this section, the definition in this section shall prevail.

The term "about" when referring to a number or a numerical range means that the number or numerical range referred to is an approximation within experimental variability (or

within statistical experimental error), and thus the number or numerical range may vary from, for example, between 1% and 15% of the stated number or numerical range.

The term "at least" prior to a number or series of numbers is understood to include the number adjacent to the term "at least", and all subsequent numbers or integers that could logically be included, as clear from context. For example, the number of nucleotides in a nucleic acid molecule must be an integer. For example, "at least 17 nucleotides of a 20-nucleotide nucleic acid molecule" means that 17, 18, 19, or 20 nucleotides have the indicated property. When at least is present before a series of numbers or a range, it is understood that "at least" can modify each of the numbers in the series or range.

As used herein, "no more than" or "or less" is understood as the value adjacent to the phrase and logical lower values or integers, as logical from context, to zero. For example, a duplex with mismatches to a target site of "no more than 2 nucleotides" has a 2, 1, or 0 mismatches. When "no more than" is present before a series of numbers or a range, it is understood that "no more than" can modify each of the numbers in the series or range.

As used herein, "up to" as in "up to 10" is understood as up to and including 10, *i.e.*, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

Ranges provided herein are understood to include all individual integer values and all subranges within the ranges.

The terms "activate," "enhance," "up-regulate the expression of," "increase the expression of," and the like, in so far as they refer to a CA2 gene, herein refer to the at least partial activation of the expression of a CA2 gene, as manifested by an increase in the amount of CA2 mRNA, which may be isolated from or detected in a first cell or group of cells in which a CA2 gene is transcribed and which has or have been treated such that the expression of a CA2 gene is increased, as compared to a second cell or group of cells substantially identical to the first cell or group of cells but which has or have not been so treated (control cells).

In some embodiments, expression of a CA2 gene is activated by at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% by administration of an iRNA as described herein. In some embodiments, a CA2 gene is activated by at least about 60%, 70%, or 80% by administration of an iRNA featured in the disclosure. In some embodiments, expression of a CA2 gene is activated by at least about 85%, 90%, or 95% or more by administration of an iRNA as described herein. In some embodiments, the CA2 gene expression is increased by at least 1-

fold, at least 2-fold, at least 5-fold, at least 10-fold, at least 50-fold, at least 100-fold, at least 500-fold, at least 1000-fold or more in cells treated with an iRNA as described herein compared to the expression in an untreated cell. Activation of expression by small dsRNAs is described, for example, in Li *et al.*, 2006 *Proc. Natl. Acad. Sci. U.S.A.* 103:17337-42, and in US2007/0111963 and US2005/226848, each of which is incorporated herein by reference.

The terms "silence," "inhibit expression of," "down-regulate expression of," "suppress expression of," and the like, in so far as they refer to CA2, herein refer to the at least partial suppression of the expression of CA2, as assessed, *e.g.*, based on CA2 mRNA expression, CA2 protein expression, or another parameter functionally linked to CA2 expression. For example, inhibition of CA2 expression may be manifested by a reduction of the amount of CA2 mRNA which may be isolated from or detected in a first cell or group of cells in which CA2 is transcribed and which has or have been treated such that the expression of CA2 is inhibited, as compared to a control. The control may be a second cell or group of cells substantially identical to the first cell or group of cells, except that the second cell or group of cells have not been so treated (control cells). The degree of inhibition is usually expressed as a percentage of a control level, *e.g.*,

$$\frac{(\text{mRNA in control cells}) - (\text{mRNA in treated cells})}{(\text{mRNA in control cells})} * 100\%$$

Alternatively, the degree of inhibition may be given in terms of a reduction of a parameter that is functionally linked to CA2 expression, *e.g.*, the amount of protein encoded by a CA2 gene. The reduction of a parameter functionally linked to CA2 expression may similarly be expressed as a percentage of a control level. In principle, CA2 silencing may be determined in any cell expressing CA2, either constitutively or by genomic engineering, and by any appropriate assay.

For example, in certain instances, expression of CA2 is suppressed by at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% by administration of an iRNA disclosed herein. In some embodiments, CA2 is suppressed by at least about 60%, 65%, 70%, 75%, or 80% by administration of an iRNA disclosed herein. In some embodiments, CA2 is suppressed by at least about 85%, 90%, 95%, 98%, 99%, or more by administration of an iRNA as described herein.

The term "antisense strand" or "guide strand" refers to the strand of an iRNA, *e.g.*, a dsRNA, which includes a region that is substantially complementary to a target sequence.

As used herein, the term "region of complementarity" refers to the region on the antisense strand that is substantially complementary to a sequence, for example a target sequence, as defined herein. Where the region of complementarity is not fully complementary to the target sequence, the mismatches may be in the internal or terminal regions of the molecule. In some embodiments, the region of complementarity comprises 0, 1, or 2 mismatches.

The term "sense strand" or "passenger strand" as used herein, refers to the strand of an iRNA that includes a region that is substantially complementary to a region of the antisense strand as that term is defined herein.

The terms "blunt" or "blunt ended" as used herein in reference to a dsRNA mean that there are no unpaired nucleotides or nucleotide analogs at a given terminal end of a dsRNA, *i.e.*, no nucleotide overhang. One or both ends of a dsRNA can be blunt. Where both ends of a dsRNA are blunt, the dsRNA is said to be blunt ended. To be clear, a "blunt ended" dsRNA is a dsRNA that is blunt at both ends, *i.e.*, no nucleotide overhang at either end of the molecule. Most often such a molecule will be double-stranded over its entire length.

As used herein, and unless otherwise indicated, the term "complementary," when used to describe a first nucleotide sequence in relation to a second nucleotide sequence, refers to the ability of an oligonucleotide or polynucleotide comprising the first nucleotide sequence to hybridize and form a duplex structure under certain conditions with an oligonucleotide or polynucleotide comprising the second nucleotide sequence, as will be understood by the skilled person. Such conditions can be, for example, "stringent conditions", including but not limited to, 400 mM NaCl, 40 mM PIPES pH 6.4, 1 mM EDTA, 50°C or 70°C for 12-16 hours followed by washing. As used herein, "stringent conditions" or "stringent hybridization conditions" refers to conditions under which an antisense compound will hybridize to its target sequence, but to a minimal number of other sequences. Stringent conditions are sequence-dependent and will be different in different circumstances, and "stringent conditions" under which antisense compounds hybridize to a target sequence are determined by the nature and composition of the antisense compounds and the assays in which they are being investigated. Other conditions, such as physiologically relevant conditions as may be encountered inside an organism, can apply. The skilled person will be able to determine the set of conditions most appropriate for a test of

complementarity of two sequences in accordance with the ultimate application of the hybridized nucleotides.

Complementary sequences within an iRNA, *e.g.*, within a dsRNA as described herein, include base-pairing of the oligonucleotide or polynucleotide comprising a first nucleotide sequence to an oligonucleotide or polynucleotide comprising a second nucleotide sequence over the entire length of one or both nucleotide sequences. Such sequences can be referred to as "fully complementary" with respect to each other herein. However, where a first sequence is referred to as "substantially complementary" with respect to a second sequence herein, the two sequences can be fully complementary, or they may form one or more, but generally not more than 5, 4, 3 or 2 mismatched base pairs upon hybridization for a duplex up to 30 base pairs. In some embodiments, the "substantially complementary" sequences disclosed herein comprise a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to the equivalent region of the target GPR146 sequence, such as about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% complementary. However, where two oligonucleotides are designed to form, upon hybridization, one or more single stranded overhangs, such overhangs shall not be regarded as mismatches with regard to the determination of complementarity. For example, a dsRNA comprising one oligonucleotide 21 nucleotides in length and another oligonucleotide 23 nucleotides in length, wherein the longer oligonucleotide comprises a sequence of 21 nucleotides that is fully complementary to the shorter oligonucleotide, may yet be referred to as "fully complementary" for the purposes described herein.

Complementary sequences, as used herein, may also include, or be formed entirely from, non-Watson-Crick base pairs and/or base pairs formed from non-natural and modified nucleotides, in as far as the above requirements with respect to their ability to hybridize are fulfilled. Such non-Watson-Crick base pairs includes, but are not limited to, G:U Wobble or Hoogsteen base pairing.

The terms "complementary," "fully complementary" and "substantially complementary" herein may be used with respect to the base matching between two oligonucleotides or polynucleotides, such as the sense strand and the antisense strand of a dsRNA, or between the antisense strand of an iRNA agent and a target sequence, as will be understood from the context of their use.

As used herein, a polynucleotide that is "substantially complementary to at least part of" a messenger RNA (mRNA) refers to a polynucleotide that is substantially complementary to a contiguous portion of the mRNA of interest (*e.g.*, an mRNA encoding a CA2 protein). For example, a polynucleotide is complementary to at least a part of a CA2 mRNA if the sequence is substantially complementary to a non-interrupted portion of an mRNA encoding CA2. The term "complementarity" refers to the capacity for pairing between nucleobases of a first nucleic acid and a second nucleic acid.

As used herein, the term "region of complementarity" refers to the region of one nucleotide sequence agent that is substantially complementary to another sequence, *e.g.*, the region of a sense sequence and corresponding antisense sequence of a dsRNA, or the antisense strand of an iRNA and a target sequence, *e.g.*, a CA2 nucleotide sequence, as defined herein. Where the region of complementarity is not fully complementary to the target sequence, the mismatches can be in the internal or terminal regions of the antisense strand of the iRNA. Generally, the most tolerated mismatches are in the terminal regions, *e.g.*, within 5, 4, 3, or 2 nucleotides of the 5'- or 3'-terminus of the iRNA agent.

"Contacting," as used herein, includes directly contacting a cell, as well as indirectly contacting a cell. For example, a cell within a subject may be contacted when a composition comprising an iRNA is administered (*e.g.*, intraocularly, topically, or intravenously) to the subject.

"Introducing into a cell," when referring to an iRNA, means facilitating or effecting uptake or absorption into the cell. Absorption or uptake of an iRNA can occur through unaided diffusive or active cellular processes, or by auxiliary agents or devices. The meaning of this term is not limited to cells *in vitro*; an iRNA may also be "introduced into a cell," wherein the cell is part of a living organism. In such an instance, introduction into the cell will include the delivery to the organism. For example, for *in vivo* delivery, iRNA can be injected into a tissue site or administered systemically. *In vivo* delivery can also be by a β-glucan delivery system, such as those described in U.S. Patent Nos. 5,032,401 and 5,607,677, and U.S. Publication No. 2005/0281781, which are hereby incorporated by reference in their entirety. *In vitro* introduction into a cell includes methods known in the art such as electroporation and lipofection. Further approaches are described herein below or known in the art. As used herein, a "disorder related to CA2 expression," a "disease related to CA2 expression," a "pathological process related to

CA2 expression," "a CA2-associated disorder," "a CA2-associated disease," or the like includes any condition, disorder, or disease in which CA2 expression is altered (*e.g.*, decreased or increased relative to a reference level, e.g., a level characteristic of a non-diseased subject). In some embodiments, CA2 expression is decreased. In some embodiments, CA2 expression is increased. In some embodiments, the decrease or increase in CA2 expression is detectable in a tissue sample from the subject (*e.g.*, in an optic nerve sample). The decrease or increase may be assessed relative the level observed in the same individual prior to the development of the disorder or relative to other individual(s) who do not have the disorder. The decrease or increase may be limited to a particular organ, tissue, or region of the body (*e.g.*, the eye). CA2-associated disorders include, but are not limited to, glaucoma or conditions associated with glaucoma.

The term "condition(s) associated with glaucoma," as used herein, means any disease or condition that is associated with an increase in intraocular pressure. Non-limiting examples of conditions associated with glaucoma that are treatable using methods provided herein include glaucoma, open-angle glaucoma, angle-closure glaucoma, ocular inflammation, systemic inflammation, anterior uveitis, acute retinal necrosis, Sturge-Weber syndrome, Axenfeld-Rieger syndrome, Marfan syndrome, homocystinuria, Weill-Marchesani syndrome, and autoimmune diseases, such as juvenile rheumatoid arthritis and Marie-Strumpell ankylosing spondylitis.

The term "double-stranded RNA," "dsRNA," or "siRNA" as used herein, refers to an iRNA that includes an RNA molecule or complex of molecules having a hybridized duplex region that comprises two anti-parallel and substantially complementary nucleic acid strands, which will be referred to as having "sense" and "antisense" orientations with respect to a target RNA. The duplex region can be of any length that permits specific degradation of a desired target RNA, *e.g.*, through a RISC pathway, but will typically range from 9 to 36 base pairs in length, *e.g.*, 15-30 base pairs in length. Considering a duplex between 9 and 36 base pairs, the duplex can be any length in this range, for example, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, or 36 and any sub-range therein between, including, but not limited to 15-30 base pairs, 15-26 base pairs, 15-23 base pairs, 15-22 base pairs, 15-21 base pairs, 15-20 base pairs, 15-19 base pairs, 15-18 base pairs, 15-17 base pairs, 18-30 base pairs, 18-26 base pairs, 18-23 base pairs, 18-22 base pairs, 18-21 base pairs, 18-20 base pairs, 19-30 base pairs, 19-26 base pairs, 19-23 base pairs, 19-22 base pairs, 19-21 base pairs, 19-20 base pairs, 20-30 base pairs, 20-26 base pairs, 20-25 base pairs, 20-24 base

pairs, 20-23 base pairs, 20-22 base pairs, 20-21 base pairs, 21-30 base pairs, 21-26 base pairs, 21-25 base pairs, 21-24 base pairs, 21-23 base pairs, or 21-22 base pairs. dsRNAs generated in the cell by processing with Dicer and similar enzymes are generally in the range of 19-22 base pairs in length. One strand of the duplex region of a dsDNA comprises a sequence that is substantially complementary to a region of a target RNA. The two strands forming the duplex structure can be from a single RNA molecule having at least one self-complementary region, or can be formed from two or more separate RNA molecules. Where the duplex region is formed from two strands of a single molecule, the molecule can have a duplex region separated by a single stranded chain of nucleotides (herein referred to as a "hairpin loop") between the 3'-end of one strand and the 5'-end of the respective other strand forming the duplex structure. The hairpin loop can comprise at least one unpaired nucleotide; in some embodiments the hairpin loop can comprise at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 20, at least 23 or more unpaired nucleotides. Where the two substantially complementary strands of a dsRNA are comprised by separate RNA molecules, those molecules need not, but can be covalently connected. In some embodiments, the two strands are connected covalently by means other than a hairpin loop, and the connecting structure is a linker.

In some embodiments, the iRNA agent may be a "single-stranded siRNA" that is introduced into a cell or organism to inhibit a target mRNA. In some embodiments, single-stranded RNAi agents can bind to the RISC endonuclease Argonaute 2, which then cleaves the target mRNA. The single-stranded siRNAs are generally 15-30 nucleotides and are optionally chemically modified. The design and testing of single-stranded siRNAs are described in U.S. Patent No. 8,101,348 and in Lima *et al.*, (2012) *Cell* 150: 883-894, the entire contents of each of which are hereby incorporated herein by reference. Any of the antisense nucleotide sequences described herein (*e.g.*, sequences provided in Tables 3-10) may be used as a single-stranded siRNA as described herein and optionally as chemically modified, *e.g.*, as described herein, *e.g.*, by the methods described in Lima *et al.*, (2012) *Cell* 150:883-894.

In some embodiments, an RNA interference agent includes a single stranded RNA that interacts with a target RNA sequence to direct the cleavage of the target RNA. Without wishing to be bound by theory, long double stranded RNA introduced into cells is broken down into siRNA by a Type III endonuclease known as Dicer (Sharp *et al.*, *Genes Dev.* 2001, 15:485). Dicer, a ribonuclease-III-like enzyme, processes the dsRNA into 19-23 base pair short interfering

RNAs with characteristic two base 3' overhangs (Bernstein, *et al.*, (2001) *Nature* 409:363). The siRNAs are then incorporated into an RNA-induced silencing complex (RISC) where one or more helicases unwind the siRNA duplex, enabling the complementary antisense strand to guide target recognition (Nykanen, *et al.*, (2001) *Cell* 107:309). Upon binding to the appropriate target mRNA, one or more endonucleases within the RISC cleaves the target to induce silencing (Elbashir, *et al.*, (2001) *Genes Dev.* 15:188). Thus, in some embodiments, the disclosure relates to a single stranded RNA that promotes the formation of a RISC complex to effect silencing of the target gene.

"G," "C," "A," "T" and "U" each generally stand for a nucleotide that contains guanine, cytosine, adenine, thymidine and uracil as a base, respectively. However, it will be understood that the terms "deoxyribonucleotide," "ribonucleotide," or "nucleotide" can also refer to a modified nucleotide, as further detailed below, or a surrogate replacement moiety. The skilled person is well aware that guanine, cytosine, adenine, and uracil may be replaced by other moieties without substantially altering the base pairing properties of an oligonucleotide comprising a nucleotide bearing such replacement moiety. For example, without limitation, a nucleotide comprising inosine as its base may base pair with nucleotides containing adenine, cytosine, or uracil. Hence, nucleotides containing uracil, guanine, or adenine may be replaced in the nucleotide sequences of dsRNA featured in the disclosure by a nucleotide containing, for example, inosine. In another example, adenine and cytosine anywhere in the oligonucleotide can be replaced with guanine and uracil, respectively to form G-U Wobble base pairing with the target mRNA. Sequences containing such replacement moieties are suitable for the compositions and methods featured in the disclosure.

As used herein, the term "iRNA," "RNAi", "iRNA agent," or "RNAi agent" or "RNAi molecule" refers to an agent that contains RNA as that term is defined herein, and which mediates the targeted cleavage of an RNA transcript, *e.g.*, via an RNA-induced silencing complex (RISC) pathway. In some embodiments, an iRNA as described herein effects inhibition of CA2 expression, *e.g.*, in a cell or mammal. Inhibition of CA2 expression may be assessed based on a reduction in the level of CA2 mRNA or a reduction in the level of the CA2 protein.

The term "linker" or "linking group" means an organic moiety that connects two parts of a compound, *e.g.*, covalently attaches two parts of a compound.

The term "lipophile" or "lipophilic moiety" broadly refers to any compound or chemical moiety having an affinity for lipids. One way to characterize the lipophilicity of the lipophilic moiety is by the octanol-water partition coefficient, $\log K_{ow}$, where K_{ow} is the ratio of a chemical's concentration in the octanol-phase to its concentration in the aqueous phase of a two-phase system at equilibrium. The octanol-water partition coefficient is a laboratory-measured property of a substance. However, it may also be predicted by using coefficients attributed to the structural components of a chemical which are calculated using first-principle or empirical methods (see, for example, Tetko et al., *J. Chem. Inf. Comput. Sci.* 41:1407-21 (2001), which is incorporated herein by reference in its entirety). It provides a thermodynamic measure of the tendency of the substance to prefer a non-aqueous or oily milieu rather than water (i.e. its hydrophilic/lipophilic balance). In principle, a chemical substance is lipophilic in character when its $\log K_{ow}$ exceeds 0. Typically, the lipophilic moiety possesses a $\log K_{ow}$ exceeding 1, exceeding 1.5, exceeding 2, exceeding 3, exceeding 4, exceeding 5, or exceeding 10. For instance, the $\log K_{ow}$ of 6-amino hexanol, for instance, is predicted to be approximately 0.7. Using the same method, the $\log K_{ow}$ of cholesteryl N-(hexan-6-ol) carbamate is predicted to be 10.7.

The lipophilicity of a molecule can change with respect to the functional group it carries. For instance, adding a hydroxyl group or amine group to the end of a lipophilic moiety can increase or decrease the partition coefficient (*e.g.*, $\log K_{ow}$) value of the lipophilic moiety.

Alternatively, the hydrophobicity of the double-stranded RNAi agent, conjugated to one or more lipophilic moieties, can be measured by its protein binding characteristics. For instance, in certain embodiments, the unbound fraction in the plasma protein binding assay of the double-stranded RNAi agent could be determined to positively correlate to the relative hydrophobicity of the double-stranded RNAi agent, which could then positively correlate to the silencing activity of the double-stranded RNAi agent.

In some embodiments, the plasma protein binding assay determined is an electrophoretic mobility shift assay (EMSA) using human serum albumin protein. An exemplary protocol of this binding assay is illustrated in detail in, *e.g.*, PCT/US2019/031170. The hydrophobicity of the double-stranded RNAi agent, measured by fraction of unbound siRNA in the binding assay, exceeds 0.15, exceeds 0.2, exceeds 0.25, exceeds 0.3, exceeds 0.35, exceeds 0.4, exceeds 0.45, or exceeds 0.5 for an enhanced *in vivo* delivery of siRNA.

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Accordingly, conjugating the lipophilic moieties to the internal position(s) of the double-stranded RNAi agent provides optimal hydrophobicity for the enhanced *in vivo* delivery of siRNA.

The term "lipid nanoparticle" or "LNP" is a vesicle comprising a lipid layer encapsulating a pharmaceutically active molecule, such as a nucleic acid molecule, *e.g.*, a RNAi agent or a plasmid from which a RNAi agent is transcribed. LNPs are described in, for example, U.S. Patent Nos. 6,858,225, 6,815,432, 8,158,601, and 8,058,069, the entire contents of which are hereby incorporated herein by reference.

As used herein, the term "modulate the expression of," refers to an at least partial "inhibition" or partial "activation" of a gene (*e.g.*, CA2 gene) expression in a cell treated with an iRNA composition as described herein compared to the expression of the corresponding gene in a control cell. A control cell includes an untreated cell, or a cell treated with a non-targeting control iRNA.

The skilled artisan will recognize that the term "RNA molecule" or "ribonucleic acid molecule" encompasses not only RNA molecules as expressed or found in nature, but also analogs and derivatives of RNA comprising one or more ribonucleotide/ribonucleoside analogs or derivatives as described herein or as known in the art. Strictly speaking, a "ribonucleoside" includes a nucleoside base and a ribose sugar, and a "ribonucleotide" is a ribonucleoside with one, two or three phosphate moieties or analogs thereof (*e.g.*, phosphorothioate). However, the terms "ribonucleoside" and "ribonucleotide" can be considered to be equivalent as used herein. The RNA can be modified in the nucleobase structure, in the ribose structure, or in the ribose-phosphate backbone structure, *e.g.*, as described herein below. However, the molecules comprising ribonucleoside analogs or derivatives must retain the ability to form a duplex. As non-limiting examples, an RNA molecule can also include at least one modified ribonucleoside including but not limited to a 2'-O-methyl modified nucleoside, a nucleoside comprising a 5' phosphorothioate group, a terminal nucleoside linked to a cholesteryl derivative or dodecanoic acid bisdecylamide group, a locked nucleoside, an abasic nucleoside, an acyclic nucleoside, a glycol nucleotide, a 2'-deoxy-2'-fluoro modified nucleoside, a 2'-amino-modified nucleoside, 2'-alkyl-modified nucleoside, morpholino nucleoside, a phosphoramidate or a non-natural base comprising nucleoside, or any combination thereof. Alternatively, or in combination, an RNA molecule can comprise at least two modified ribonucleosides, at least 3, at least 4, at least 5, at

least 6, at least 7, at least 8, at least 9, at least 10, at least 15, at least 20 or more, up to the entire length of the dsRNA molecule. The modifications need not be the same for each of such a plurality of modified ribonucleosides in an RNA molecule. In some embodiments, modified RNAs contemplated for use in methods and compositions described herein are peptide nucleic acids (PNAs) that have the ability to form the required duplex structure and that permit or mediate the specific degradation of a target RNA, *e.g.*, via a RISC pathway. For clarity, it is understood that the term "iRNA" does not encompass a naturally occurring double stranded DNA molecule or a 100% deoxynucleoside-containing DNA molecule.

In some aspects, a modified ribonucleoside includes a deoxyribonucleoside. In such an instance, an iRNA agent can comprise one or more deoxynucleosides, including, for example, a deoxynucleoside overhang(s), or one or more deoxynucleosides within the double stranded portion of a dsRNA. In certain embodiments, the RNA molecule comprises a percentage of deoxyribonucleosides of at least 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95% or higher (but not 100%) deoxyribonucleosides, *e.g.*, in one or both strands.

As used herein, the term "nucleotide overhang" refers to at least one unpaired nucleotide that protrudes from the duplex structure of an iRNA, *e.g.*, a dsRNA. For example, when a 3'-end of one strand of a dsRNA extends beyond the 5'-end of the other strand, or vice versa, there is a nucleotide overhang. A dsRNA can comprise an overhang of at least one nucleotide; alternatively, the overhang can comprise at least two nucleotides, at least three nucleotides, at least four nucleotides, or at least five nucleotides or more. A nucleotide overhang can comprise or consist of a nucleotide/nucleoside analog, including a deoxynucleotide/nucleoside. The overhang(s) may be on the sense strand, the antisense strand or any combination thereof. Furthermore, the nucleotide(s) of an overhang can be present on the 5' end, 3' end or both ends of either an antisense or sense strand of a dsRNA.

In some embodiments, the antisense strand of a dsRNA has a 1-10 nucleotide overhang at the 3' end and/or the 5' end. In some embodiments, the sense strand of a dsRNA has a 1-10 nucleotide overhang at the 3' end and/or the 5' end. In some embodiments, one or more of the nucleotides in the overhang is replaced with a nucleoside thiophosphate.

As used herein, a "pharmaceutical composition" comprises a pharmacologically effective amount of a therapeutic agent (*e.g.*, an iRNA) and a pharmaceutically acceptable carrier. As used herein, "pharmacologically effective amount," "therapeutically effective amount" or simply

"effective amount" refers to that amount of an agent (*e.g.*, iRNA) effective to produce the intended pharmacological, therapeutic or preventive result. For example, in a method of treating a disorder related to CA2 expression (*e.g.*, glaucoma or conditions associated with glaucoma), an effective amount includes an amount effective to reduce one or more symptoms associated with the disorder, *e.g.*, an amount effective to (a) inhibit or reduce intraocular pressure; (b) inhibit or reduce the expression or activity of CA2; (c) decrease the amount of aqueous humor; (d) inhibit or reduce optic nerve damage; or (e) inhibit or reduce retinal ganglion cell death or an amount effective to reduce the risk of developing conditions associated with the disorder. For example, if a given clinical treatment is considered effective when there is at least a 10% reduction in a measurable parameter associated with a disease or disorder, a therapeutically effective amount of a drug for the treatment of that disease or disorder is the amount necessary to obtain at least a 10% reduction in that parameter. For example, a therapeutically effective amount of an iRNA targeting CA2 can reduce a level of CA2 mRNA or a level of CA2 protein by any measurable amount, *e.g.*, by at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%.

The term "pharmaceutically acceptable carrier" refers to a carrier for administration of a therapeutic agent. Such carriers include, but are not limited to, saline, buffered saline, dextrose, water, glycerol, ethanol, and combinations thereof. The term specifically excludes cell culture medium. For drugs administered orally, pharmaceutically acceptable carriers include, but are not limited to pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavoring agents, coloring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate, and lactose, while corn starch and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatin, while the lubricating agent, if present, will generally be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate, to delay absorption in the gastrointestinal tract. Agents included in drug formulations are described further herein below.

As used herein, the term "SNALP" refers to a stable nucleic acid-lipid particle. A SNALP represents a vesicle of lipids coating a reduced aqueous interior comprising a nucleic acid such as an iRNA or a plasmid from which an iRNA is transcribed. SNALPs are described, *e.g.*, in U.S. Patent Application Publication Nos. 2006/0240093, 2007/0135372, and in

International Application No. WO 2009/082817. These applications are incorporated herein by reference in their entirety. In some embodiments, the SNALP is a SPLP. As used herein, the term "SPLP" refers to a nucleic acid-lipid particle comprising plasmid DNA encapsulated within a lipid vesicle.

As used herein, the term "strand comprising a sequence" refers to an oligonucleotide comprising a chain of nucleotides that is described by the sequence referred to using the standard nucleotide nomenclature.

As used herein, a "subject" to be treated according to the methods described herein, includes a human or non-human animal, *e.g.*, a mammal. The mammal may be, for example, a rodent (*e.g.*, a rat or mouse) or a primate (*e.g.*, a monkey). In some embodiments, the subject is a human.

A "subject in need thereof" includes a subject having, suspected of having, or at risk of developing a disorder related to CA2 expression, e.g., overexpression (*e.g.*, glaucoma or conditions associated with glaucoma). In some embodiments, the subject has, or is suspected of having, a disorder related to CA2 expression or overexpression. In some embodiments, the subject is at risk of developing a disorder related to CA2 expression or overexpression.

As used herein, "target sequence" refers to a contiguous portion of the nucleotide sequence of an mRNA molecule formed during the transcription of a gene, *e.g.*, CA2, including mRNA that is a product of RNA processing of a primary transcription product. The target portion of the sequence will be at least long enough to serve as a substrate for iRNA-directed cleavage at or near that portion. For example, the target sequence will generally be from 9-36 nucleotides in length, *e.g.*, 15-30 nucleotides in length, including all sub-ranges therebetween. As non-limiting examples, the target sequence can be from 15-30 nucleotides, 15-26 nucleotides, 15-23 nucleotides, 15-22 nucleotides, 15-21 nucleotides, 15-20 nucleotides, 15-19 nucleotides, 15-18 nucleotides, 15-17 nucleotides, 18-30 nucleotides, 18-26 nucleotides, 18-23 nucleotides, 18-22 nucleotides, 18-21 nucleotides, 18-20 nucleotides, 19-30 nucleotides, 19-26 nucleotides, 19-23 nucleotides, 19-22 nucleotides, 19-21 nucleotides, 19-20 nucleotides, 20-30 nucleotides, 20-26 nucleotides, 20-25 nucleotides, 20-24 nucleotides, 20-23 nucleotides, 20-22 nucleotides, 20-21 nucleotides, 21-30 nucleotides, 21-26 nucleotides, 21-25 nucleotides, 21-24 nucleotides, 21-23 nucleotides, or 21-22 nucleotides.

As used herein, the phrases "therapeutically effective amount" and "prophylactically effective amount" and the like refer to an amount that provides a therapeutic benefit in the treatment, prevention, or management of any disorder or pathological process related to CA2 expression (*e.g.*, glaucoma or conditions associated with glaucoma). The specific amount that is therapeutically effective may vary depending on factors known in the art, such as, for example, the type of disorder or pathological process, the patient's history and age, the stage of the disorder or pathological process, and the administration of other therapies.

In the context of the present disclosure, the terms "treat," "treatment," and the like mean to prevent, delay, relieve or alleviate at least one symptom associated with a disorder related to CA2 expression, or to slow or reverse the progression or anticipated progression of such a disorder. For example, the methods featured herein, when employed to treat glaucoma or conditions associated with glaucoma, may serve to reduce or prevent one or more symptoms of glaucoma or conditions associated with glaucoma, as described herein, or to reduce the risk or severity of associated conditions. Thus, unless the context clearly indicates otherwise, the terms "treat," "treatment," and the like are intended to encompass prophylaxis, *e.g.*, prevention of disorders and/or symptoms of disorders related to CA2 expression. Treatment can also mean prolonging survival as compared to expected survival in the absence of treatment.

By "lower" in the context of a disease marker or symptom is meant any decrease, *e.g.*, a statistically or clinically significant decrease in such level. The decrease can be, for example, at least 10%, at least 20%, at least 30%, at least 40%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%. The decrease can be down to a level accepted as within the range of normal for an individual without such disorder.

As used herein, "CA2" refers to "carbonic anhydrase 2" the corresponding mRNA ("CA2 mRNA"), or the corresponding protein ("CA2 protein"). The sequence of a human CA2 mRNA transcript can be found at SEQ ID NO: 1.

The term "substituted" refers to the replacement of one or more hydrogen radicals in a given structure with the radical of a specified substituent including, but not limited to: alkyl, alkenyl, alkynyl, aryl, heterocyclyl, halo, thiol, alkylthio, arylthio, alkylthioalkyl, arylthioalkyl, alkylsulfonyl, alkylsulfonylalkyl, arylsulfonylalkyl, alkoxy, aryloxy, aralkoxy, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, alkoxycarbonyl, aryloxycarbonyl, haloalkyl, amino, trifluoromethyl, cyano, nitro, alkylamino, arylamino, alkylaminoalkyl, arylaminoalkyl,

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aminoalkylamino, hydroxy, alkoxyalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, acyl, aralkoxycarbonyl, carboxylic acid, sulfonic acid, sulfonyl, phosphonic acid, aryl, heteroaryl, heterocyclic, and aliphatic. It is understood that the substituent can be further substituted.

The term "alkyl" refers to saturated and unsaturated non-aromatic hydrocarbon chains that may be a straight chain or branched chain, containing the indicated number of carbon atoms (these include without limitation propyl, allyl, or propargyl), which may be optionally inserted with N, O, or S. For example, "(C1-C6) alkyl" means a radical having from 1 6 carbon atoms in a linear or branched arrangement. "(C1-C6) alkyl" includes, for example, methyl, ethyl, propyl, iso-propyl, n-butyl, tert-butyl, pentyl and hexyl. In certain embodiments, a lipophilic moiety of the instant disclosure can include a C6-C18 alkyl hydrocarbon chain.

The term "alkylene" refers to an optionally substituted saturated aliphatic branched or straight chain divalent hydrocarbon radical having the specified number of carbon atoms. For example, "(C1-C6) alkylene" means a divalent saturated aliphatic radical having from 1-6 carbon atoms in a linear arrangement, e.g., $[(CH_2)_n]$, where n is an integer from 1 to 6. "(C1-C6) alkylene" includes methylene, ethylene, propylene, butylene, pentylene and hexylene. Alternatively, "(C1-C6) alkylene" means a divalent saturated radical having from 1-6 carbon atoms in a branched arrangement, for example: $[(CH_2CH_2CH_2CH_2CH(CH_3)]$, $[(CH_2CH_2CH_2CH_2C(CH_3)_2]$, $[(CH_2C(CH_3)_2CH(CH_3))]$, and the like. The term "alkylenedioxo" refers to a divalent species of the structure —O—R—O—, in which R represents an alkylene.

The term "mercapto" refers to an —SH radical. The term "thioalkoxy" refers to an —S— alkyl radical.

The term "halo" refers to any radical of fluorine, chlorine, bromine or iodine. "Halogen" and "halo" are used interchangeably herein.

As used herein, the term "cycloalkyl" means a saturated or unsaturated nonaromatic hydrocarbon ring group having from 3 to 14 carbon atoms, unless otherwise specified. For example, "(C3-C10) cycloalkyl" means a hydrocarbon radical of a (3-10)-membered saturated aliphatic cyclic hydrocarbon ring. Examples of cycloalkyl groups include, but are not limited to, cyclopropyl, methyl-cyclopropyl, 2,2-dimethyl-cyclobutyl, 2-ethyl-cyclopentyl, cyclohexyl, etc. Cycloalkyls may include multiple spiro- or fused rings. Cycloalkyl groups are optionally mono-, di-, tri-, tetra-, or penta-substituted on any position as permitted by normal valency.

As used herein, the term "alkenyl" refers to a non-aromatic hydrocarbon radical, straight or branched, containing at least one carbon-carbon double bond, and having from 2 to 10 carbon atoms unless otherwise specified. Up to five carbon-carbon double bonds may be present in such groups. For example, "C2-C6" alkenyl is defined as an alkenyl radical having from 2 to 6 carbon atoms. Examples of alkenyl groups include, but are not limited to, ethenyl, propenyl, butenyl, and cyclohexenyl. The straight, branched, or cyclic portion of the alkenyl group may contain double bonds and is optionally mono-, di-, tri-, tetra-, or penta-substituted on any position as permitted by normal valency. The term "cycloalkenyl" means a monocyclic hydrocarbon group having the specified number of carbon atoms and at least one carbon-carbon double bond.

As used herein, the term "alkynyl" refers to a hydrocarbon radical, straight or branched, containing from 2 to 10 carbon atoms, unless otherwise specified, and containing at least one carbon-carbon triple bond. Up to 5 carbon-carbon triple bonds may be present. Thus, "C2-C6 alkynyl" means an alkynyl radical having from 2 to 6 carbon atoms. Examples of alkynyl groups include, but are not limited to, ethynyl, 2-propynyl, and 2-butynyl. The straight or branched portion of the alkynyl group may contain triple bonds as permitted by normal valency, and may be optionally mono-, di-, tri-, tetra-, or penta-substituted on any position as permitted by normal valency.

As used herein, "alkoxyl" or "alkoxy" refers to an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. For example, "(C1-C3)alkoxy" includes methoxy, ethoxy and propoxy. For example, "(C1-C6)alkoxy", is intended to include C1, C2, C3, C4, C5, and C6 alkoxy groups. For example, "(C1-C8)alkoxy", is intended to include C1, C2, C3, C4, C5, C6, C7, and C8 alkoxy groups. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, n-pentoxy, s-pentoxy, n-heptoxy, and n-octoxy. "Alkylthio" means an alkyl radical attached through a sulfur linking atom. The terms "alkylamino" or "aminoalkyl", means an alkyl radical attached through an NH linkage. "Dialkylamino" means two alkyl radical attached through a nitrogen linking atom. The amino groups may be unsubstituted, monosubstituted, or di-substituted. In some embodiments, the two alkyl radicals are the same (e.g., N,N-dimethylamino). In some embodiments, the two alkyl radicals are different (e.g., N-ethyl-N-methylamino).

As used herein, "aryl" or "aromatic" means any stable monocyclic or polycyclic carbon ring of up to 7 atoms in each ring, wherein at least one ring is aromatic. Examples of aryl groups include, but are not limited to, phenyl, naphthyl, anthracenyl, tetrahydronaphthyl, indanyl, and biphenyl. In cases where the aryl substituent is bicyclic and one ring is non-aromatic, it is understood that attachment is via the aromatic ring. Aryl groups are optionally mono-, di-, tri-, tetra-, or penta-substituted on any position as permitted by normal valency. The term "arylalkyl" or the term "aralkyl" refers to alkyl substituted with an aryl. The term "arylalkoxy" refers to an alkoxy substituted with aryl.

"Hetero" refers to the replacement of at least one carbon atom in a ring system with at least one heteroatom selected from N, S and O. "Hetero" also refers to the replacement of at least one carbon atom in an acyclic system. A hetero ring system or a hetero acyclic system may have, for example, 1, 2 or 3 carbon atoms replaced by a heteroatom.

As used herein, the term "heteroaryl" represents a stable monocyclic or polycyclic ring of up to 7 atoms in each ring, wherein at least one ring is aromatic and contains from 1 to 4 heteroatoms selected from the group consisting of O, N and S. Examples of heteroaryl groups include, but are not limited to, acridinyl, carbazolyl, cinnolinyl, quinoxalinyl, pyrrazolyl, indolyl, benzotriazolyl, furanyl, thienyl, benzothienyl, benzofuranyl, benzimidazolonyl, benzoxazolonyl, quinolinyl, isoquinolinyl, dihydroisoindolonyl, imidazopyridinyl, isoindolonyl, indazolyl, oxazolyl, oxadiazolyl, isoxazolyl, indolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, tetrahydroquinoline. "Heteroaryl" is also understood to include the N-oxide derivative of any nitrogen-containing heteroaryl. In cases where the heteroaryl substituent is bicyclic and one ring is non-aromatic or contains no heteroatoms, it is understood that attachment is via the aromatic ring or via the heteroatom containing ring. Heteroaryl groups are optionally mono-, di-, tri-, tetra-, or penta-substituted on any position as permitted by normal valency.

As used herein, the term "heterocycle," "heterocyclic," or "heterocyclyl" means a 3- to 14-membered aromatic or nonaromatic heterocycle containing from 1 to 4 heteroatoms selected from the group consisting of O, N and S, including polycyclic groups. As used herein, the term "heterocyclic" is also considered to be synonymous with the terms "heterocycle" and "heterocyclyl" and is understood as also having the same definitions set forth herein. "Heterocyclyl" includes the above mentioned heteroaryls, as well as dihydro and tetrahydro analogs thereof. Examples of heterocyclyl groups include, but are not limited to, azetidinyl,

benzoimidazolyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxooxazolidinyl, oxazolyl, oxazoline, oxopiperazinyl, oxopyrrolidinyl, oxomorpholinyl, isoxazoline, oxetanyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridazinyl, pyridyl, pyridinonyl, pyrimidyl, pyrimidinonyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, tetrahydropyranyl, tetrahydrofuranyl, tetrahydrothiopyranyl, tetrahydroisoquinolinyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyridin-2-onyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzoimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, dioxidothiomorpholinyl, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl, and N-oxides thereof. Attachment of a heterocyclyl substituent can occur via a carbon atom or via a heteroatom. Heterocyclyl groups are optionally mono-, di-, tri-, tetra-, or penta-substituted on any position as permitted by normal valency.

"Heterocycloalkyl" refers to a cycloalkyl residue in which one to four of the carbons is replaced by a heteroatom such as oxygen, nitrogen or sulfur. Examples of heterocycles whose radicals are heterocyclyl groups include tetrahydropyran, morpholine, pyrrolidine, piperidine, thiazolidine, oxazole, oxazoline, isoxazole, dioxane, tetrahydrofuran and the like.

The term "heteroaryl" refers to an aromatic 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S (e.g., carbon atoms and 1-3, 1-6, or 1-9 heteroatoms of N, O, or S if monocyclic, bicyclic, or tricyclic, respectively), wherein 0, 1, 2, 3, or 4 atoms of each ring may be substituted by a substituent. Examples of heteroaryl groups include pyridyl, furyl or furanyl, imidazolyl, benzimidazolyl, pyrimidinyl, thiophenyl or thienyl, quinolinyl, indolyl, thiazolyl, and the like. The term "heteroarylalkyl" or the term "heteroaralkyl" refers to an alkyl substituted with a heteroaryl. The term "heteroarylalkoxy" refers to an alkoxy substituted with heteroaryl.

The term "cycloalkyl" as employed herein includes saturated and partially unsaturated cyclic hydrocarbon groups having 3 to 12 carbons, for example, 3 to 8 carbons, and, for example, 3 to 6 carbons, wherein the cycloalkyl group additionally may be optionally substituted. Cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl.

The term "acyl" refers to an alkylcarbonyl, cycloalkylcarbonyl, arylcarbonyl, heterocyclylcarbonyl, or heteroarylcarbonyl substituent, any of which may be further substituted by substituents.

As used herein, "keto" refers to any alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, heteroaryl, or aryl group as defined herein attached through a carbonyl bridge.

Examples of keto groups include, but are not limited to, alkanoyl (e.g., acetyl, propionyl, butanoyl, pentanoyl, hexanoyl), alkenoyl (e.g., acryloyl) alkynoyl (e.g., ethynoyl, propynoyl, butynoyl, pentynoyl, hexynoyl), aryloyl (e.g., benzoyl), heteroaryloyl (e.g., pyrroloyl, imidazoloyl, quinolinoyl, pyridinoyl).

As used herein, "alkoxycarbonyl" refers to any alkoxy group as defined above attached through a carbonyl bridge (i.e., —C(O)O-alkyl). Examples of alkoxycarbonyl groups include, but are not limited to, methoxycarbonyl, ethoxycarbonyl, iso-propoxycarbonyl, n-propoxycarbonyl, t-butoxycarbonyl, benzyloxycarbonyl or n-pentoxycarbonyl.

As used herein, "aryloxycarbonyl" refers to any aryl group as defined herein attached through an oxycarbonyl bridge (i.e., —C(O)O-aryl). Examples of aryloxycarbonyl groups include, but are not limited to, phenoxycarbonyl and naphthyloxycarbonyl.

As used herein, "heteroaryloxycarbonyl" refers to any heteroaryl group as defined herein attached through an oxycarbonyl bridge (i.e., —C(O)O-heteroaryl). Examples of heteroaryloxycarbonyl groups include, but are not limited to, 2-pyridyloxycarbonyl, 2-oxazolyloxycarbonyl, 4-thiazolyloxycarbonyl, or pyrimidinyloxycarbonyl.

The term "oxo" refers to an oxygen atom, which forms a carbonyl when attached to carbon, an N-oxide when attached to nitrogen, and a sulfoxide or sulfone when attached to sulfur.

The person of ordinary skill in the art would readily understand and appreciate that the compounds and compositions disclosed herein may have certain atoms (e.g., N, O, or S atoms) in a protonated or deprotonated state, depending upon the environment in which the compound or

composition is placed. Accordingly, as used herein, the structures disclosed herein envisage that certain functional groups, such as, for example, OH, SH, or NH, may be protonated or deprotonated. The disclosure herein is intended to cover the disclosed compounds and compositions regardless of their state of protonation based on the pH of the environment, as would be readily understood by the person of ordinary skill in the art.

II. iRNA Agents

Described herein are iRNA agents that modulate (*e.g.*, inhibit) the expression of CA2.

In some embodiments, the iRNA agent activates the expression of CA2 in a cell or mammal.

In some embodiments, the iRNA agent includes double-stranded ribonucleic acid (dsRNA) molecules for inhibiting the expression of CA2 in a cell or in a subject (*e.g.*, in a mammal, *e.g.*, in a human), where the dsRNA includes an antisense strand having a region of complementarity which is complementary to at least a part of an mRNA formed in the expression of CA2, and where the region of complementarity is 30 nucleotides or less in length, generally 19-24 nucleotides in length, and where the dsRNA, upon contact with a cell expressing CA2, inhibits the expression of CA2, *e.g.*, by at least 10%, 20%, 30%, 40%, or 50% as compared to a similar cell not contacted with the RNAi agent or an RNAi agent not complimentary to the CA2 gene.

The modulation (*e.g.*, inhibition) of expression of CA2 can be assayed by, for example, a PCR or branched DNA (bDNA)-based method, or by a protein-based method, such as by Western blot. Expression of CA2 in cell culture, such as in COS cells, ARPE-19 cells, hTERT RPE-1 cells, RPE-J cells, HeLa cells, primary hepatocytes, HepG2 cells, primary cultured cells or in a biological sample from a subject can be assayed by measuring CA2 mRNA levels, such as by bDNA or TaqMan assay, or by measuring protein levels, such as by immunofluorescence analysis, using, for example, Western Blotting or flow cytometric techniques.

A dsRNA typically includes two RNA strands that are sufficiently complementary to hybridize to form a duplex structure under conditions in which the dsRNA will be used. One strand of a dsRNA (the antisense strand) typically includes a region of complementarity that is substantially complementary, or fully complementary, to a target sequence, derived from the sequence of an mRNA formed during the expression of CA2. The other strand (the sense strand)

typically includes a region that is complementary to the antisense strand, such that the two strands hybridize and form a duplex structure when combined under suitable conditions. Generally, the duplex structure is between 15 and 30 inclusive, more generally between 18 and 25 inclusive, yet more generally between 19 and 24 inclusive, and most generally between 19 and 21 base pairs in length, inclusive. Similarly, the region of complementarity to the target sequence is between 15 and 30 inclusive, more generally between 18 and 25 inclusive, yet more generally between 19 and 24 inclusive, and most generally between 19 and 21 nucleotides in length, inclusive.

In some embodiments, the dsRNA is between 15 and 20 nucleotides in length, inclusive, and in other embodiments, the dsRNA is between 25 and 30 nucleotides in length, inclusive. As the ordinarily skilled person will recognize, the targeted region of an RNA targeted for cleavage will most often be part of a larger RNA molecule, often an mRNA molecule. Where relevant, a "part" of an mRNA target is a contiguous sequence of an mRNA target of sufficient length to be a substrate for RNAi-directed cleavage (*i.e.*, cleavage through a RISC pathway). dsRNAs having duplexes as short as 9 base pairs can, under some circumstances, mediate RNAi-directed RNA cleavage. Most often a target will be at least 15 nucleotides in length, *e.g.*, 15-30 nucleotides in length.

One of skill in the art will also recognize that the duplex region is a primary functional portion of a dsRNA, *e.g.*, a duplex region of 9 to 36, *e.g.*, 15-30 base pairs. Thus, in some embodiments, to the extent that it becomes processed to a functional duplex of *e.g.*, 15-30 base pairs that targets a desired RNA for cleavage, an RNA molecule or complex of RNA molecules having a duplex region greater than 30 base pairs is a dsRNA. Thus, an ordinarily skilled artisan will recognize that in some embodiments, then, an miRNA is a dsRNA. In some embodiments, a dsRNA is not a naturally occurring miRNA. In some embodiments, an iRNA agent useful to target CA2 expression is not generated in the target cell by cleavage of a larger dsRNA.

A dsRNA as described herein may further include one or more single-stranded nucleotide overhangs. The dsRNA can be synthesized by standard methods known in the art as further discussed below, *e.g.*, by use of an automated DNA synthesizer, such as are commercially available from, for example, Biosearch, Applied Biosystems, Inc.

In some embodiments, CA2 is a human CA2.

In specific embodiments, the dsRNA comprises a sense strand that comprises or consists of a sense sequence selected from the sense sequences provided in Tables 3-10 and an antisense strand that comprises or consists of an antisense sequence selected from the antisense sequences provided in Tables 3-10.

In some aspects, a dsRNA will include at least sense and antisense nucleotide sequences, whereby the sense strand is selected from the sequences provided in Tables 3-10 and the corresponding antisense strand is selected from the sequences provided in Tables 3-10.

In these aspects, one of the two sequences is complementary to the other of the two sequences, with one of the sequences being substantially complementary to a sequence of an mRNA generated by the expression of CA2. As such, a dsRNA will include two oligonucleotides, where one oligonucleotide is described as the sense strand, and the second oligonucleotide is described as the corresponding antisense strand. As described elsewhere herein and as known in the art, the complementary sequences of a dsRNA can also be contained as self-complementary regions of a single nucleic acid molecule, as opposed to being on separate oligonucleotides.

The skilled person is well aware that dsRNAs having a duplex structure of between 20 and 23, but specifically 21, base pairs have been hailed as particularly effective in inducing RNA interference (Elbashir *et al.*, *EMBO* 2001, 20:6877-6888). However, others have found that shorter or longer RNA duplex structures can be effective as well.

In the embodiments described above, by virtue of the nature of the oligonucleotide sequences provided in Tables 3-10, dsRNAs described herein can include at least one strand of a length of minimally 19 nucleotides. It can be reasonably expected that shorter duplexes having one of the sequences of Tables 3-10 minus only a few nucleotides on one or both ends will be similarly effective as compared to the dsRNAs described above.

In some embodiments, the dsRNA has a partial sequence of at least 15, 16, 17, 18, 19, 20, or more contiguous nucleotides from one of the sequences of Tables 3-10.

In some embodiments, the dsRNA has an antisense sequence that comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides of an antisense sequence provided in Tables 3-10 and a sense sequence that comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides of a corresponding sense sequence provided in Tables 3-10.

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In some embodiments, the dsRNA comprises an antisense sequence that comprises at least 15, 16, 17, 18, 19, 20, 21, 22, or 23 contiguous nucleotides of an antisense sequence provided in Tables 3-10 and a sense sequence that comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides of a corresponding sense sequence provided in Tables 3-10.

In some such embodiments, the dsRNA, although it comprises only a portion of the sequences provided in Tables 3-10 is equally effective in inhibiting a level of CA2 expression as is a dsRNA that comprises the full-length sequences provided in Tables 3-10. In some embodiments, the dsRNA differs in its inhibition of a level of expression of CA2 by not more than 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 % inhibition compared with a dsRNA comprising the full sequence disclosed herein.

The iRNAs of Tables 3-10 were designed based on human CA2 sequence. Without wishing to be bound by theory, CA2 sequence is conserved sufficiently between species such that certain iRNAs designed based on a human sequence have activity against CA2 from primates, such as cynomolgus monkey, and other species, including, for example, mouse, rat, and rabbit.

Consequently, in some embodiments, an iRNA of Tables 3-10 decreases CA2 protein or CA2 mRNA levels in a cell. In some embodiments, the cell is a rodent cell (e.g., a rat cell), or a primate cell (e.g., a cynomolgus monkey cell or a human cell). In some embodiments, CA2 protein or CA2 mRNA levels are reduced by at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 95%. In some embodiments, the iRNA of Tables 3-10 that inhibits CA2 in a human cell has less than 5, 4, 3, 2, or 1 mismatches to the corresponding portion of human CA2. In some embodiments, the iRNA of Tables 3-10 that inhibits CA2 in a human cell has no mismatches to the corresponding portion of human CA2.

iRNAs designed based on rodent sequences can have utility, e.g., for inhibiting CA2 in human cells, e.g., for therapeutic purposes, or for inhibiting CA2 in rodent cells, e.g., for research characterizing CA2 in a rodent model.

In some embodiments, an iRNA described herein comprises an antisense strand comprising at least 15 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, of a portion of nucleotide sequence of SEQ ID NO: 2. In some embodiments, an iRNA described herein comprises a sense strand comprising at least 15 contiguous nucleotides, with 0, or 1, 2, or 3

mismatches, of the corresponding portion of the nucleotide sequence of SEQ ID NO: 1. A human CA2 mRNA may have the sequence of SEQ ID NO: 1 provided herein.

In some embodiments, an iRNA described herein includes at least 15 contiguous nucleotides from one of the sequences provided in Tables 3-10, and may optionally be coupled to additional nucleotide sequences taken from the region contiguous to the selected sequence in CA2.

While a target sequence is generally 15-30 nucleotides in length, there is wide variation in the suitability of particular sequences in this range for directing cleavage of any given target RNA. Various software packages and the guidelines set out herein provide guidance for the identification of optimal target sequences for any given gene target, but an empirical approach can also be taken in which a "window" or "mask" of a given size (as a non-limiting example, 21 nucleotides) is literally or figuratively (including, *e.g.*, in silico) placed on the target RNA sequence to identify sequences in the size range that may serve as target sequences. By moving the sequence "window" progressively one nucleotide upstream or downstream of an initial target sequence location, the next potential target sequence can be identified, until the complete set of possible sequences is identified for any given target size selected. This process, coupled with systematic synthesis and testing of the identified sequences (using assays described herein or known in the art) to identify those sequences that perform optimally can identify those RNA sequences that, when targeted with an iRNA agent, mediate the best inhibition of target gene expression. Thus, it is contemplated that further optimization of inhibition efficiency can be achieved by progressively "walking the window" one nucleotide upstream or downstream of the given sequences to identify sequences with equal or better inhibition characteristics.

Further, it is contemplated that for any sequence identified, *e.g.*, in Tables 3-10, further optimization can be achieved by systematically either adding or removing nucleotides to generate longer or shorter sequences and testing those and sequences generated by walking a window of the longer or shorter size up or down the target RNA from that point. Again, coupling this approach to generating new candidate targets with testing for effectiveness of iRNAs based on those target sequences in an inhibition assay as known in the art or as described herein can lead to further improvements in the efficiency of inhibition. Further still, such optimized sequences can be adjusted by, *e.g.*, the introduction of modified nucleotides as described herein or as known in the art, addition or changes in overhang, or other modifications

as known in the art and/or discussed herein to further optimize the molecule (*e.g.*, increasing serum stability or circulating half-life, increasing thermal stability, enhancing transmembrane delivery, targeting to a particular location or cell type, increasing interaction with silencing pathway enzymes, increasing release from endosomes, *etc.*) as an expression inhibitor.

In some embodiments, the disclosure provides an iRNA of any of Tables 3-10 that is un-modified or un-conjugated. In some embodiments, an RNAi agent of the disclosure has a nucleotide sequence as provided in any of Tables 3-10, but lacks one or more ligand or moiety shown in the tables. A ligand or moiety (*e.g.*, a lipophilic ligand or moiety) can be included in any of the positions provided in the instant application.

An iRNA as described herein can contain one or more mismatches to the target sequence. In some embodiments, an iRNA as described herein contains no more than 3 mismatches. In some embodiments, when the antisense strand of the iRNA contains mismatches to a target sequence, the area of mismatch is not located in the center of the region of complementarity. In some embodiments, when the antisense strand of the iRNA contains mismatches to the target sequence, the mismatch is restricted to be within the last 5 nucleotides from either the 5' or 3' end of the region of complementarity. For example, for a 23 nucleotide iRNA agent RNA strand which is complementary to a region of CA2, the RNA strand generally does not contain any mismatch within the central 13 nucleotides. The methods described herein, or methods known in the art can be used to determine whether an iRNA containing a mismatch to a target sequence is effective in inhibiting the expression of CA2. For example, Jackson *et al.* (*Nat. Biotechnol.* 2003;21: 635–637) described an expression profile study where the expression of a small set of genes with sequence identity to the MAPK14 siRNA only at 12–18 nt of the sense strand, was down-regulated with similar kinetics to MAPK14. Similarly, Lin *et al.*, (*Nucleic Acids Res.* 2005; 33(14): 4527–4535) using qPCR and reporter assays, showed that a 7 nt complementation between a siRNA and a target is sufficient to cause mRNA degradation of the target. Consideration of the efficacy of iRNAs with mismatches in inhibiting expression of CA2 is important, especially if the particular region of complementarity in a CA2 gene is known to have polymorphic sequence variation within the population.

An RNA target may have regions, or spans of the target RNA's nucleotide sequence, which are relatively more susceptible or amenable than other regions of the RNA target to mediating cleavage of the RNA target via RNA interference induced by the binding of an RNAi

agent to that region. The increased susceptibility to RNA interference within such "hotspot regions" (or simply "hotspots") means that iRNA agents targeting the region will likely have higher efficacy in inducing iRNA interference than iRNA agents which target other regions of the target RNA. For example, without being bound by theory, the accessibility of a target region of a target RNA may influence the efficacy of iRNA agents which target that region, with some hotspot regions having increased accessibility. Secondary structures, for instance, that form in the RNA target (e.g., within or proximate to hotspot regions) may affect the ability of the iRNA agent to bind the target region and induce RNA interference.

According to certain aspects of the invention, an iRNA agent may be designed to target a hotspot region of any of the target RNAs described herein, including any identified portions of a target RNA (e.g., a particular exon). As used herein, a hotspot region may refer to an approximately 19-200, 19-150, 19-100, 19-75, 19-50, 21-200, 21-150, 21-100, 21-75, 21-50, 50-200, 50-150, 50-100, 50-75, 75-200, 75-150, 75-100, 100-200, or 100-150 nucleotide region of a target RNA sequence for which targeting using RNAi agents provides an observably higher probability of efficacious silencing relative to targeting other regions of the same target RNA. According to certain aspects of the invention, a hotspot region may comprise a limited region of the target RNA, and in some cases, a substantially limited region of the target, including for example, less than half of the length of the target RNA, such as about 5%, 10%, 15%, 20%, 25%, or 30% of the lenth of the target RNA. Conversely, the other regions against which a hotspot is compared may cumulatively comprise at least a majority of the length of the target RNA. For example, the other regions may cumulatively comprise at least about 60%, or at least about 70%, or at least about 80%, or at least about 90%, or at least about 95% of the length of the target RNA.

Compared regions of the target RNA may be empirically evaluated for identification of hotspots using efficacy data obtained from in vitro or in vivo screening assays. For example, RNAi agents targeting various regions that span a target RNA may be compared for frequency of efficacious iRNA agents (e.g., the amount by which target gene expression is inhibited, such as measured by mRNA expression or protein expression) that bind each region. In general, a hotspot can be recognized by observing clustering of multiple efficacious RNAi agents that bind to a limited region of the RNA target. A hotspot may be sufficiently characterized as such by observing efficacy of iRNA agents which cumulatively span at least about 60% of the target

region identified as a hotspot, such as about 70%, about 80%, about 90%, or about 95% or more of the length of the region, including both ends of the region (i.e. at least about 60%, 70%, 80%, 90%, or 95% or more of the nucleotides within the region, including the nucleotides at each end of the region, were targeted by an iRNA agent). According to some aspects of the invention, an iRNA agent which demonstrates at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% inhibition over the region (e.g., no more than about 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, 10%, or 5% mRNA remaining) may be identified as efficacious.

Amenibility to targeting of RNA regions may also be assessed using quantitative comparison of inhibition measurements across different regions of a defined size (e.g, 25, 30, 40, 50, 60, 70, 80, 90, or 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, or 200 nts). For example, an average level of inhibition may be determined for each region and the averages of each region may be compared. The average level of inhibition within a hotspot region may be substantially higher than the average of averages for all evaluated regions. According to some aspects, the average level of inhibition in a hotspot region may be at least about 10%, 20%, 30%, 40%, or 50% higher than the average of averages. According to some aspects, the average level of inhibition in a hotspot region may be at least about 1.0, 1.1, 1.2, 1.3, 1.4, 1.5 1.6, 1.7, 1.8. 1.9, or 2.0 standard deviations above the average of averages. The average level of inhibition may be higher by a statistically significant (e.g., $p < 0.05$) amount. According to some aspects, each inhibition measurement within a hotspot region may be above a threshold amount (e.g., at or below a threshold amount of mRNA remaining). According to some aspects, each inhibition measurement within the region may be substantially higher than an average of all inhibition measurements across all the measured regions. For example, each inhibition measurement in a hotspot region may be at least about 10%, 20%, 30%, 40%, or 50% higher than the average of all inhibition measurements. According to some aspects, each inhibition measurement may be at least about 1.0, 1.1, 1.2, 1.3, 1.4, 1.5 1.6, 1.7, 1.8. 1.9, or 2.0 standard deviations above the average of all inhibition measurements. Each inhibition measurement may be higher by a statistically significant (e.g., $p < 0.05$) amount than the average of all inhibition measurements. A standard for evaluating a hotspot may comprise various combinations of the above standards where compatible (e.g., an average level of inhibition of at least about a first amount and having no inhibition measurements below a threshold level of a second amount, lesser than the first amount).

It is therefore expressly contemplated that any iRNA agent, including the specific exemplary iRNA agents described herein, which targets a hotspot region of a target RNA, may be preferably selected for inducing RNA interference of the target mRNA as targeting such a hotspot region is likely to exhibit a robust inhibitory response relative to targeting a region which is not a hotspot region. RNAi agents targeting target sequences that substantially overlap (e.g., by at least about 70%, 75%, 80%, 85%, 90%, 95% of the target sequence length) or, preferably, that reside fully within the hotspot region may be considered to target the hotspot region. Hotspot regions of the RNA target(s) of the instant invention may include any region for which the data disclosed herein demonstrates higher frequency of targeting by efficacious RNAi agents, including by any of the standards described elsewhere herein, whether or not the range(s) of such hotspot region(s) are explicitly specified.

In various embodiments, a dsRNA agent of the present invention targets a hotspot region of an mRNA encoding CA2.

In some embodiments, at least one end of a dsRNA has a single-stranded nucleotide overhang of 1 to 4, generally 1 or 2 nucleotides. In some embodiments, dsRNAs having at least one nucleotide overhang have superior inhibitory properties relative to their blunt-ended counterparts. In some embodiments, the RNA of an iRNA (*e.g.*, a dsRNA) is chemically modified to enhance stability or other beneficial characteristics. The nucleic acids featured in the disclosure may be synthesized and/or modified by methods well established in the art, such as those described in "Current protocols in nucleic acid chemistry," Beaucage, S.L. *et al.* (Edrs.), John Wiley & Sons, Inc., New York, NY, USA, which is hereby incorporated herein by reference. Modifications include, for example, (a) end modifications, *e.g.*, 5' end modifications (phosphorylation, conjugation, inverted linkages, *etc.*) 3' end modifications (conjugation, DNA nucleotides, inverted linkages, *etc.*), (b) base modifications, *e.g.*, replacement with stabilizing bases, destabilizing bases, or bases that base pair with an expanded repertoire of partners, removal of bases (abasic nucleotides), or conjugated bases, (c) sugar modifications (*e.g.*, at the 2' position or 4' position, or having an acyclic sugar) or replacement of the sugar, as well as (d) backbone modifications, including modification or replacement of the phosphodiester linkages. Specific examples of RNA compounds useful in this disclosure include, but are not limited to, RNAs containing modified backbones or no natural internucleoside linkages. RNAs having modified backbones include, among others, those that do not have a phosphorus atom in the

backbone. For the purposes of this specification, and as sometimes referenced in the art, modified RNAs that do not have a phosphorus atom in their internucleoside backbone can also be considered to be oligonucleosides. In particular embodiments, the modified RNA will have a phosphorus atom in its internucleoside backbone.

Modified RNA backbones include, for example, phosphorothioates, chiral phosphorothioates, phosphorodithioates, phosphotriesters, aminoalkylphosphotriesters, methyl and other alkyl phosphonates including 3'-alkylene phosphonates and chiral phosphonates, phosphinates, phosphoramidates including 3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, and boranophosphates having normal 3'-5' linkages, 2'-5' linked analogs of these, and those) having inverted polarity wherein the adjacent pairs of nucleoside units are linked 3'-5' to 5'-3' or 2'-5' to 5'-2'. Various salts, mixed salts and free acid forms are also included.

Representative U.S. patents that teach the preparation of the above phosphorus-containing linkages include, but are not limited to, U.S. Pat. Nos. 3,687,808; 4,469,863; 4,476,301; 5,023,243; 5,177,195; 5,188,897; 5,264,423; 5,276,019; 5,278,302; 5,286,717; 5,321,131; 5,399,676; 5,405,939; 5,453,496; 5,455,233; 5,466,677; 5,476,925; 5,519,126; 5,536,821; 5,541,316; 5,550,111; 5,563,253; 5,571,799; 5,587,361; 5,625,050; 6,028,188; 6,124,445; 6,160,109; 6,169,170; 6,172,209; 6, 239,265; 6,277,603; 6,326,199; 6,346,614; 6,444,423; 6,531,590; 6,534,639; 6,608,035; 6,683,167; 6,858,715; 6,867,294; 6,878,805; 7,015,315; 7,041,816; 7,273,933; 7,321,029; and US Pat RE39464, each of which is herein incorporated by reference.

Modified RNA backbones that do not include a phosphorus atom therein have backbones that are formed by short chain alkyl or cycloalkyl internucleoside linkages, mixed heteroatoms and alkyl or cycloalkyl internucleoside linkages, or one or more short chain heteroatomic or heterocyclic internucleoside linkages. These include those having morpholino linkages (formed in part from the sugar portion of a nucleoside); siloxane backbones; sulfide, sulfoxide and sulfone backbones; formacetyl and thioformacetyl backbones; methylene formacetyl and thioformacetyl backbones; alkene containing backbones; sulfamate backbones; methyleneimino and methylenehydrazino backbones; sulfonate and sulfonamide backbones; amide backbones; and others having mixed N, O, S and CH_2 component parts.

Representative U.S. patents that teach the preparation of the above oligonucleosides include, but are not limited to, U.S. Pat. Nos. 5,034,506; 5,166,315; 5,185,444; 5,214,134; 5,216,141; 5,235,033; 5,64,562; 5,264,564; 5,405,938; 5,434,257; 5,466,677; 5,470,967; 5,489,677; 5,541,307; 5,561,225; 5,596,086; 5,602,240; 5,608,046; 5,610,289; 5,618,704; 5,623,070; 5,663,312; 5,633,360; 5,677,437; and, 5,677,439, each of which is herein incorporated by reference.

In other RNA mimetics suitable or contemplated for use in iRNAs, both the sugar and the internucleoside linkage, *i.e.*, the backbone, of the nucleotide units are replaced with alternate groups. The nucleobase units are maintained for hybridization with an appropriate nucleic acid target compound. One such oligomeric compound, an RNA mimetic that has been shown to have excellent hybridization properties, is referred to as a peptide nucleic acid (PNA). In PNA compounds, the sugar backbone of an RNA is replaced with an amide containing backbone, in particular an aminoethylglycine backbone. The nucleobases are retained and are bound directly or indirectly to aza nitrogen atoms of the amide portion of the backbone. Representative U.S. patents that teach the preparation of PNA compounds include, but are not limited to, U.S. Pat. Nos. 5,539,082; 5,714,331; and 5,719,262, each of which is herein incorporated by reference. Further teaching of PNA compounds can be found, for example, in Nielsen *et al.*, Science, 1991, 254, 1497-1500.

Some embodiments featured in the disclosure include RNAs with phosphorothioate backbones and oligonucleosides with heteroatom backbones, and in particular --CH_2--NH--CH_2-, --CH_2--N(CH_3)--O--CH_2--[known as a methylene (methylimino) or MMI backbone], --CH_2--O--N(CH_3)--CH_2--, --CH_2--N(CH_3)--N(CH_3)--CH_2-- and --N(CH_3)--CH_2--CH_2-- of the above-referenced U.S. Pat. No. 5,489,677, and the amide backbones of the above-referenced U.S. Pat. No. 5,602,240. In some embodiments, the RNAs featured herein have morpholino backbone structures of the above-referenced U.S. Pat. No. 5,034,506. The native phosphodiester backbone can be represented as -O-P(O)(OH)-OCH_2-.

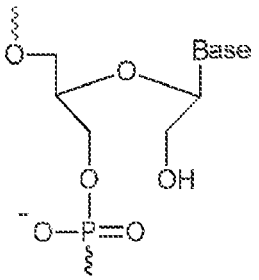
Modified RNAs may also contain one or more substituted sugar moieties. The iRNAs, *e.g.*, dsRNAs, featured herein can include one of the following at the 2' position: OH; F; O-, S-, or N-alkyl; O-, S-, or N-alkenyl; O-, S- or N-alkynyl; or O-alkyl-O-alkyl, wherein the alkyl, alkenyl and alkynyl may be substituted or unsubstituted C_1 to C_{10} alkyl or C_2 to C_{10} alkenyl and alkynyl. Exemplary suitable modifications include $O[(CH_2)_nO]_mCH_3$, $O(CH_2)_nOCH_3$,

$O(CH_2)_nNH_2$, $O(CH_2)_nCH_3$, $O(CH_2)_nONH_2$, and $O(CH_2)_nON[(CH_2)_nCH_3)]_2$, where n and m are from 1 to about 10. In other embodiments, dsRNAs include one of the following at the 2' position: C_1 to C_{10} lower alkyl, substituted lower alkyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH_3, OCN, Cl, Br, CN, CF_3, OCF_3, $SOCH_3$, SO_2CH_3, ONO_2, NO_2, N_3, NH_2, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, an RNA cleaving group, a reporter group, an intercalator, a group for improving the pharmacokinetic properties of an iRNA, or a group for improving the pharmacodynamic properties of an iRNA, and other substituents having similar properties. In some embodiments, the modification includes a 2'-methoxyethoxy (2'-O--$CH_2CH_2OCH_3$, also known as 2'-O-(2-methoxyethyl) or 2'-MOE) (Martin *et al.*, *Helv. Chim. Acta,* 1995, 78:486-504) *i.e.*, an alkoxy-alkoxy group. Another exemplary modification is 2'-dimethylaminooxyethoxy, *i.e.*, a $O(CH_2)_2ON(CH_3)_2$ group, also known as 2'-DMAOE, and 2'-dimethylaminoethoxyethoxy (also known in the art as 2'-O-dimethylaminoethoxyethyl or 2'-DMAEOE), *i.e.*, 2'-O--CH_2--O--CH_2--$N(CH_3)_2$.

In other embodiments, an iRNA agent comprises one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) acyclic nucleotides (or nucleosides). In certain embodiments, the sense strand or the antisense strand, or both sense strand and antisense strand, include less than five acyclic nucleotides per strand (*e.g.*, four, three, two or one acyclic nucleotides per strand). The one or more acyclic nucleotides can be found, for example, in the double-stranded region, of the sense or antisense strand, or both strands; at the 5'-end, the 3'-end, both of the 5' and 3'-ends of the sense or antisense strand, or both strands, of the iRNA agent. In some embodiments, one or more acyclic nucleotides are present at positions 1 to 8 of the sense or antisense strand, or both. In some embodiments, one or more acyclic nucleotides are found in the antisense strand at positions 4 to 10 (*e.g.*, positions 6-8) from the 5'-end of the antisense strand. In some embodiments, the one or more acyclic nucleotides are found at one or both 3'-terminal overhangs of the iRNA agent.

The term "acyclic nucleotide" or "acyclic nucleoside" as used herein refers to any nucleotide or nucleoside having an acyclic sugar, *e.g.*, an acyclic ribose. An exemplary acyclic nucleotide or nucleoside can include a nucleobase, *e.g.*, a naturally occurring or a modified nucleobase (*e.g.*, a nucleobase as described herein). In certain embodiments, a bond between any of the ribose carbons (C1, C2, C3, C4, or C5), is independently or in combination absent

from the nucleotide. In some embodiments, the bond between C2-C3 carbons of the ribose ring is absent, *e.g.*, an acyclic 2'-3'-seco-nucleotide monomer. In other embodiments, the bond between C1-C2, C3-C4, or C4-C5 is absent (*e.g.*, a 1'-2', 3'-4' or 4'-5'-seco nucleotide monomer). Exemplary acyclic nucleotides are disclosed in US 8,314,227, incorporated herein by reference in its entirely. For example, an acyclic nucleotide can include any of monomers D-J in Figures 1-2 of US 8,314,227. In some embodiments, the acyclic nucleotide includes the following monomer:



wherein Base is a nucleobase, *e.g.*, a naturally occurring or a modified nucleobase (*e.g.*, a nucleobase as described herein).

In certain embodiments, the acyclic nucleotide can be modified or derivatized, *e.g.*, by coupling the acyclic nucleotide to another moiety, *e.g.*, a ligand (*e.g.*, a GalNAc, a cholesterol ligand), an alkyl, a polyamine, a sugar, a polypeptide, among others.

In other embodiments, the iRNA agent includes one or more acyclic nucleotides and one or more LNAs (*e.g.*, an LNA as described herein). For example, one or more acyclic nucleotides and/or one or more LNAs can be present in the sense strand, the antisense strand, or both. The number of acyclic nucleotides in one strand can be the same or different from the number of LNAs in the opposing strand. In certain embodiments, the sense strand and/or the antisense strand comprises less than five LNAs (*e.g.*, four, three, two or one LNAs) located in the double stranded region or a 3'-overhang. In other embodiments, one or two LNAs are located in the double stranded region or the 3'-overhang of the sense strand. Alternatively, or in combination, the sense strand and/or antisense strand comprises less than five acyclic nucleotides (*e.g.*, four, three, two or one acyclic nucleotides) in the double-stranded region or a 3'-overhang. In some embodiments, the sense strand of the iRNA agent comprises one or two LNAs in the 3'-overhang of the sense strand, and one or two acyclic nucleotides in the double-stranded region of the antisense strand (*e.g.*, at positions 4 to 10 (*e.g.*, positions 6-8) from the 5'-end of the antisense strand) of the iRNA agent.

In other embodiments, inclusion of one or more acyclic nucleotides (alone or in addition to one or more LNAs) in the iRNA agent results in one or more (or all) of: (i) a reduction in an off-target effect; (ii) a reduction in passenger strand participation in RNAi; (iii) an increase in specificity of the guide strand for its target mRNA; (iv) a reduction in a microRNA off-target effect; (v) an increase in stability; or (vi) an increase in resistance to degradation, of the iRNA molecule.

Other modifications include 2'-methoxy (2'-OCH_3), 2'-5 aminopropoxy (2'-$OCH_2CH_2CH_2NH_2$) and 2'-fluoro (2'-F). Similar modifications may also be made at other positions on the RNA of an iRNA, particularly the 3' position of the sugar on the 3' terminal nucleotide or in 2'-5' linked dsRNAs and the 5' position of 5' terminal nucleotide. iRNAs may also have sugar mimetics such as cyclobutyl moieties in place of the pentofuranosyl sugar. Representative U.S. patents that teach the preparation of such modified sugar structures include, but are not limited to, U.S. Pat. Nos. 4,981,957; 5,118,800; 5,319,080; 5,359,044; 5,393,878; 5,446,137; 5,466,786; 5,514,785; 5,519,134; 5,567,811; 5,576,427; 5,591,722; 5,597,909; 5,610,300; 5,627,053; 5,639,873; 5,646,265; 5,658,873; 5,670,633; and 5,700,920, certain of which are commonly owned with the instant application, and each of which is herein incorporated by reference.

An iRNA may also include nucleobase (often referred to in the art simply as "base") modifications or substitutions. As used herein, "unmodified" or "natural" nucleobases include the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C) and uracil (U). Modified nucleobases include other synthetic and natural nucleobases such as 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl uracil and cytosine, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl anal other 8-substituted adenines and guanines, 5-halo, particularly 5-bromo, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine and 7-methyladenine, 8-azaguanine and 8-azaadenine, 7-deazaguanine and 7-daazaadenine and 3-deazaguanine and 3-deazaadenine.

Further modified nucleobases include those disclosed in U.S. Pat. No. 3,687,808, those disclosed in Modified Nucleosides in Biochemistry, Biotechnology and Medicine, Herdewijn, P.

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ed. Wiley-VCH, 2008; those disclosed in The Concise Encyclopedia of Polymer Science and Engineering, pages 858-859, Kroschwitz, J. L, ed. John Wiley & Sons, 1990, these disclosed by Englisch *et al.*, *Angewandte Chemie*, International Edition, 1991, 30, 613, and those disclosed by Sanghvi, Y S., Chapter 15, *dsRNA Research and Applications*, pages 289-302, Crooke, S. T. and Lebleu, B., Ed., CRC Press, 1993. Certain of these modified nucleobases are particularly useful for increasing the binding affinity of the oligomeric compounds featured in the disclosure. These include 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and O-6 substituted purines, including 2-aminopropyladenine, 5-propynyluracil and 5-propynylcytosine. 5-methylcytosine substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2°C (Sanghvi, Y. S., Crooke, S. T. and Lebleu, B., Eds., dsRNA Research and Applications, CRC Press, Boca Raton, 1993, pp. 276-278) and are exemplary base substitutions, even more particularly when combined with 2'-O-methoxyethyl sugar modifications.

Representative U.S. patents that teach the preparation of certain of the above noted modified nucleobases as well as other modified nucleobases include, but are not limited to, the above noted U.S. Pat. No. 3,687,808, as well as U.S. Pat. Nos. 4,845,205; 5,130,302; 5,134,066; 5,175,273; 5,367,066; 5,432,272; 5,457,187; 5,459,255; 5,484,908; 5,502,177; 5,525,711; 5,552,540; 5,587,469; 5,594,121, 5,596,091; 5,614,617; 5,681,941; 6,015,886; 6,147,200; 6,166,197; 6,222,025; 6,235,887; 6,380,368; 6,528,640; 6,639,062; 6,617,438; 7,045,610; 7,427,672; and 7,495,088, each of which is herein incorporated by reference, and U.S. Pat. No. 5,750,692, also herein incorporated by reference.

The RNA of an iRNA can also be modified to include one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) bicyclic sugar moieties. A "bicyclic sugar" is a furanosyl ring modified by the bridging of two atoms. A "bicyclic nucleoside" ("BNA") is a nucleoside having a sugar moiety comprising a bridge connecting two carbon atoms of the sugar ring, thereby forming a bicyclic ring system. In certain embodiments, the bridge connects the 4′-carbon and the 2′-carbon of the sugar ring. Thus, in some embodiments an agent of the disclosure may include one or more locked nucleic acids (LNAs) (also referred to herein as "locked nucleotides"). In some embodiments, a locked nucleic acid is a nucleotide having a modified ribose moiety in which the ribose moiety comprises an extra bridge connecting, *e.g.*, the 2' and 4' carbons. This structure effectively "locks" the ribose in the 3'-endo structural conformation. The addition of locked nucleic acids to siRNAs has been shown to increase siRNA stability in serum, increase thermal

stability, and to reduce off-target effects (Elmen, J. *et al.*, (2005) *Nucleic Acids Research* 33(1):439-447; Mook, OR. *et al.*, (2007) *Mol Canc Ther* 6(3):833-843; Grunweller, A. *et al.*, (2003) *Nucleic Acids Research* 31(12):3185-3193).

Examples of bicyclic nucleosides for use in the polynucleotides of the disclosure include without limitation nucleosides comprising a bridge between the 4′ and the 2′ ribosyl ring atoms. In certain embodiments, the antisense polynucleotide agents of the disclosure include one or more bicyclic nucleosides comprising a 4′ to 2′ bridge. Examples of such 4′ to 2′ bridged bicyclic nucleosides, include but are not limited to 4′-(CH_2)—O-2′ (LNA); 4′-(CH_2)—S-2′; 4′-(CH_2)2—O-2′ (ENA); 4′-CH(CH_3)—O-2′ (also referred to as "constrained ethyl" or "cEt") and 4′-CH(CH_2OCH_3)—O-2′ (and analogs thereof; see, *e.g.*, U.S. Pat. No. 7,399,845); 4′-C(CH_3)(CH_3)—O-2′ (and analogs thereof; see *e.g.*, US Patent No. 8,278,283); 4′-CH_2—N(OCH_3)-2′ (and analogs thereof; see *e.g.*, US Patent No. 8,278,425); 4′-CH_2—O—N(CH_3)-2′ (see, e.g., U.S. Patent Publication No. 2004/0171570); 4′-CH_2—N(R)—O-2′, wherein R is H, C_1-C_{12} alkyl, or a protecting group (see, *e.g.*, U.S. Pat. No. 7,427,672); 4′-CH_2—C(H)(CH_3)-2′ (see, *e.g.*, Chattopadhyaya *et al.*, *J. Org. Chem.*, 2009, 74, 118-134); and 4′-CH_2—C(=CH_2)-2′ (and analogs thereof; see, *e.g.*, US Patent No. 8,278,426). The contents of each of the foregoing are incorporated herein by reference for the methods provided therein. Representative U.S. Patents that teach the preparation of locked nucleic acids include, but are not limited to, the following: U.S. Pat. Nos. 6,268,490; 6,670,461; 6,794,499; 6,998,484; 7,053,207; 7,084,125; 7,399,845, and 8,314,227, each of which is herein incorporated by reference in its entirety. Exemplary LNAs include but are not limited to, a 2', 4'-C methylene bicyclo nucleotide (see for example Wengel *et al.*, International PCT 5 Publication No. WO 00/66604 and WO 99/14226).

Any of the foregoing bicyclic nucleosides can be prepared having one or more stereochemical sugar configurations including for example α-L-ribofuranose and β-D-ribofuranose (see WO 99/14226).

A RNAi agent of the disclosure can also be modified to include one or more constrained ethyl nucleotides. As used herein, a "constrained ethyl nucleotide" or "cEt" is a locked nucleic acid comprising a bicyclic sugar moiety comprising a 4'-CH(CH3)-0-2' bridge. In some embodiments, a constrained ethyl nucleotide is in the S conformation referred to herein as "S-cEt."

A RNAi agent of the disclosure may also include one or more "conformationally restricted nucleotides" ("CRN"). CRN are nucleotide analogs with a linker connecting the C2'and C4' carbons of ribose or the C3 and -C5' carbons of ribose. CRN lock the ribose ring into a stable conformation and increase the hybridization affinity to mRNA. The linker is of sufficient length to place the oxygen in an optimal position for stability and affinity resulting in less ribose ring puckering.

Representative publications that teach the preparation of certain of the above noted CRN include, but are not limited to, US 2013/0190383; and WO 2013/036868, the contents of each of which are hereby incorporated herein by reference for the methods provided therein.

In some embodiments, a RNAi agent of the disclosure comprises one or more monomers that are UNA (unlocked nucleic acid) nucleotides. UNA is unlocked acyclic nucleic acid, wherein any of the bonds of the sugar has been removed, forming an unlocked "sugar" residue. In one example, UNA also encompasses monomer with bonds between C1'-C4' have been removed (i.e. the covalent carbon-oxygen-carbon bond between the C1' and C4' carbons). In another example, the C2'-C3' bond (i.e. the covalent carbon-carbon bond between the C2' and C3' carbons) of the sugar has been removed (see *Nuc. Acids Symp. Series*, 52, 133-134 (2008) and Fluiter et al., *Mol. Biosyst.*, 2009, 10, 1039).

Representative U.S. publications that teach the preparation of UNA include, but are not limited to, US8,314,227; and US Patent Publication Nos. 2013/0096289; 2013/0011922; and 2011/0313020, the contents of each of which are hereby incorporated herein by reference for the methods provided therein.

An RNAi agent of the disclosure may also include one or more "cyclohexene nucleic acids" or ("CeNA"). CeNA are nucleotide analogs with a replacement of the furanose moiety of DNA by a cyclohexene ring. Incorporation of cylcohexenyl nucleosides in a DNA chain increases the stability of a DNA/RNA hybrid. CeNA is stable against degradation in serum and a CeNA/RNA hybrid is able to activate E. Coli RNase H, resulting in cleavage of the RNA strand. (see Wang et al., *Am. Chem. Soc. 2000, 122, 36, 8595–8602,* hereby incorporated by reference).

In other embodiments, the iRNA agents include one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) G-clamp nucleotides. A G-clamp nucleotide is a modified cytosine analog wherein the modifications confer the ability to hydrogen bond both Watson-Crick and Hoogsteen faces of a complementary guanine within a duplex, see for example Lin and Matteucci, 1998, *J.*

Am. Chem. Soc., 120, 8531-8532. A single G-clamp analog substitution within an oligonucleotide can result in substantially enhanced helical thermal stability and mismatch discrimination when hybridized to complementary oligonucleotides. The inclusion of such nucleotides in the iRNA molecules can result in enhanced affinity and specificity to nucleic acid targets, complementary sequences, or template strands.

Potentially stabilizing modifications to the ends of RNA molecules can include N-(acetylaminocaproyl)-4-hydroxyprolinol (Hyp-C6-NHAc), N-(caproyl-4-hydroxyprolinol (Hyp-C6), N-(acetyl-4-hydroxyprolinol (Hyp-NHAc), thymidine-2'-O-deoxythymidine (ether), N-(aminocaproyl)-4-hydroxyprolinol (Hyp-C6-amino), 2-docosanoyl-uridine-3"- phosphate, inverted base dT(idT) and others. Disclosure of this modification can be found in PCT Publication No. WO 2011/005861.

Other modifications of a RNAi agent of the disclosure include a 5' phosphate or 5' phosphate mimic, *e.g.*, a 5'-terminal phosphate or phosphate mimic on the antisense strand of a RNAi agent. Suitable phosphate mimics are disclosed in, for example US 2012/0157511, the contents of which are incorporated herein by reference for the methods provided therein. In one embodiment, the double stranded RNAi agent of the invention further comprises a 5'-phosphate or a 5'-phosphate mimic at the 5' nucleotide of the antisense strand. In another embodiment, the double stranded RNAi agent further comprises a 5'-phosphate mimic at the 5' nucleotide of the antisense strand. In a specific embodiment, the 5'-phosphate mimic is a 5'-vinyl phosphonate (5'-VP). In one embodiment, the phosphate mimic is a 5'-cyclopropyl phosphonate (VP). In some embodiments, the 5'-end of the antisense strand of the double-stranded iRNA agent does not contain a 5'-vinyl phosphonate (VP).

In one embodiment, at least one of the modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a glycol modified nucleotide (GNA), e.g., Ggn, Cgn, Tgn, or Agn, a nucleotide with a 2' phosphate, e.g., G2p, C2p, A2p or U2p, and, a vinyl-phosphonate nucleotide; and combinations thereof. In other embodiments, each of the duplexes of Tables 5, 6, 8, and 10 may be particularly modified to provide another double-stranded iRNA agent of the present disclosure. In one example, the 3'-terminus of each sense duplex may be modified by removing the 3'-terminal L96 ligand and exchanging the two phosphodiester internucleotide linkages between the three 3'-terminal nucleotides with phosphorothioate

internucleotide linkages. That is, the three 3'-terminal nucleotides (N) of a sense sequence of the formula:

5'- N1-... -Nn-2Nn-1NnL96 3'

may be replaced with

5'- N1-... -Nn-2sNn-1sNn 3'.

That is, for example, AD-1559459, the sense sequence:

asgsaucgGfuGfCfCfgauuccu**gcuL96**

may be replaced with

asgsaucgGfuGfCfCfgauuccu**gsesu**

while the antisense sequence remains unchanged to provide another double-stranded iRNA agent of the present disclosure.

III. iRNA Motifs

In certain aspects of the disclosure, the double-stranded RNAi agents of the disclosure include agents with chemical modifications as disclosed, for example, in WO 2013/075035, the contents of which are incorporated herein by reference for the methods provided therein. As shown herein and in WO 2013/075035, a superior result may be obtained by introducing one or more motifs of three identical modifications on three consecutive nucleotides into a sense strand or antisense strand of an RNAi agent, particularly at or near the cleavage site. In some embodiments, the sense strand and antisense strand of the RNAi agent may otherwise be completely modified. The introduction of these motifs interrupts the modification pattern, if present, of the sense or antisense strand. The RNAi agent may be optionally conjugated with a lipophilic moiety or ligand, *e.g.*, a C16 moiety or ligand, for instance on the sense strand. The RNAi agent may be optionally modified with a (*S*)-glycol nucleic acid (GNA) modification, for instance on one or more residues of the antisense strand. The resulting RNAi agents present superior gene silencing activity.

In some embodiments, the sense strand sequence may be represented by formula (I):

$5'\ n_p\text{-}N_a\text{-}(X\ X\ X)_i\text{-}N_b\text{-}Y\ Y\ Y\ \text{-}N_b\text{-}(Z\ Z\ Z)_j\text{-}N_a\text{-}n_q\ 3'$ (I)

wherein:

i and j are each independently 0 or 1;

p and q are each independently 0-6;

each N_a independently represents an oligonucleotide sequence comprising 0-25 modified nucleotides, each sequence comprising at least two differently modified nucleotides;

each N_b independently represents an oligonucleotide sequence comprising 0-10 modified nucleotides;

each n_p and n_q independently represent an overhang nucleotide;

wherein Nb and Y do not have the same modification; and

XXX, YYY and ZZZ each independently represent one motif of three identical modifications on three consecutive nucleotides. In some embodiments, YYY is all 2'-F modified nucleotides.

In some embodiments, the N_a and/or N_b comprise modifications of alternating pattern.

In some embodiments, the YYY motif occurs at or near the cleavage site of the sense strand. For example, when the RNAi agent has a duplex region of 17-23 nucleotides in length, the YYY motif can occur at or the vicinity of the cleavage site (*e.g.*: can occur at positions 6, 7, 8; 7, 8, 9; 8, 9, 10; 9, 10, 11; 10, 11,12 or 11, 12, 13) of the sense strand, the count starting from the 1st nucleotide, from the 5'-end; or optionally, the count starting at the 1st paired nucleotide within the duplex region, from the 5'-end.

In some embodiments, i is 1 and j is 0, or i is 0 and j is 1, or both i and j are 1. The sense strand can therefore be represented by the following formulas:

5' n_p-N_a-YYY-N_b-ZZZ-N_a-n_q 3' (Ib),

5' n_p-N_a-XXX-N_b-YYY-N_a-n_q 3' (Ic); or

5' n_p-N_a-XXX-N_b-YYY-N_b-ZZZ-N_a-n_q 3' (Id).

When the sense strand is represented by formula (Ib), N_b represents an oligonucleotide sequence comprising 0-10, 0-7, 0-5, 0-4, 0-2 or 0 modified nucleotides. Each N_a independently can represent an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

When the sense strand is represented as formula (Ic), N_b represents an oligonucleotide sequence comprising 0-10, 0-7, 0-5, 0-4, 0-2 or 0 modified nucleotides. Each N_a can independently represent an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

When the sense strand is represented as formula (Id), each N_b independently represents an oligonucleotide sequence comprising 0-10, 0-7, 0-5, 0-4, 0-2 or 0 modified nucleotides. In some

embodiments, N_b is 0, 1, 2, 3, 4, 5 or 6. Each N_a can independently represent an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

Each of X, Y and Z may be the same or different from each other.

In other embodiments, i is 0 and j is 0, and the sense strand may be represented by the formula:

$5'\ n_p\text{-}N_a\text{-}YYY\text{-}\ N_a\text{-}n_q\ 3'$ (Ia).

When the sense strand is represented by formula (Ia), each N_a independently can represent an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

In some embodiments, the antisense strand sequence of the RNAi may be represented by formula (Ie):

$5'\ n_{q'}\text{-}N_a'\text{-}(Z'Z'Z')_k\text{-}N_b'\text{-}Y'Y'Y'\text{-}N_b'\text{-}(X'X'X')_l\text{-}N'_a\text{-}n_p'\ 3'$ (Ie)

wherein:

k and l are each independently 0 or 1;

p' and q' are each independently 0-6;

each N_a' independently represents an oligonucleotide sequence comprising 0-25 modified nucleotides, each sequence comprising at least two differently modified nucleotides;

each N_b' independently represents an oligonucleotide sequence comprising 0-10 modified nucleotides;

each n_p' and n_q' independently represent an overhang nucleotide;

wherein N_b' and Y' do not have the same modification;

and

X'X'X', Y'Y'Y', and Z'Z'Z' each independently represent one of three identical modification on three consecutive nucleotides.

In some embodiments, the N_a' and/or N_b' comprise modification of alternating pattern.

The Y'Y'Y' motif occurs at or near the cleavage site of the antisense strand. For example, when the RNAi agent has a duplex region of 17-23 nucleotides in length, the Y'Y'Y' motif can occur at positions 9, 10, 11; 10, 11, 12; 11, 12, 13; 12, 13, 14; or 13, 14, 15 of the antisense strand, with the count starting from the 1st nucleotide, from the 5'-end; or optionally, the count starting at the 1st paired nucleotide within the duplex region, from the 5'- end. In some embodiments, the Y'Y'Y' motif occurs at positions 11, 12, 13.

In some embodiments, Y'Y'Y' motif is all 2'-O-me modified nucleotides.

In on embodiment, k is 1 and l is 0, or k is 0 and l is 1, or both 5 k and l are 1.

The antisense strand can therefore be represented by the following formulas:

5' n_q'-N_a'-Z'Z'Z'-N_b'-Y'Y'Y'-N_a'-n_p' 3' (Ig);

5' n_q'-N_a'-Y'Y'Y'-N_b'-X'X'X'-n_p' 3' (Ih); or

5' n_q'-N_a'- Z'Z'Z'-N_b'-Y'Y'Y'-N_b'- X'X'X'-N_a'-n_p' 3' (Ii).

When the antisense strand is represented by formula (Igib), N_b' represents an oligonucleotide sequence comprising 0-10, 0-7, 0-5, 0-4, 0-2 or 0 modified nucleotides. Each N_a' independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

When the antisense strand is represented as formula (Ii), each N_b' independently represents an oligonucleotide sequence comprising 0-10, 0-7, 0-5, 0-4, 0-2 or 0 modified nucleotides. Each N_a' independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides. In some embodiments, N_b is 0, 1, 2, 3, 4, 5 or 6.

In other embodiments, k is 0 and l is 0 and the antisense strand may be represented by the formula:

5' n_p'-N_a'-Y'Y'Y'- N_a'-n_q' 3' (If).

When the antisense strand is represented as formula (If), each Na' independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

Each of X', Y' and Z' may be the same or different from each other.

Each nucleotide of the sense strand and antisense strand may be independently modified with LNA, HNA, CeNA, GNA, 2'-methoxyethyl, 2'-O-methyl, 2'-O-allyl, 2'-C- allyl, 2'-hydroxyl, or 2'-fluoro. For example, each nucleotide of the sense strand and antisense strand is independently modified with 2'-O-methyl or 2'-fluoro. Each X, Y, Z, X', Y' and Z', in particular, may represent a 2'-O-methyl modification or a 2'-fluoro modification.

In some embodiments, the sense strand of the RNAi agent may contain YYY motif occurring at 9, 10 and 11 positions of the strand when the duplex region is 21 nt, the count starting from the 1st nucleotide from the 5'-end, or optionally, the count starting at the 1st paired nucleotide within the duplex region, from the 5'- end; and Y represents 2'-F modification. The sense strand may additionally contain XXX motif or ZZZ motifs as wing modifications at the opposite end of the duplex region; and XXX and ZZZ each independently represents a 2'-OMe modification or 2'-F modification.

In some embodiments the antisense strand may Y'Y'Y' motif occurring at positions 11, 12, 13 of the strand, the count starting from the 1st nucleotide from the 5'-end, or optionally, the count starting at the 1st paired nucleotide within the duplex region, from the 5'- end; and Y' represents 2'-O-methyl modification. The antisense strand may additionally contain X'X'X' motif or Z'Z'Z' motifs as wing modifications at the opposite end of the duplex region; and X'X'X' and Z'Z'Z' each independently represents a 2'-OMe modification or 2'-F modification.

The sense strand represented by any one of the above formulas (Ia), (Ib), (Ic), and (Id) forms a duplex with an antisense strand being represented by any one of formulas (If), (Ig), (Ih), and (Ii), respectively.

Accordingly, certain RNAi agents for use in the methods of the disclosure may comprise a sense strand and an antisense strand, each strand having 14 to 30 nucleotides, the RNAi duplex represented by formula (Ij):

sense: 5' n_p -N_a-(XXX)i -N_b- YYY -N_b -(ZZZ)j-N_a-n_q 3'

antisense: 3' n_p'-Na'-(X'X'X')k-N_b'-Y'Y'Y'-N_b'-(Z'Z'Z')l-N_a'-n_q' 5' (Ij)

wherein,

i, j, k, and l are each independently 0 or 1;

p, p', q, and q' are each independently 0-6;

each N_a and N_a' independently represents an oligonucleotide sequence comprising 0-25 modified nucleotides, each sequence comprising at least two differently modified nucleotides;

each N_b and N_b' independently represents an oligonucleotide sequence comprising 0-10 modified nucleotides;

wherein

each n_p', n_p, n_q', and n_q, each of which may or may not be present independently represents an overhang nucleotide; and

XXX, YYY, ZZZ, X'X'X', Y'Y'Y', and Z'Z'Z' each independently represent one motif of three identical modifications on three consecutive nucleotides.

In some embodiments, i is 0 and j is 0; or i is 1 and j is 0; or i is 0 and j is 1; or both i and j are 0; or both i and j are 1. In some embodiments, k is 0 and l is 0; or k is 1 and l is 0; k is 0 and l is 1; or both k and l are 0; or both k and l are 1.

Exemplary combinations of the sense strand and antisense strand forming a RNAi duplex include the formulas below:

5' n_p -N_a-Y Y Y-N_a-n_q 3'

3' n_p' -N_a'- Y'Y'Y'-N_a'n_q' 5' (Ik)

5' n_p -N_a -Y Y Y -N_b -Z Z Z -N_a-n_q 3'

3' n_p -N_a'- Y'Y'Y'-N_b'- Z'Z'Z'- Na'-nq' 5' (Il)

5' n_p -N_a - X X X -N_b- Y Y Y -N_a-n_q 3'

3' n_p -N_a'- X'X'X' -N_b'- Y'Y'Y'- Na'-n_q' 5' (Im)

5' n_p -N_a - X X X -N_b -Y Y Y - N_b- Z Z Z-N_a-n_q 3'

3' n_p -N_a'- X'X'X'-N_b'- Y'Y'Y'-N_b'- Z'Z'Z'-Na'-n_q' 5' (In)

When the RNAi agent is represented by formula (Ik), each N_a independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

When the RNAi agent is represented by formula (Il), each N_b independently represents an oligonucleotide sequence comprising 1-10, 1-7, 1-5 or 1-4 modified nucleotides. Each N_a independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

When the RNAi agent is represented as formula (Im), each N_b, N_b' independently represents an oligonucleotide sequence comprising 0-10, 0-7, 0-5, 0-4, 0-2 or 0 modified nucleotides. Each N_a independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

When the RNAi agent is represented as formula (In), each N_b, N_b' independently represents an oligonucleotide sequence comprising 0-10, 0-7, 0-5, 0-4, 0-2 or 0 modified nucleotides. Each N_a, N_a' independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides. Each of N_a, N_a', N_b and N_b' independently comprises modifications of alternating pattern.

Each of X, Y and Z in formulas (Ij), (Ik), (Il), (Im), and (In) may be the same or different from each other.

When the RNAi agent is represented by formula (Ij), (Ik), (Il), (Im), and (In), at least one of the Y nucleotides may form a base pair with one of the Y' nucleotides. Alternatively, at least two of the Y nucleotides form base pairs with the corresponding Y' nucleotides; or all three of the Y nucleotides all form base pairs with the corresponding Y' nucleotides.

When the RNAi agent is represented by formula (Il) or (In), at least one of the Z nucleotides may form a base pair with one of the Z' nucleotides. Alternatively, at least two of

the Z nucleotides form base pairs with the corresponding Z' nucleotides; or all three of the Z nucleotides all form base pairs with the corresponding Z' nucleotides.

When the RNAi agent is represented as formula (Im) or (In), at least one of the X nucleotides may form a base pair with one of the X' nucleotides. Alternatively, at least two of the X nucleotides form base pairs with the corresponding X' nucleotides; or all three of the X nucleotides all form base pairs with the corresponding X' nucleotides.

In some embodiments, the modification on the Y nucleotide is different than the modification on the Y' nucleotide, the modification on the Z nucleotide is different than the modification on the Z' nucleotide, and/or the modification on the X nucleotide is different than the modification on the X' nucleotide.

In some embodiments, when the RNAi agent is represented by formula (IIId), the N_a modifications are 2'-O-methyl or 2'-fluoro modifications. In some embodiments, when the RNAi agent is represented by formula (In), the N_a modifications are 2'-O-methyl or 2'-fluoro modifications and $n_p' > 0$ and at least one n_p' is linked to a neighboring nucleotide a via phosphorothioate linkage. In some embodiments, when the RNAi agent is represented by formula (In), the N_a modifications are 2'-O-methyl or 2'-fluoro modifications, $n_p' > 0$ and at least one n_p' is linked to a neighboring nucleotide via phosphorothioate linkage, and the sense strand is conjugated to one or more moieties or ligands (*e.g.*, one or more lipophilic moieties, optionally one or more C16 moieties, or one or more GalNAc moieties) attached through a bivalent or trivalent branched linker. In some embodiments, when the RNAi agent is represented by formula (In), the N_a modifications are 2'-O-methyl or 2'-fluoro modifications, $n_p' > 0$ and at least one n_p' is linked to a neighboring nucleotide via phosphorothioate linkage, the sense strand comprises at least one phosphorothioate linkage, and the sense strand is conjugated to one or more moieties or ligands (*e.g.*, one or more lipophilic moieties, optionally one or more C16 moieties, or one or more GalNAc moieties) attached through a bivalent or trivalent branched linker.

In some embodiments, when the RNAi agent is represented by formula (Ik), the N_a modifications are 2'-O-methyl or 2'-fluoro modifications, $n_p' > 0$ and at least one n_p' is linked to a neighboring nucleotide via phosphorothioate linkage, the sense strand comprises at least one phosphorothioate linkage, and the sense strand is conjugated to one or more moieties or ligands (*e.g.*, one or more lipophilic moieties, optionally one or more C16 moieties, or one or more GalNAc moieties) attached through a bivalent or trivalent branched linker.

In some embodiments, the RNAi agent is a multimer containing at least two duplexes represented by formula (Ij), (Ik), (Il), (Im), and (In), wherein the duplexes are connected by a linker. The linker can be cleavable or non-cleavable. Optionally, the multimer further comprises a ligand. Each of the duplexes can target the same gene or two different genes; or each of the duplexes can target same gene at two different target sites.

In some embodiments, the RNAi agent is a multimer containing three, four, five, six or more duplexes represented by formula (Ij), (Ik), (Il), (Im), and (In), wherein the duplexes are connected by a linker. The linker can be cleavable or non-cleavable. Optionally, the multimer further comprises a ligand. Each of the duplexes can target the same gene or two different genes; or each of the duplexes can target same gene at two different target sites.

In some embodiments, two RNAi agents represented by formula (Ij), (Ik), (Il), (Im), and (In) are linked to each other at the 5' end, and one or both of the 3' ends and are optionally conjugated to a ligand. Each of the agents can target the same gene or two different genes; or each of the agents can target same gene at two different target sites.

Various publications describe multimeric RNAi agents that can be used in the methods of the disclosure. Such publications include WO2007/091269, WO2010/141511, WO2007/117686, WO2009/014887, and WO2011/031520; and US 7858769, the contents of each of which are hereby incorporated herein by reference for the methods provided therein. In certain embodiments, the RNAi agents of the disclosure may include GalNAc ligands.

As described in more detail below, the RNAi agent that contains conjugations of one or more carbohydrate moieties to a RNAi agent may improve one or more properties of the RNAi agent. In many cases, the carbohydrate moiety will be attached to a modified subunit of the RNAi agent. For example, the ribose sugar of one or more ribonucleotide subunits of a dsRNA agent can be replaced with another moiety, *e.g.*, a non-carbohydrate (*e.g.*, cyclic) carrier to which is attached a carbohydrate ligand. A ribonucleotide subunit in which the ribose sugar of the subunit has been so replaced is referred to herein as a ribose replacement modification subunit (RRMS). A cyclic carrier may be a carbocyclic ring system, *i.e.*, all ring atoms are carbon atoms, or a heterocyclic ring system, *i.e.*, one or more ring atoms may be a heteroatom, *e.g.*, nitrogen, oxygen, sulfur. The cyclic carrier may be a monocyclic ring system, or may contain two or more rings, *e.g.* fused rings. The cyclic carrier may be a fully saturated ring system, or it may contain one or more double bonds.

The ligand may be attached to the polynucleotide via a carrier. The carriers include (i) at least one "backbone attachment point," such as two "backbone attachment points" and (ii) at least one "tethering attachment point." A "backbone attachment point" as used herein refers to a functional group, *e.g.* a hydroxyl group, or generally, a bond available for, and that is suitable for incorporation of the carrier into the backbone, *e.g.*, the phosphate, or modified phosphate, *e.g.*, sulfur containing, backbone, of a ribonucleic acid. A "tethering attachment point" (TAP) in some embodiments refers to a constituent ring atom of the cyclic carrier, *e.g.*, a carbon atom or a heteroatom (distinct from an atom which provides a backbone attachment point), that connects a selected moiety. The moiety can be, *e.g.*, a carbohydrate, *e.g.* monosaccharide, disaccharide, trisaccharide, tetrasaccharide, oligosaccharide, and polysaccharide. Optionally, the selected moiety is connected by an intervening tether to the cyclic carrier. Thus, the cyclic carrier will often include a functional group, *e.g.*, an amino group, or generally, provide a bond, that is suitable for incorporation or tethering of another chemical entity, *e.g.*, a ligand to the constituent ring.

The RNAi agents may be conjugated to a ligand *via* a carrier, wherein the carrier can be cyclic group or acyclic group. The cyclic group can be selected from pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, [1,3]dioxolane, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl, tetrahydrofuryl and and decalin. The acyclic group can be a serinol backbone or diethanolamine backbone.

In certain specific embodiments, the RNAi agent for use in the methods of the disclosure is an agent selected from the group of agents listed in any one of Tables 3-10. These agents may further comprise a ligand. The ligand can be attached to the sense strand, antisense strand or both strands, at the 3'-end, 5'-end, or both ends. For instance, the ligand may be conjugated to the sense strand, in particular, the 3'-end of the sense strand.

IV. iRNA Conjugates

The iRNA agents disclosed herein can be in the form of conjugates. The conjugate may be attached at any suitable location in the iRNA molecule, *e.g.*, at the 3' end or the 5' end of the sense or the antisense strand. The conjugates are optionally attached via a linker.

In some embodiments, an iRNA agent described herein is chemically linked to one or more ligands, moieties or conjugates, which may confer functionality, *e.g.*, by affecting (*e.g.*, enhancing) the activity, cellular distribution or cellular uptake of the iRNA. Such moieties include but are not limited to lipid moieties such as a cholesterol moiety (Letsinger *et al.*, *Proc. Natl. Acid. Sci. USA*, 1989, 86: 6553-6556), cholic acid (Manoharan *et al.*, *Biorg. Med. Chem. Let.*, 1994, 4:1053-1060), a thioether, *e.g.*, beryl-S-tritylthiol (Manoharan *et al.*, *Ann. N.Y. Acad. Sci.*, 1992, 660:306-309; Manoharan *et al.*, *Biorg. Med. Chem. Let.*, 1993, 3:2765-2770), a thiocholesterol (Oberhauser *et al.*, *Nucl. Acids Res.*, 1992, 20:533-538), an aliphatic chain, *e.g.*, dodecandiol or undecyl residues (Saison-Behmoaras *et al.*, *EMBO J*, 1991, 10:1111-1118; Kabanov *et al.*, *FEBS Lett.*, 1990, 259:327-330; Svinarchuk *et al.*, *Biochimie*, 1993, 75:49-54), a phospholipid, *e.g.*, di-hexadecyl-rac-glycerol or triethyl-ammonium 1,2-di-O-hexadecyl-rac-glycero-3-phosphonate (Manoharan *et al.*, *Tetrahedron Lett.*, 1995, 36:3651-3654; Shea *et al.*, *Nucl. Acids Res.*, 1990, 18:3777-3783), a polyamine or a polyethylene glycol chain (Manoharan *et al.*, *Nucleosides & Nucleotides*, 1995, 14:969-973), or adamantane acetic acid (Manoharan *et al.*, *Tetrahedron Lett.*, 1995, 36:3651-3654), a palmityl moiety (Mishra *et al.*, *Biochim. Biophys. Acta*, 1995, 1264:229-237), or an octadecylamine or hexylamino-carbonyloxycholesterol moiety (Crooke *et al.*, *J. Pharmacol. Exp. Ther.*, 1996, 277:923-937).

In some embodiments, a ligand alters the distribution, targeting or lifetime of an iRNA agent into which it is incorporated. In some embodiments, a ligand provides an enhanced affinity for a selected target, *e.g.*, molecule, cell or cell type, compartment, *e.g.*, a cellular or organ compartment, tissue, organ or region of the body, as, *e.g.*, compared to a species absent such a ligand. Typical ligands will not take part in duplex pairing in a duplexed nucleic acid.

Ligands can include a naturally occurring substance, such as a protein (*e.g.*, human serum albumin (HSA), low-density lipoprotein (LDL), or globulin); carbohydrate (*e.g.*, a dextran, pullulan, chitin, chitosan, inulin, cyclodextrin or hyaluronic acid); or a lipid. The ligand may also be a recombinant or synthetic molecule, such as a synthetic polymer, *e.g.*, a synthetic

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polyamino acid. Examples of polyamino acids include polyamino acid is a polylysine (PLL), poly L-aspartic acid, poly L-glutamic acid, styrene-maleic acid anhydride copolymer, poly(L-lactide-co-glycolied) copolymer, divinyl ether-maleic anhydride copolymer, N-(2-hydroxypropyl)methacrylamide copolymer (HMPA), polyethylene glycol (PEG), polyvinyl alcohol (PVA), polyurethane, poly(2-ethylacryllic acid), N-isopropylacrylamide polymers, or polyphosphazine. Examples of polyamines include: polyethylenimine, polylysine (PLL), spermine, spermidine, polyamine, pseudopeptide-polyamine, peptidomimetic polyamine, dendrimer polyamine, arginine, amidine, protamine, cationic lipid, cationic porphyrin, quaternary salt of a polyamine, or an α helical peptide.

Ligands can also include targeting groups, *e.g.*, a cell or tissue targeting agent, *e.g.*, a lectin, glycoprotein, lipid or protein, *e.g.*, an antibody, that binds to a specified cell type such as an ocular cell. A targeting group can be a thyrotropin, melanotropin, lectin, glycoprotein, surfactant protein A, Mucin carbohydrate, multivalent lactose, multivalent galactose, N-acetyl-galactosamine, N-acetyl-gulucosamine multivalent mannose, multivalent fucose, glycosylated polyaminoacids, multivalent galactose, transferrin, bisphosphonate, polyglutamate, polyaspartate, a lipid, cholesterol, a steroid, bile acid, folate, vitamin B12, biotin, or an RGD peptide or RGD peptide mimetic.

Other examples of ligands include dyes, intercalating agents (*e.g.* acridines), cross-linkers (*e.g.* psoralene, mitomycin C), porphyrins (TPPC4, texaphyrin, Sapphyrin), polycyclic aromatic hydrocarbons (*e.g.*, phenazine, dihydrophenazine), artificial endonucleases (*e.g.* EDTA), lipophilic molecules, *e.g.*, cholesterol, cholic acid, adamantane acetic acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-Bis-O(hexadecyl)glycerol, geranyloxyhexyl group, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl group, palmitic acid, myristic acid,O3-(oleoyl)lithocholic acid, O3-(oleoyl)cholenic acid, dimethoxytrityl, or phenoxazine)and peptide conjugates (*e.g.*, antennapedia peptide, Tat peptide), alkylating agents, phosphate, amino, mercapto, PEG (*e.g.*, PEG-40K), mPEG, $[mPEG]_2$, polyamino, alkyl, substituted alkyl, radiolabeled markers, enzymes, haptens (*e.g.* biotin), transport/absorption facilitators (*e.g.*, aspirin, vitamin E, folic acid), synthetic ribonucleases (*e.g.*, imidazole, bisimidazole, histamine, imidazole clusters, acridine-imidazole conjugates, Eu3+ complexes of tetraazamacrocycles), dinitrophenyl, HRP, or AP.

Ligands can be proteins, *e.g.*, glycoproteins, or peptides, *e.g.*, molecules having a specific affinity for a co-ligand, or antibodies *e.g.*, an antibody, that binds to a specified cell type such as an ocular cell. Ligands may also include hormones and hormone receptors. They can also include non-peptidic species, such as lipids, lectins, carbohydrates, vitamins, cofactors, multivalent lactose, multivalent galactose, N-acetyl-galactosamine, N-acetyl-glucosamine multivalent mannose, or multivalent fucose. The ligand can be, for example, a lipopolysaccharide, an activator of p38 MAP kinase, or an activator of NF-κB.

The ligand can be a substance, *e.g.*, a drug, which can increase the uptake of the iRNA agent into the cell, for example, by disrupting the cell's cytoskeleton, *e.g.*, by disrupting the cell's microtubules, microfilaments, and/or intermediate filaments. The drug can be, for example, taxon, vincristine, vinblastine, cytochalasin, nocodazole, japlakinolide, latrunculin A, phalloidin, swinholide A, indanocine, or myoservin.

In some embodiments, a ligand attached to an iRNA as described herein acts as a pharmacokinetic modulator (PK modulator). PK modulators include lipophiles, bile acids, steroids, phospholipid analogues, peptides, protein binding agents, polyethylene glycol (PEG), vitamins *etc*. Exemplary PK modulators include, but are not limited to, cholesterol, fatty acids, cholic acid, lithocholic acid, dialkylglycerides, diacylglyceride, phospholipids, sphingolipids, naproxen, ibuprofen, vitamin E, biotin *etc*. Oligonucleotides that comprise a number of phosphorothioate linkages are also known to bind to serum protein, thus short oligonucleotides, *e.g.*, oligonucleotides of about 5 bases, 10 bases, 15 bases or 20 bases, comprising multiple of phosphorothioate linkages in the backbone are also amenable to the present disclosure as ligands (*e.g.* as PK modulating ligands). In addition, aptamers that bind serum components (*e.g.* serum proteins) are also suitable for use as PK modulating ligands in the embodiments described herein.

Ligand-conjugated oligonucleotides of the disclosure may be synthesized by the use of an oligonucleotide that bears a pendant reactive functionality, such as that derived from the attachment of a linking molecule onto the oligonucleotide (described below). This reactive oligonucleotide may be reacted directly with commercially available ligands, ligands that are synthesized bearing any of a variety of protecting groups, or ligands that have a linking moiety attached thereto.

The oligonucleotides used in the conjugates of the present disclosure may be conveniently and routinely made through the well-known technique of solid-phase synthesis. Equipment for such synthesis is sold by several vendors including, for example, Applied Biosystems (Foster City, Calif.). Any other means for such synthesis known in the art may additionally or alternatively be employed. It is also known to use similar techniques to prepare other oligonucleotides, such as the phosphorothioates and alkylated derivatives.

In the ligand-conjugated oligonucleotides and ligand-molecule bearing sequence-specific linked nucleosides of the present disclosure, the oligonucleotides and oligonucleosides may be assembled on a suitable DNA synthesizer utilizing standard nucleotide or nucleoside precursors, or nucleotide or nucleoside conjugate precursors that already bear the linking moiety, ligand-nucleotide or nucleoside-conjugate precursors that already bear the ligand molecule, or non-nucleoside ligand-bearing building blocks.

When using nucleotide-conjugate precursors that already bear a linking moiety, the synthesis of the sequence-specific linked nucleosides is typically completed, and the ligand molecule is then reacted with the linking moiety to form the ligand-conjugated oligonucleotide. In some embodiments, the oligonucleotides or linked nucleosides of the present disclosure are synthesized by an automated synthesizer using phosphoramidites derived from ligand-nucleoside conjugates in addition to the standard phosphoramidites and non-standard phosphoramidites that are commercially available and routinely used in oligonucleotide synthesis.

A. *Lipophilic Moieties*

In certain embodiments, the lipophilic moiety is an aliphatic, cyclic such as alicyclic, or polycyclic such as polyalicyclic compound, such as a steroid (*e.g.*, sterol) or a linear or branched aliphatic hydrocarbon. The lipophilic moiety may generally comprise a hydrocarbon chain, which may be cyclic or acyclic. The hydrocarbon chain may comprise various substituents or one or more heteroatoms, such as an oxygen or nitrogen atom. Such lipophilic aliphatic moieties include, without limitation, saturated or unsaturated C_4-C_{30} hydrocarbon (*e.g.*, C_6-C_{18} hydrocarbon), saturated or unsaturated fatty acids, waxes (*e.g.*, monohydric alcohol esters of fatty acids and fatty diamides), terpenes (*e.g.*, C_{10} terpenes, C_{15} sesquiterpenes, C_{20} diterpenes, C_{30} triterpenes, and C_{40} tetraterpenes), and other polyalicyclic hydrocarbons. For instance, the lipophilic moiety may contain a C_4-C_{30} hydrocarbon chain (*e.g.*, C_4-C_{30} alkyl or alkenyl). In

some embodiments the lipophilic moiety contains a saturated or unsaturated C_6-C_{18} hydrocarbon chain (*e.g.*, a linear C_6-C_{18} alkyl or alkenyl). In some embodiments, the lipophilic moiety contains a saturated or unsaturated C16 hydrocarbon chain (*e.g.*, a linear C16 alkyl or alkenyl).

In some embodiments, the lipophilic moiety is a C6-C30 acid (e.g., hexanoic acid, heptanoic acid, octanoic acid, nonanoic acid, decanoic acid, undecanoic acid, dodcanoic acid, tridecanoic acid, tetradecanoic acid, pentadecanoic acid, hexadecanoic acid, heptadecanoic acid, octadecanoic acid, oleic acid, linoleic acid, arachidonic acid, cis-4,7,10,13,16,19-docosahexanoic acid, vitamin A, vitamin E, cholesterol etc.) or a C6-C30 alcohol (e.g., hexanol, heptanol, octanol, nonanol, decanol, undecanol, dodcanol, tridecanol, tetradecanol, pentadecanol, hexadecanol, heptadecanol, octadecanol, oleyl alcohol, linoleyl alcohol, arachidonic alcohol, cis-4,7,10,13,16,19-docosahexanol, retinol, vitamin E, cholesterol etc.).

The lipophilic moiety may be attached to the RNAi agent by any method known in the art, including via a functional grouping already present in the lipophilic moiety or introduced into the RNAi agent, such as a hydroxy group (*e.g.*, —CO—CH_2—OH). The functional groups already present in the lipophilic moiety or introduced into the RNAi agent include, but are not limited to, hydroxyl, amine, carboxylic acid, sulfonate, phosphate, thiol, azide, and alkyne.

Conjugation of the RNAi agent and the lipophilic moiety may occur, for example, through formation of an ether or a carboxylic or carbamoyl ester linkage between the hydroxy and an alkyl group R—, an alkanoyl group RCO— or a substituted carbamoyl group RNHCO—. The alkyl group R may be cyclic (*e.g.*, cyclohexyl) or acyclic (*e.g.*, straight-chained or branched; and saturated or unsaturated). Alkyl group R may be a butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl or octadecyl group, or the like.

In some embodiments, the lipophilic moiety is conjugated to the double-stranded RNAi agent via a linker a linker containing an ether, thioether, urea, carbonate, amine, amide, maleimide-thioether, disulfide, phosphodiester, sulfonamide linkage, a product of a click reaction (*e.g.*, a triazole from the azide-alkyne cycloaddition), or carbamate.

In another embodiment, the lipophilic moiety is a steroid, such as sterol. Steroids are polycyclic compounds containing a perhydro-1,2-cyclopentanophenanthrene ring system. Steroids include, without limitation, bile acids (*e.g.*, cholic acid, deoxycholic acid and dehydrocholic acid), cortisone, digoxigenin, testosterone, cholesterol, and cationic steroids, such

as cortisone. A "cholesterol derivative" refers to a compound derived from cholesterol, for example by substitution, addition or removal of substituents.

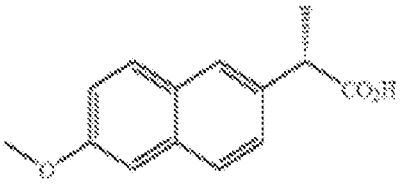
In another embodiment, the lipophilic moiety is an aromatic moiety. In this context, the term "aromatic" refers broadly to mono- and polyaromatic hydrocarbons. Aromatic groups include, without limitation, C_6-C_{14} aryl moieties comprising one to three aromatic rings, which may be optionally substituted; "aralkyl" or "arylalkyl" groups comprising an aryl group covalently linked to an alkyl group, either of which may independently be optionally substituted or unsubstituted; and "heteroaryl" groups. As used herein, the term "heteroaryl" refers to groups having 5 to 14 ring atoms, preferably 5, 6, 9, or 10 ring atoms; having 6, 10, or 14π electrons shared in a cyclic array, and having, in addition to carbon atoms, one to about three heteroatoms selected from the group consisting of nitrogen (N), oxygen (O), and sulfur (S).

As employed herein, a "substituted" alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclic group is one having one to about four, preferably one to about three, more preferably one or two, non-hydrogen substituents. Suitable substituents include, without limitation, halo, hydroxy, nitro, haloalkyl, alkyl, alkaryl, aryl, aralkyl, alkoxy, aryloxy, amino, acylamino, alkylcarbamoyl, arylcarbamoyl, aminoalkyl, alkoxycarbonyl, carboxy, hydroxyalkyl, alkanesulfonyl, arenesulfonyl, alkanesulfonamido, arenesulfonamido, aralkylsulfonamido, alkylcarbonyl, acyloxy, cyano, and ureido groups.

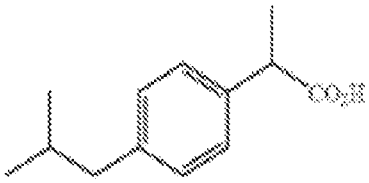
In some embodiments, the lipophilic moiety is an aralkyl group, *e.g.*, a 2-arylpropanoyl moiety. The structural features of the aralkyl group are selected so that the lipophilic moiety will bind to at least one protein in vivo. In certain embodiments, the structural features of the aralkyl group are selected so that the lipophilic moiety binds to serum, vascular, or cellular proteins. In certain embodiments, the structural features of the aralkyl group promote binding to albumin, an immunoglobulin, a lipoprotein, α-2-macroglubulin, or α-1-glycoprotein.

In certain embodiments, the ligand is naproxen or a structural derivative of naproxen. Procedures for the synthesis of naproxen can be found in U.S. Pat. No. 3,904,682 and U.S. Pat. No. 4,009,197, which are hereby incorporated by reference in their entirety. Naproxen has the

chemical name (S)-6-Methoxy-α-methyl-2-naphthaleneacetic acid and the structure is



In certain embodiments, the ligand is ibuprofen or a structural derivative of ibuprofen. Procedures for the synthesis of ibuprofen can be found in US3,228,831, which is incorporated herein by reference for the methods provided therein. The structure of ibuprofen is



Additional exemplary aralkyl groups are illustrated in US 7,626,014, which is incorporated herein by reference for the methods provided therein.

In another embodiment, suitable lipophilic moieties include lipid, cholesterol, retinoic acid, cholic acid, adamantane acetic acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-bis-O(hexadecyl)glycerol, geranyloxyhexyanol, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl group, palmitic acid, myristic acid, O3-(oleoyl)lithocholic acid, O3-(oleoyl)cholenic acid, ibuprofen, naproxen, dimethoxytrityl, or phenoxazine.

In certain embodiments, more than one lipophilic moiety can be incorporated into the double-strand RNAi agent, particularly when the lipophilic moiety has a low lipophilicity or hydrophobicity. In some embodiments, two or more lipophilic moieties are incorporated into the same strand of the double-strand RNAi agent. In some embodiments, each strand of the double-strand RNAi agent has one or more lipophilic moieties incorporated. In some embodiments, two or more lipophilic moieties are incorporated into the same position (i.e., the same nucleobase, same sugar moiety, or same internucleosidic linkage) of the double-strand RNAi agent. This can be achieved by, *e.g.*, conjugating the two or more lipophilic moieties via a carrier, or conjugating the two or more lipophilic moieties via a branched linker, or conjugating the two or more lipophilic moieties via one or more linkers, with one or more linkers linking the lipophilic moieties consecutively.

The lipophilic moiety may be conjugated to the RNAi agent via a direct attachment to the ribosugar of the RNAi agent. Alternatively, the lipophilic moiety may be conjugated to the double-strand RNAi agent via a linker or a carrier.

In certain embodiments, the lipophilic moiety may be conjugated to the RNAi agent via one or more linkers (tethers).

In some embodiments, the lipophilic moiety is conjugated to the double-stranded RNAi agent via a linker containing an ether, thioether, urea, carbonate, amine, amide, maleimide-thioether, disulfide, phosphodiester, sulfonamide linkage, a product of a click reaction (*e.g.*, a triazole from the azide-alkyne cycloaddition), or carbamate.

B. Lipid Conjugates

In some embodiments, the ligand is a lipid or lipid-based molecule. Such a lipid or lipid-based molecule can typically bind a serum protein, such as human serum albumin (HSA). An HSA binding ligand allows for vascular distribution of the conjugate to a target tissue. For example, the target tissue can be the eye. Other molecules that can bind HSA can also be used as ligands. For example, neproxin or aspirin can be used. A lipid or lipid-based ligand can (a) increase resistance to degradation of the conjugate, (b) increase targeting or transport into a target cell or cell membrane, and/or (c) can be used to adjust binding to a serum protein, *e.g.*, HSA.

A lipid-based ligand can be used to modulate, *e.g.*, control (*e.g.*, inhibit) the binding of the conjugate to a target tissue. For example, a lipid or lipid-based ligand that binds to HSA more strongly will be less likely to be targeted to the kidney and therefore less likely to be cleared from the body. A lipid or lipid-based ligand that binds to HSA less strongly can be used to target the conjugate to the kidney.

In some embodiments, the lipid-based ligand binds HSA. For example, the ligand can bind HSA with a sufficient affinity such that distribution of the conjugate to a non-kidney tissue is enhanced. However, the affinity is typically not so strong that the HSA-ligand binding cannot be reversed.

In some embodiments, the lipid-based ligand binds HSA weakly or not at all, such that distribution of the conjugate to the kidney is enhanced. Other moieties that target to kidney cells can also be used in place of or in addition to the lipid-based ligand.

In another aspect, the ligand is a moiety, *e.g.*, a vitamin, which is taken up by a target cell, *e.g.*, a proliferating cell. These are particularly useful for treating disorders characterized by unwanted cell proliferation, *e.g.*, of the malignant or non-malignant type, *e.g.*, cancer cells. Exemplary vitamins include vitamin A, E, and K. Other exemplary vitamins include B vitamin, *e.g.*, folic acid, B12, riboflavin, biotin, pyridoxal or other vitamins or nutrients taken up by cancer cells. Also included are HSA and low-density lipoprotein (LDL).

C. Cell Permeation Agents

In another aspect, the ligand is a cell-permeation agent, such as a helical cell-permeation agent. In some embodiments, the agent is amphipathic. An exemplary agent is a peptide such as tat or antennopedia. If the agent is a peptide, it can be modified, including a peptidylmimetic, invertomers, non-peptide or pseudo-peptide linkages, and use of D-amino acids. The helical agent is typically an α-helical agent, and can have a lipophilic and a lipophobic phase.

The ligand can be a peptide or peptidomimetic. A peptidomimetic (also referred to herein as an oligopeptidomimetic) is a molecule capable of folding into a defined three-dimensional structure similar to a natural peptide. The attachment of peptide and peptidomimetics to iRNA agents can affect pharmacokinetic distribution of the iRNA, such as by enhancing cellular recognition and absorption. The peptide or peptidomimetic moiety can be about 5-50 amino acids long, *e.g.*, about 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 amino acids long.

A peptide or peptidomimetic can be, for example, a cell permeation peptide, cationic peptide, amphipathic peptide, or hydrophobic peptide (*e.g.*, consisting primarily of Tyr, Trp or Phe). The peptide moiety can be a dendrimer peptide, constrained peptide or crosslinked peptide. In another alternative, the peptide moiety can include a hydrophobic membrane translocation sequence (MTS). An exemplary hydrophobic MTS-containing peptide is RFGF having the amino acid sequence AAVALLPAVLLALLAP (SEQ ID NO: 3). An RFGF analogue (*e.g.*, amino acid sequence AALLPVLLAAP (SEQ ID NO: 4)) containing a hydrophobic MTS can also be a targeting moiety. The peptide moiety can be a "delivery" peptide, which can carry large polar molecules including peptides, oligonucleotides, and protein across cell membranes. For example, sequences from the HIV Tat protein (GRKKRRQRRRPPQ (SEQ ID NO: 5)) and the *Drosophila Antennapedia* protein (RQIKIWFQNRRMKWKK (SEQ ID NO: 6)) have been found to be capable of functioning as delivery peptides. A peptide or peptidomimetic can be

encoded by a random sequence of DNA, such as a peptide identified from a phage-display library, or one-bead-one-compound (OBOC) combinatorial library (Lam *et al.*, *Nature*, 354:82-84, 1991). Typically, the peptide or peptidomimetic tethered to a dsRNA agent via an incorporated monomer unit is a cell targeting peptide such as an arginine-glycine-aspartic acid (RGD)-peptide, or RGD mimic. A peptide moiety can range in length from about 5 amino acids to about 40 amino acids. The peptide moieties can have a structural modification, such as to increase stability or direct conformational properties. Any of the structural modifications described below can be utilized.

An RGD peptide for use in the compositions and methods of the disclosure may be linear or cyclic, and may be modified, *e.g.*, glycosylated or methylated, to facilitate targeting to a specific tissue(s). RGD-containing peptides and peptidomimetics may include D-amino acids, as well as synthetic RGD mimics. In addition to RGD, one can use other moieties that target the integrin ligand. In some embodiments, conjugates of this ligand target PECAM-1 or VEGF.

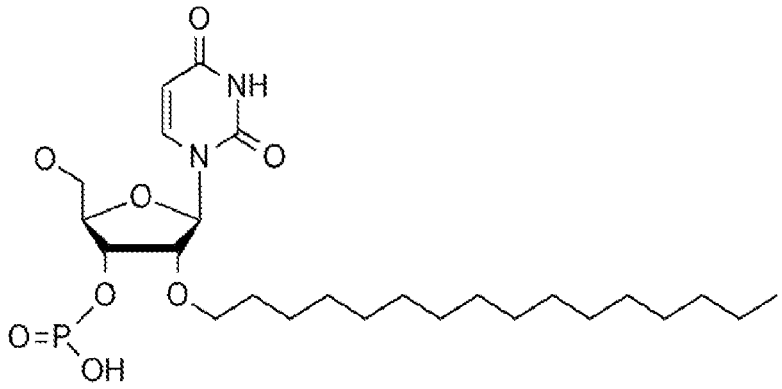
An RGD peptide moiety can be used to target a particular cell type, *e.g.*, an ocular cell, a tumor cell, such as an endothelial tumor cell or a breast cancer tumor cell (Zitzmann *et al.*, *Cancer Res.*, 62:5139-43, 2002). An RGD peptide can facilitate targeting of an dsRNA agent to tumors of a variety of other tissues, including the lung, kidney, spleen, or liver (Aoki *et al.*, *Cancer Gene Therapy* 8:783-787, 2001). Typically, the RGD peptide will facilitate targeting of an iRNA agent to the eye or kidney. The RGD peptide can be linear or cyclic, and can be modified, *e.g.*, glycosylated or methylated to facilitate targeting to specific tissues. For example, a glycosylated RGD peptide can deliver a iRNA agent to a tumor cell expressing $\alpha v\beta_3$ (Haubner *et al.*, *Jour. Nucl. Med.*, 42:326-336, 2001).

A "cell permeation peptide" is capable of permeating a cell, *e.g.*, a microbial cell, such as a bacterial or fungal cell, or a mammalian cell, such as a human cell. A microbial cell-permeating peptide can be, for example, an α-helical linear peptide (*e.g.*, LL-37 or Ceropin P1), a disulfide bond-containing peptide (*e.g.*, α -defensin, β-defensin or bactenecin), or a peptide containing only one or two dominating amino acids (*e.g.*, PR-39 or indolicidin). A cell permeation peptide can also include a nuclear localization signal (NLS). For example, a cell permeation peptide can be a bipartite amphipathic peptide, such as MPG, which is derived from the fusion peptide domain of HIV-1 gp41 and the NLS of SV40 large T antigen (Simeoni *et al.*, *Nucl. Acids Res.* 31:2717-2724, 2003).

D. Carbohydrate Conjugates and Ligands

In some embodiments of the compositions and methods of the disclosure, an iRNA oligonucleotide further comprises a carbohydrate. The carbohydrate conjugated iRNA are advantageous for the *in vivo* delivery of nucleic acids, as well as compositions suitable for *in vivo* therapeutic use, as described herein. As used herein, "carbohydrate" refers to a compound which is either a carbohydrate *per se* made up of one or more monosaccharide units having at least 6 carbon atoms (which can be linear, branched or cyclic) with an oxygen, nitrogen or sulfur atom bonded to each carbon atom; or a compound having as a part thereof a carbohydrate moiety made up of one or more monosaccharide units each having at least six carbon atoms (which can be linear, branched or cyclic), with an oxygen, nitrogen or sulfur atom bonded to each carbon atom. Representative carbohydrates include the sugars (mono-, di-, tri- and oligosaccharides containing from about 4, 5, 6, 7, 8, or 9 monosaccharide units), and polysaccharides such as starches, glycogen, cellulose and polysaccharide gums. Specific monosaccharides include C5 and above (*e.g.*, C5, C6, C7, or C8) sugars; di- and trisaccharides include sugars having two or three monosaccharide units (*e.g.*, C5, C6, C7, or C8).

In certain embodiments, the compositions and methods of the disclosure include a C16 ligand. In exemplary embodiments, the C16 ligand of the disclosure has the following structure (exemplified here below for a uracil base, yet attachment of the C16 ligand is contemplated for a nucleotide presenting any base (C, G, A, etc.) or possessing any other modification as presented herein, provided that 2' ribo attachment is preserved) and is attached at the 2' position of the ribo within a residue that is so modified:



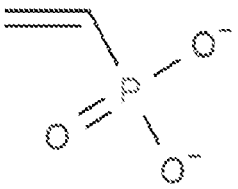
Chemical Formula: $C_{25}H_{43}N_2O_8P$
Exact Mass: 530.2757
Molecular Weight: 530.5913

As shown above, a C16 ligand-modified residue presents a straight chain alkyl at the 2'-ribo position of an exemplary residue (here, a Uracil) that is so modified.

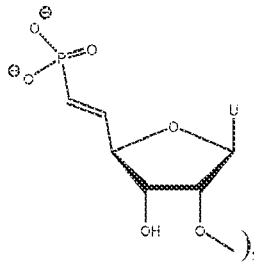
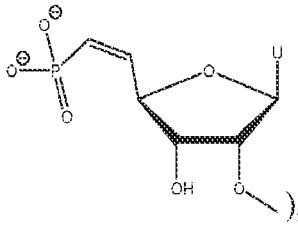
In some embodiments, a carbohydrate conjugate of a RNAi agent of the instant disclosure further comprises one or more additional ligands as described above, such as, but not limited to, a PK modulator or a cell permeation peptide.

Additional carbohydrate conjugates (and linkers) suitable for use in the present disclosure include those described in WO 2014/179620 and WO 2014/179627, the entire contents of each of which are incorporated herein by reference.

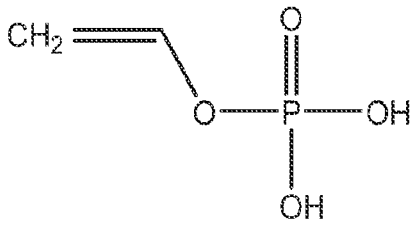
In certain embodiments, the compositions and methods of the disclosure include a vinyl phosponate (VP) modification of an RNAi agent as described herein. In exemplary embodiments, a vinyl phosphonate of the disclosure has the following structure:



A vinyl phosponate of the instant disclosure may be attached to either the antisense or the sense strand of a dsRNA of the disclosure. In certain embodiments, a vinyl phosphonate of the instant disclosure is attached to the antisense strand of a dsRNA, optionally at the 5' end of the antisense strand of the dsRNA. The dsRNA agent can comprise a phosphorus-containing group at the 5'-end of the sense strand or antisense strand. The 5'-end phosphorus-containing group can be 5'-end phosphate (5'-P), 5'-end phosphorothioate (5'-PS), 5'-end phosphorodithioate (5'-

PS2), 5'-end vinylphosphonate (5'-VP), 5'-end methylphosphonate (MePhos), or 5'-deoxy-5'-C-malonyl. When the 5'-end phosphorus-containing group is 5'-end vinylphosphonate (5'-VP), the 5'-VP can be either 5'-E-VP isomer (i.e., trans-vinylphosphonate, ), 5'-Z-VP isomer (i.e., cis-vinylphosphonate, ), or mixtures thereof.

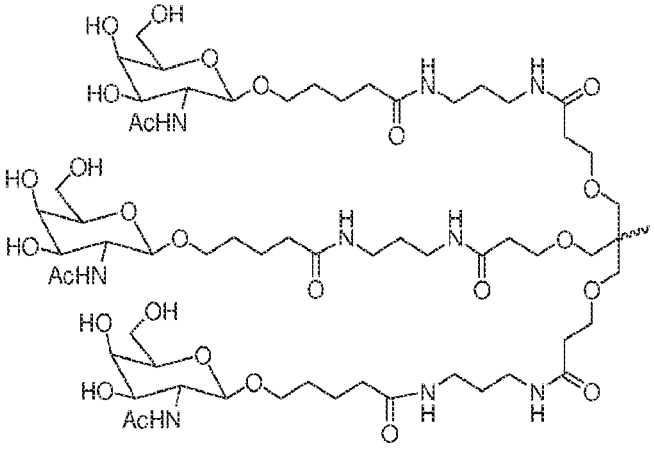
Vinyl phosphate modifications are also contemplated for the compositions and methods of the instant disclosure. An exemplary vinyl phosphate structure is:



In some embodiments, a carbohydrate conjugate comprises a monosaccharide. In some embodiments, the monosaccharide is an N-acetylgalactosamine (GalNAc). GalNAc conjugates, which comprise one or more N-acetylgalactosamine (GalNAc) derivatives, are described, for example, in U.S. Patent No. 8,106,022, the entire content of which is hereby incorporated herein by reference. In some embodiments, the GalNAc conjugate serves as a ligand that targets the iRNA to particular cells. In some embodiments, the GalNAc conjugate targets the iRNA to liver cells, *e.g.*, by serving as a ligand for the asialoglycoprotein receptor of liver cells (*e.g.*, hepatocytes).

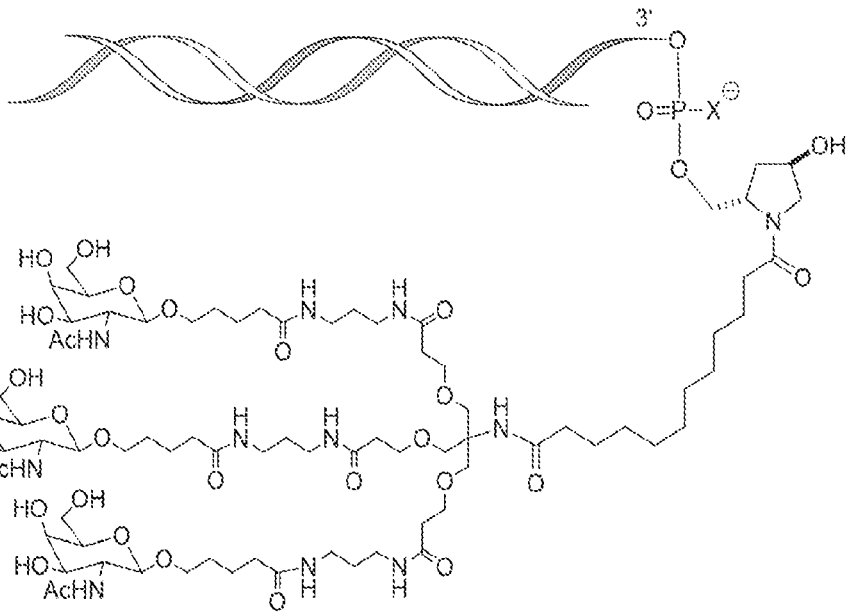
In some embodiments, the carbohydrate conjugate comprises one or more GalNAc derivatives. The GalNAc derivatives may be attached via a linker, *e.g.*, a bivalent or trivalent branched linker. In some embodiments the GalNAc conjugate is conjugated to the 3' end of the sense strand. In some embodiments, the GalNAc conjugate is conjugated to the iRNA agent (*e.g.*, to the 3' end of the sense strand) via a linker, *e.g.*, a linker as described herein.

In some embodiments, the GalNAc conjugate is

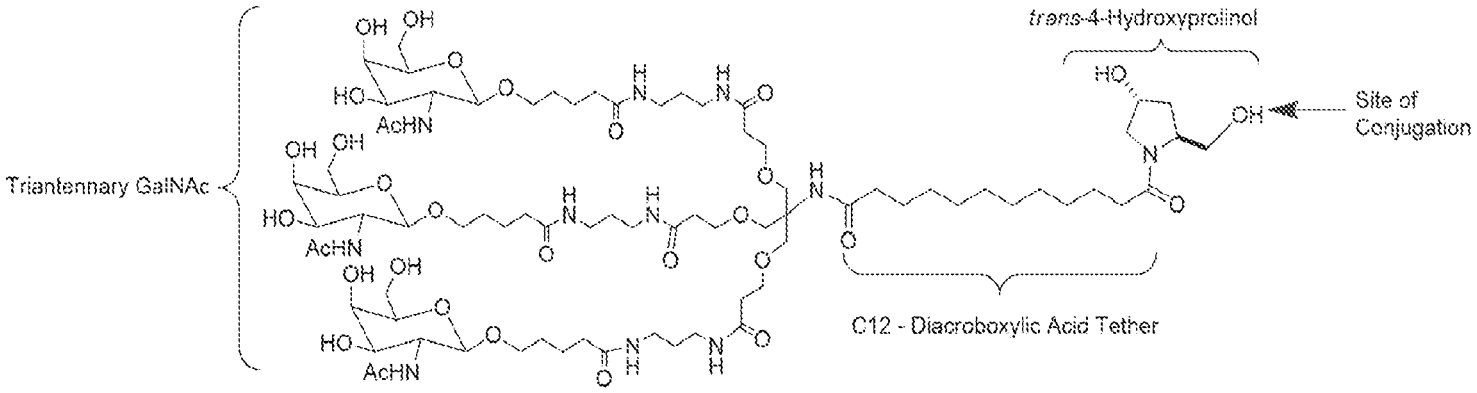


Formula II.

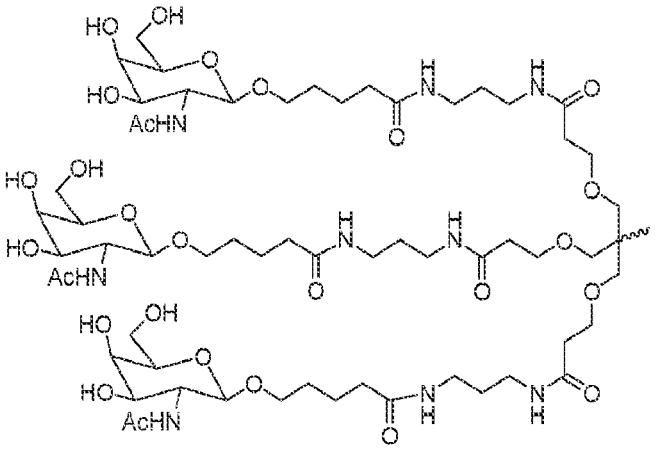
In some embodiments, the RNAi agent is attached to the carbohydrate conjugate via a linker as shown in the following schematic, wherein X is O or S:



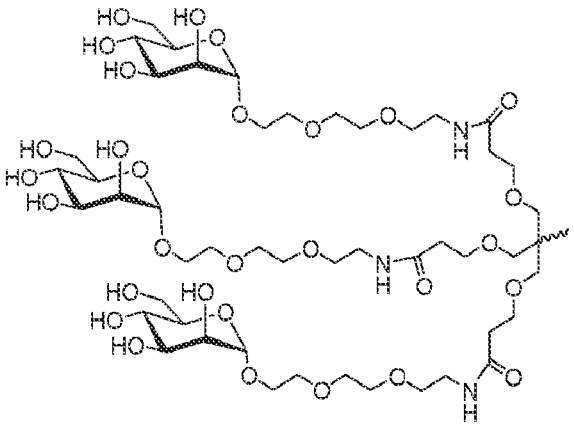
In some embodiments, the RNAi agent is conjugated to L96 as defined in Table 2 and shown below:



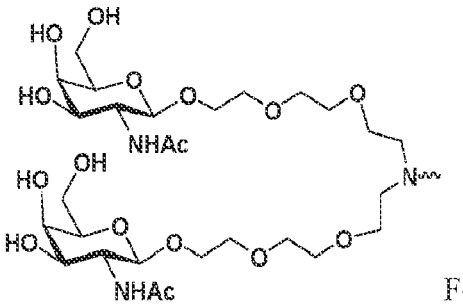
In some embodiments, a carbohydrate conjugate for use in the compositions and methods of the disclosure is selected from the group consisting of:



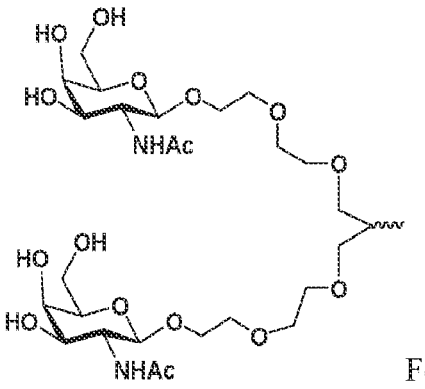
Formula II,



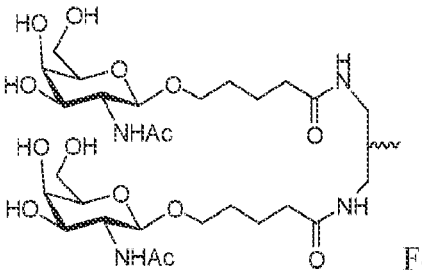
Formula III,



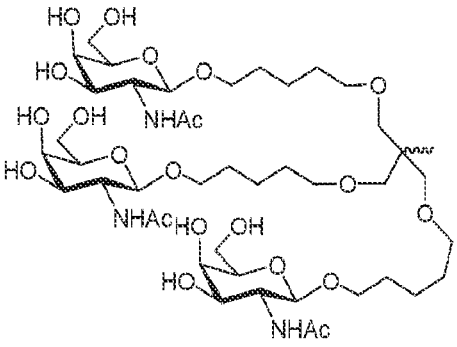
Formula IV,



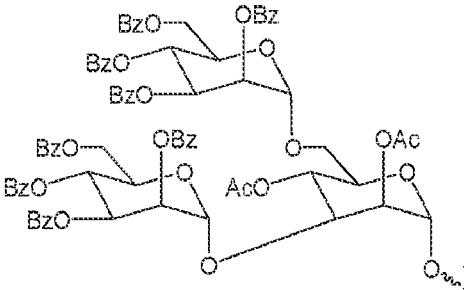
Formula V,



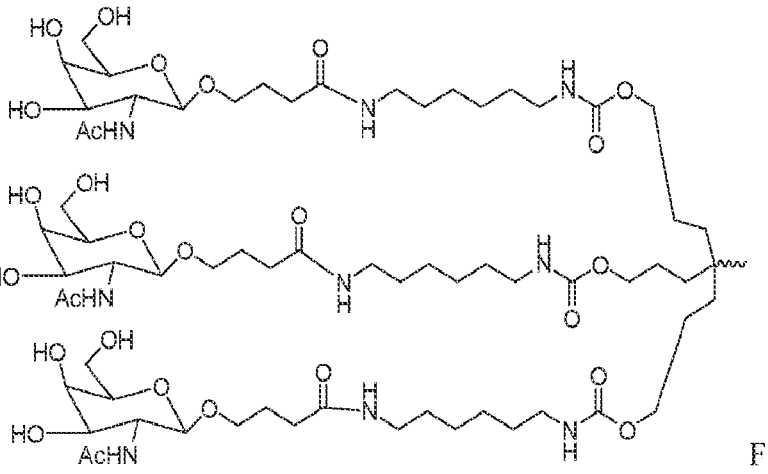
Formula VI,



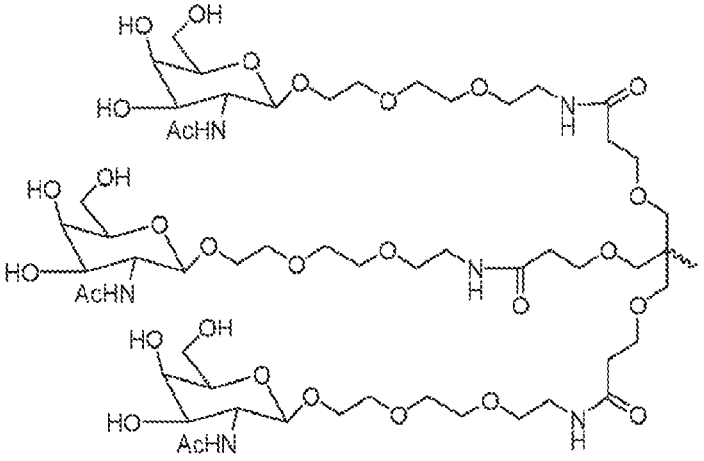
Formula VII,



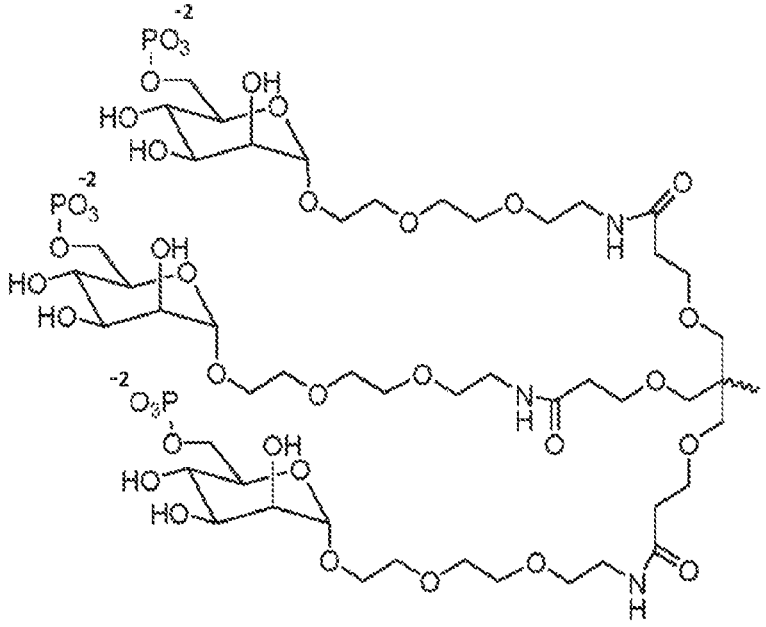
Formula VIII,



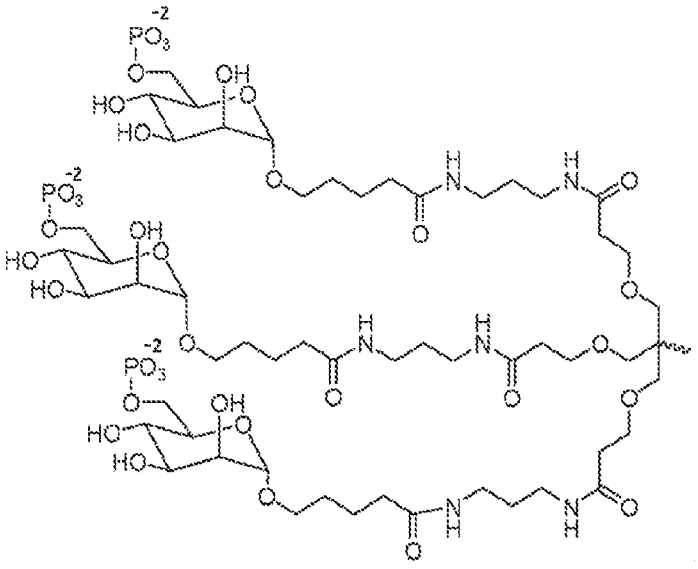
Formula IX,



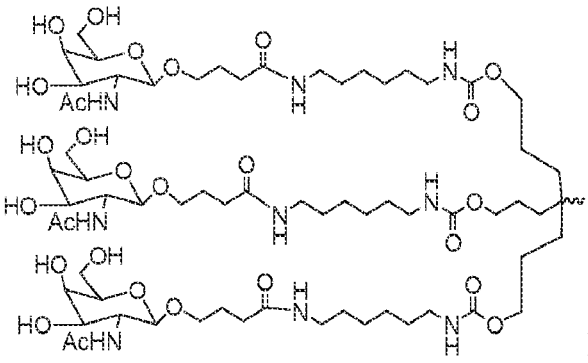
Formula X,



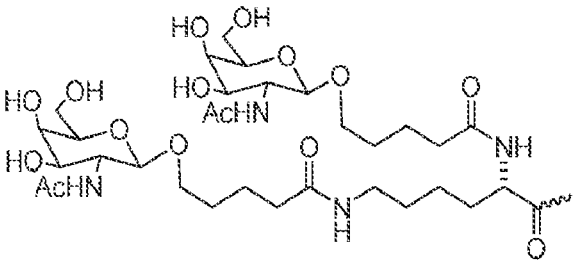
Formula XI,



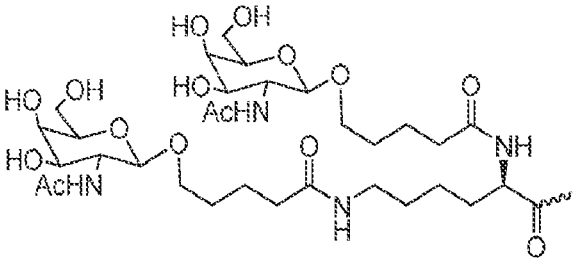
Formula XII,



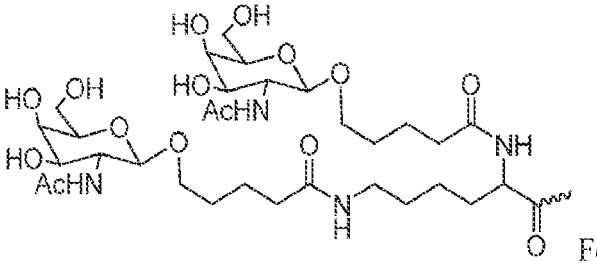
Formula XIII,



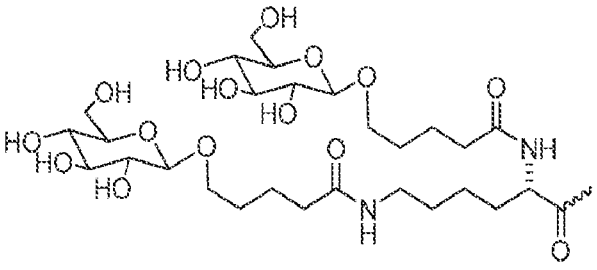
Formula XIV,



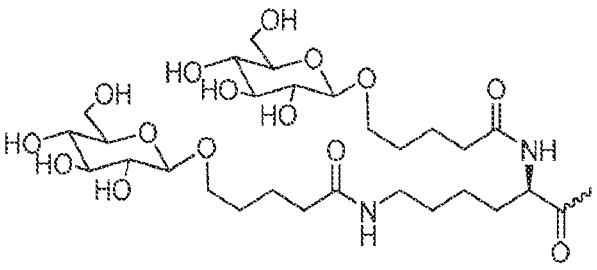
Formula XV,



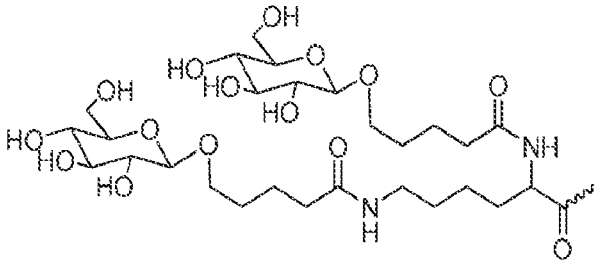
Formula XVI,



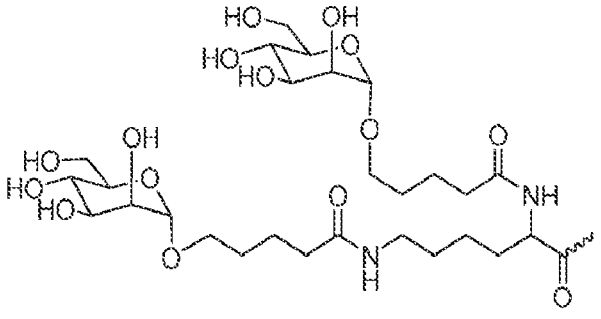
Formula XVII,



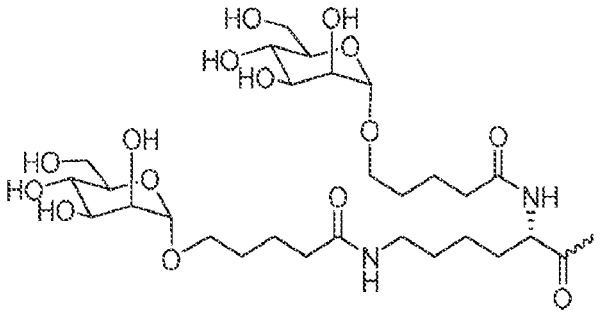
Formula XVIII,



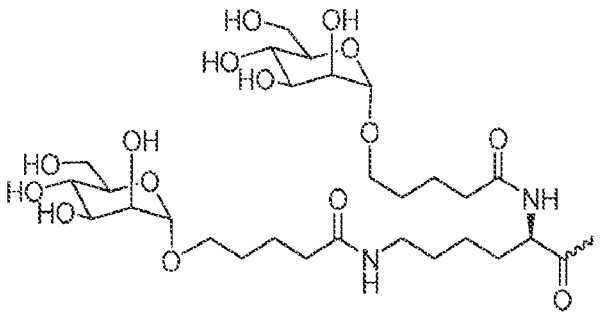
Formula XIX,



Formula XX,

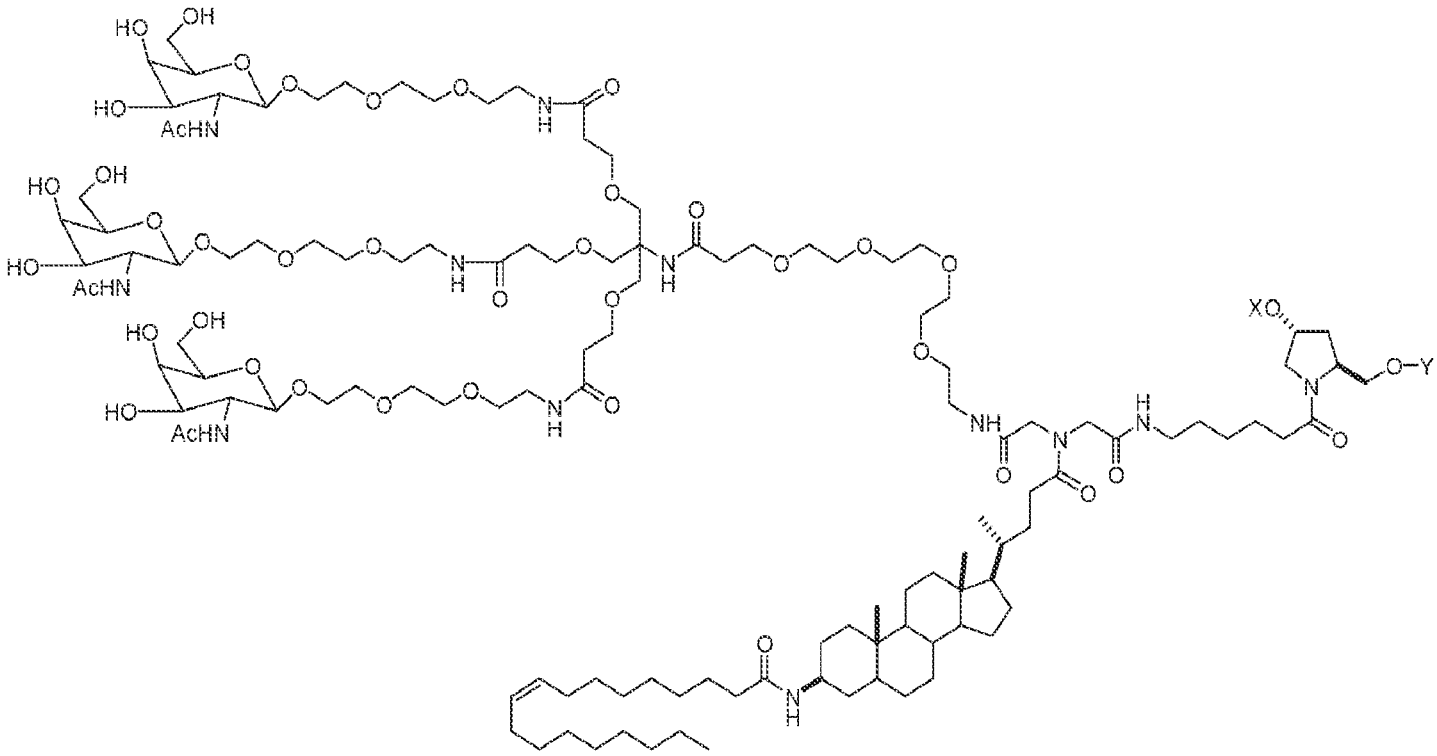


Formula XXI,



Formula XXII.

Another representative carbohydrate conjugate for use in the embodiments described herein includes, but is not limited to,

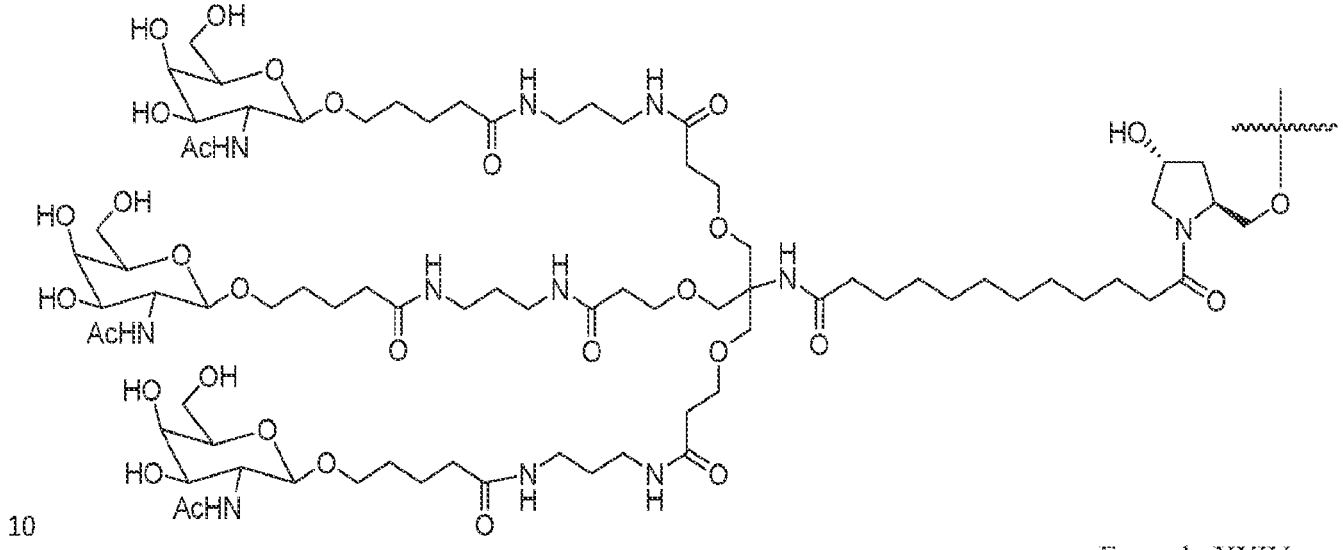


Formula XXIII,

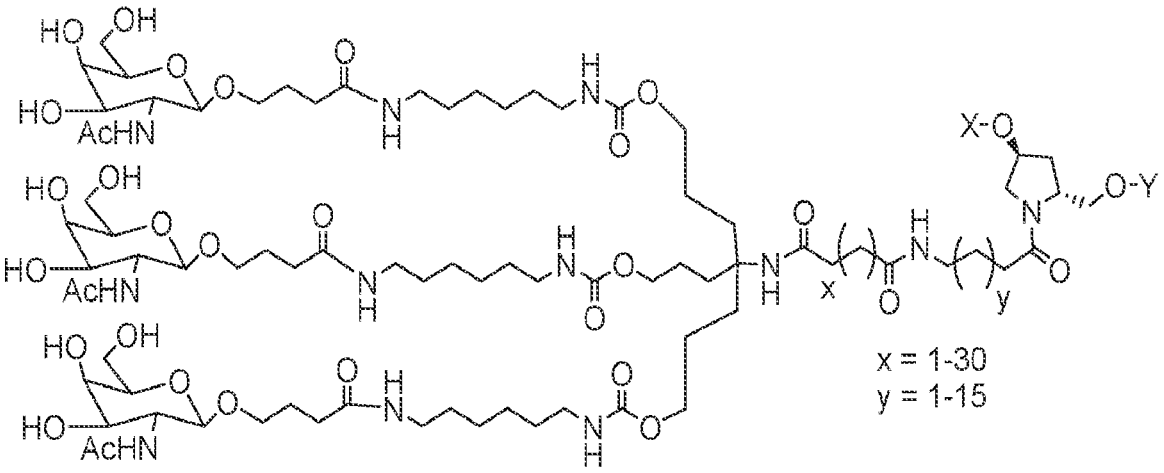
when one of X or Y is an oligonucleotide, the other is a hydrogen.

In some embodiments, the carbohydrate conjugate further comprises one or more additional ligands as described above, such as, but not limited to, a PK modulator and/or a cell permeation peptide.

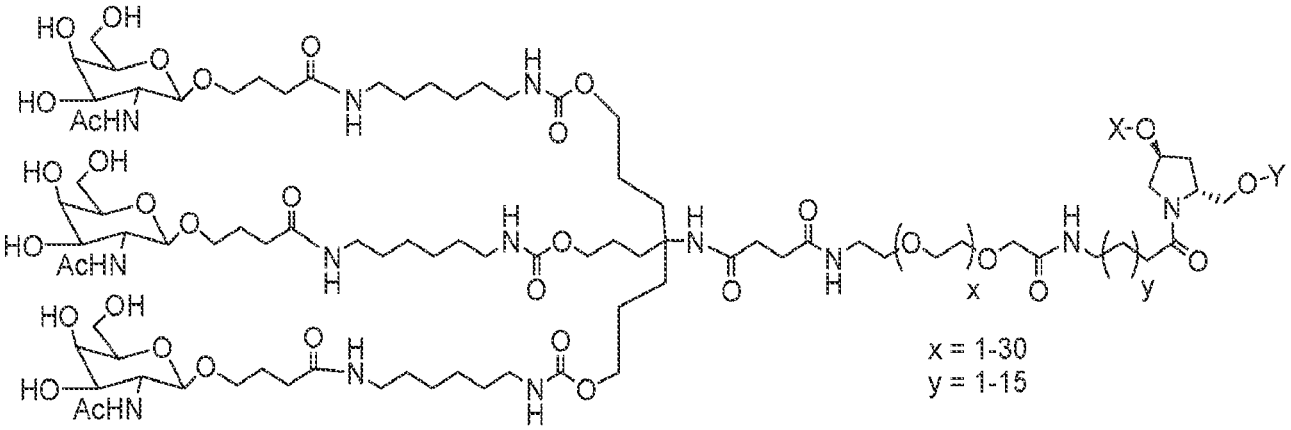
In some embodiments, an iRNA of the disclosure is conjugated to a carbohydrate through a linker. Non-limiting examples of iRNA carbohydrate conjugates with linkers of the compositions and methods of the disclosure include, but are not limited to,



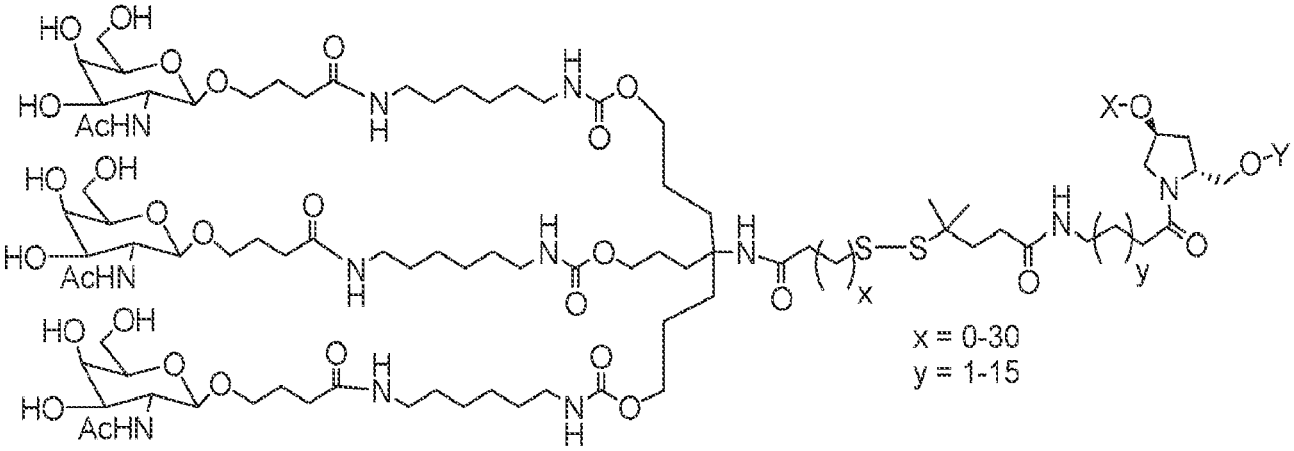
Formula XXIV,



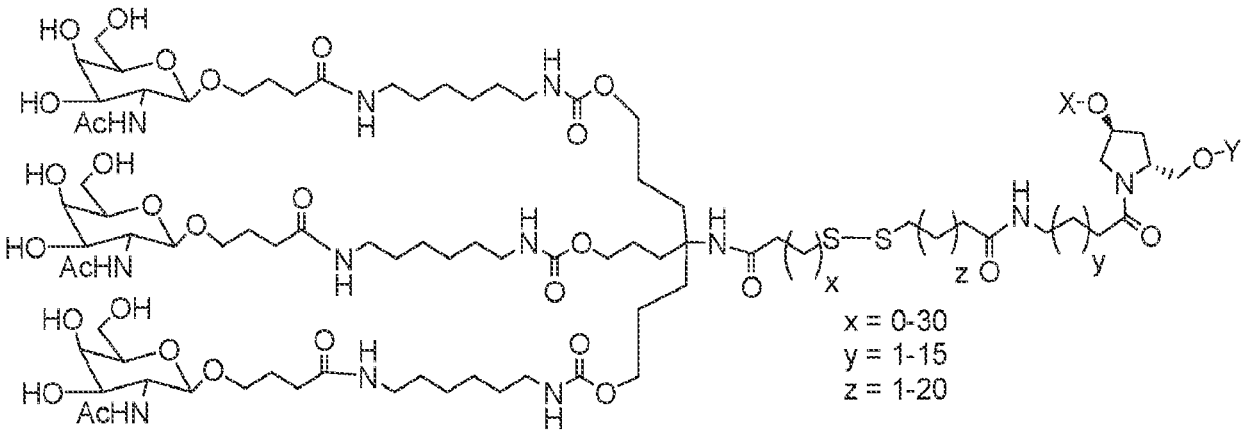
Formula XXV,



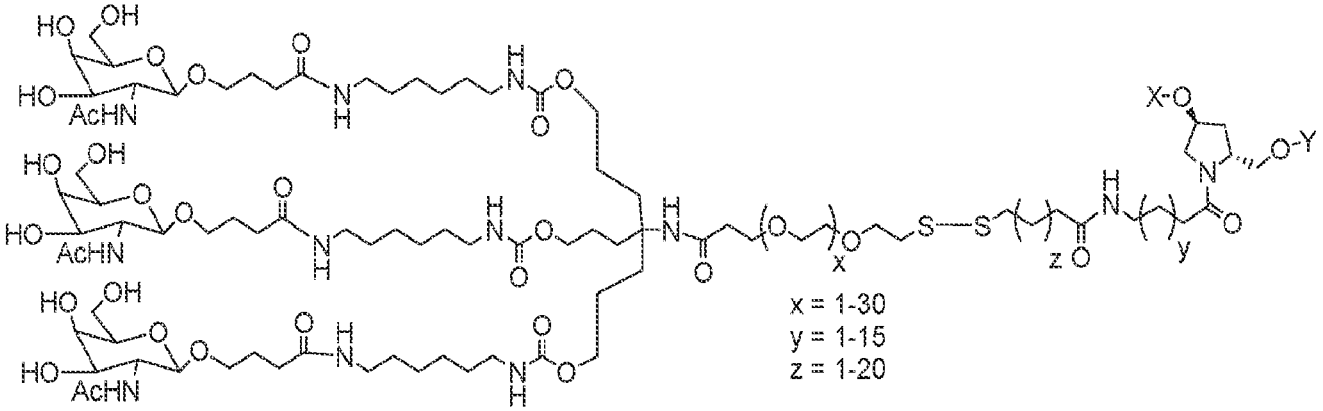
Formula XXVI,



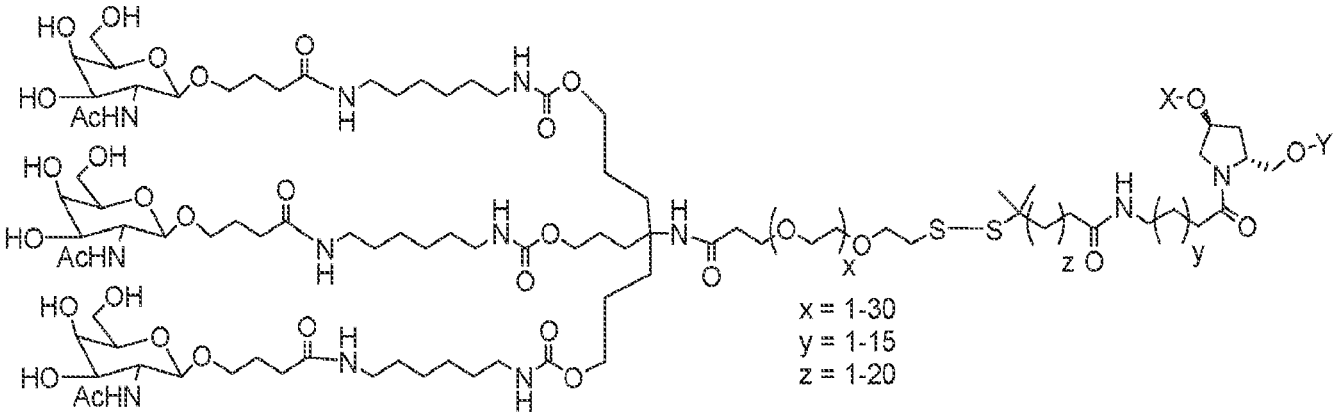
Formula XXVII,



Formula XXVIII,



Formula XXIX, and



Formula XXX,

when one of X or Y is an oligonucleotide, the other is a hydrogen.

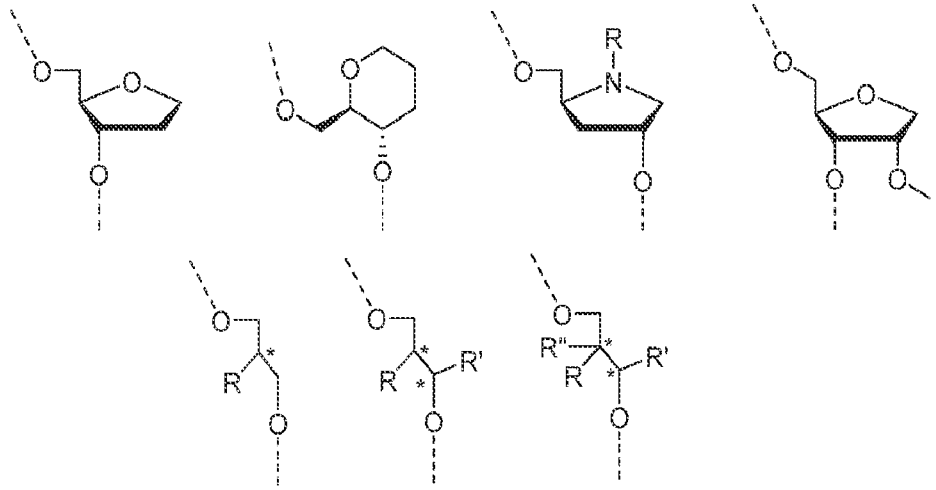
E. *Thermally Destabilizing Modifications*

In certain embodiments, a dsRNA molecule can be optimized for RNA interference by incorporating thermally destabilizing modifications in the seed region of the antisense strand (*i.e.*, at positions 2-9 of the 5'-end of the antisense strand) to reduce or inhibit off-target gene silencing. It has been discovered that dsRNAs with an antisense strand comprising at least one

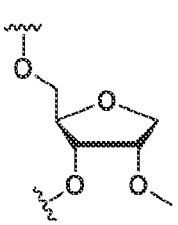
thermally destabilizing modification of the duplex within the first 9 nucleotide positions, counting from the 5' end, of the antisense strand have reduced off-target gene silencing activity. Accordingly, in some embodiments, the antisense strand comprises at least one (*e.g.*, one, two, three, four, five, or more) thermally destabilizing modification of the duplex within the first 9 nucleotide positions of the 5' region of the antisense strand. In some embodiments, one or more thermally destabilizing modification(s) of the duplex is/are located in positions 2-9, or positions 4-8, from the 5'-end of the antisense strand. In some further embodiments, the thermally destabilizing modification(s) of the duplex is/are located at position 6, 7, or 8 from the 5'-end of the antisense strand. In still some further embodiments, the thermally destabilizing modification of the duplex is located at position 7 from the 5'-end of the antisense strand. The term "thermally destabilizing modification(s)" includes modification(s) that would result with a dsRNA with a lower overall melting temperature (Tm), such as a Tm with one, two, three, or four degrees lower than the Tm of the dsRNA without having such modification(s). In some embodiments, the thermally destabilizing modification of the duplex is located at position 2, 3, 4, 5, or 9 from the 5'-end of the antisense strand.

The thermally destabilizing modifications can include, but are not limited to, abasic modification; mismatch with the opposing nucleotide in the opposing strand; and sugar modification such as 2'-deoxy modification or acyclic nucleotide, *e.g.*, unlocked nucleic acids (UNA) or glycol nucleic acid (GNA).

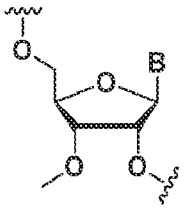
Exemplified abasic modifications include, but are not limited to, the following:



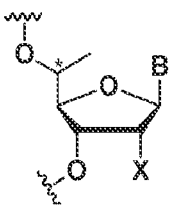
Wherein R = H, Me, Et or OMe; R' = H, Me, Et or OMe; R" = H, Me, Et or OMe



Mod2
(2'-OMe Abasic Spacer)

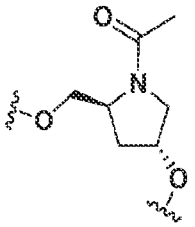


Mod3
(3'-OMe)



Mod4
(5'-Me)

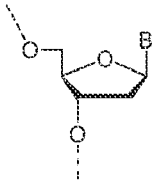
X = OMe, F



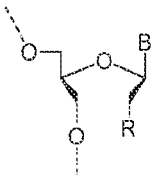
Mod5
(Hyp-spacer)

wherein B is a modified or unmodified nucleobase.

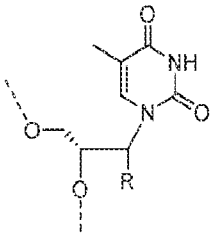
Exemplified sugar modifications include, but are not limited to the following:



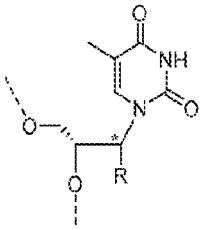
2'-deoxy



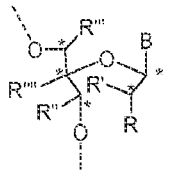
unlocked nucleic acid
R= H, OH, O-alkyl



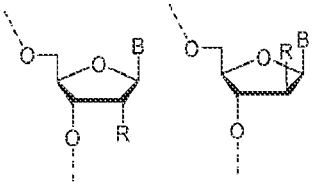
glycol nucleic acid
R= H, OH, O-alkyl



glycol nucleic acid
R= H, OH, O-alkyl



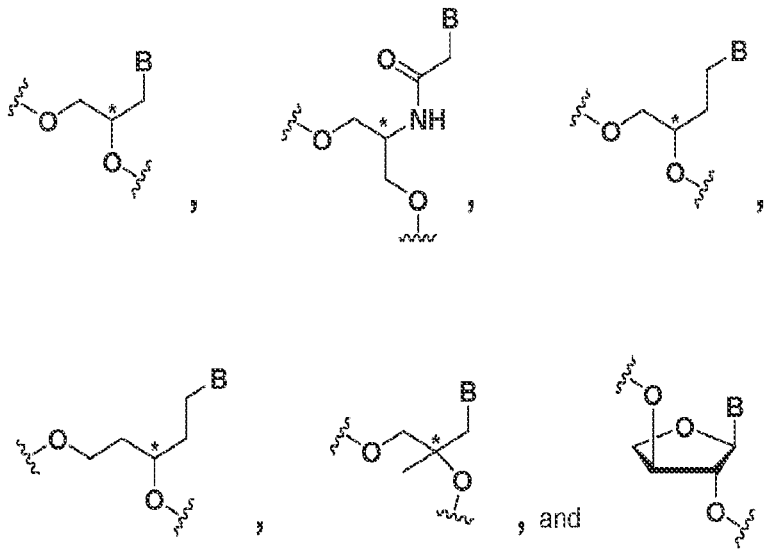
unlocked nucleic acid
R= H, OH, CH_3, CH_2CH_3, O-alkyl, NH_2, NHMe, NMe_2
R' = H, OH, CH_3, CH_2CH_3, O-alkyl, NH_2, NHMe, NMe_2
R'' = H, OH, CH_3, CH_2CH_3, O-alkyl, NH_2, NHMe, NMe_2
R''' = H, OH, CH_3, CH_2CH_3, O-alkyl, NH_2, NHMe, NMe_2
R'''' = H, OH, CH_3, CH_2CH_3, O-alkyl, NH_2, NHMe, NMe_2



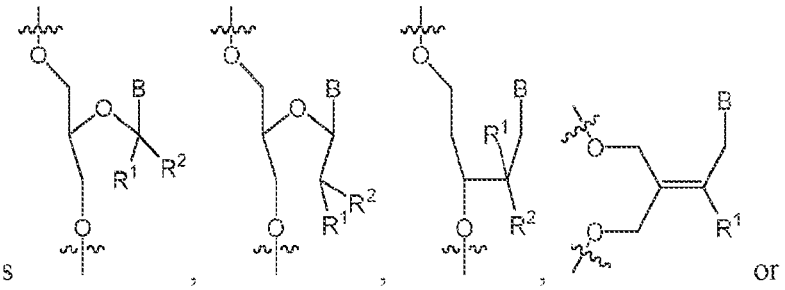
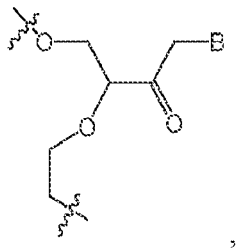
R = H, methyl, ethyl

wherein B is a modified or unmodified nucleobase.

In some embodiments the thermally destabilizing modification of the duplex is selected from the group consisting of:

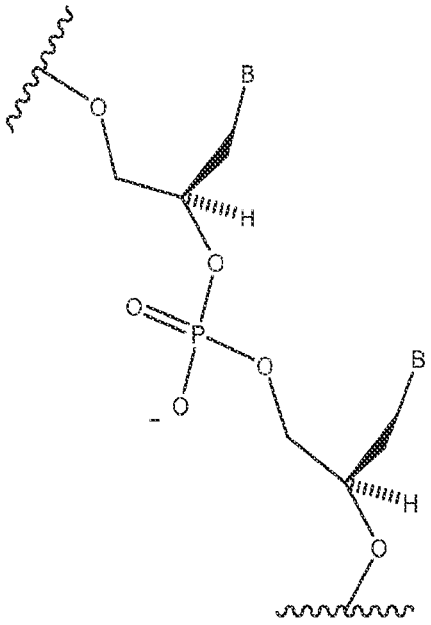


wherein B is a modified or unmodified nucleobase and the asterisk on each structure represents either *R*, *S* or *racemic*.

The term "acyclic nucleotide" refers to any nucleotide having an acyclic ribose sugar, for example, where any of bonds between the ribose carbons (*e.g.*, C1'-C2', C2'-C3', C3'-C4', C4'-O4', or C1'-O4') is absent or at least one of ribose carbons or oxygen (*e.g.*, C1', C2', C3', C4', or O4') are independently or in combination absent from the nucleotide. In some embodiments, acyclic nucleotide is  or  , wherein B is a modified or unmodified nucleobase, R^1 and R^2 independently are H, halogen, OR_3, or alkyl; and R_3 is H, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl or sugar). The term "UNA" refers to unlocked acyclic nucleic acid, wherein any of the bonds of the sugar has been removed, forming an unlocked "sugar" residue. In one example, UNA also encompasses monomers with bonds between C1'-C4' being removed (i.e. the covalent carbon-oxygen-carbon bond between the C1' and C4' carbons). In another example, the C2'-C3' bond (i.e. the covalent carbon-carbon bond between the C2' and C3' carbons) of the sugar is removed

(see Mikhailov et. al., Tetrahedron Letters, 26 (17): 2059 (1985); and Fluiter et al., Mol. Biosyst., 10: 1039 (2009), which are hereby incorporated by reference in their entirety). The acyclic derivative provides greater backbone flexibility without affecting the Watson-Crick pairings. The acyclic nucleotide can be linked via 2'-5' or 3'-5' linkage.

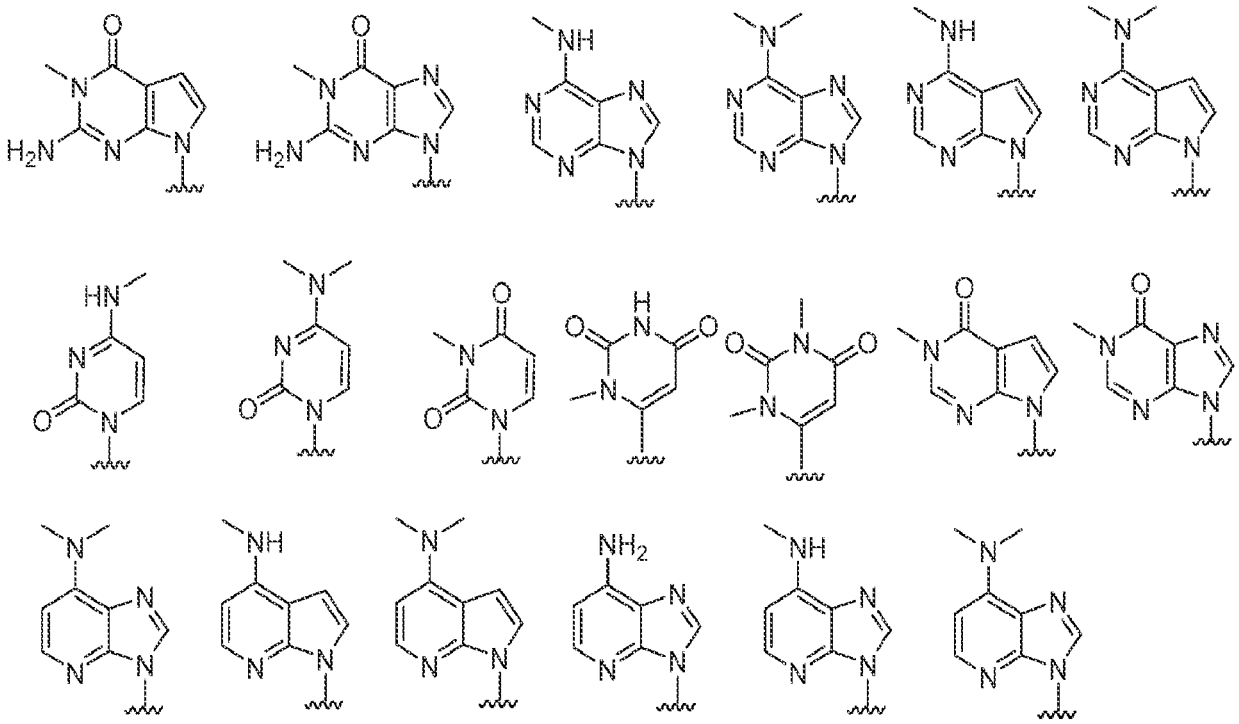
The term 'GNA' refers to glycol nucleic acid which is a polymer similar to DNA or RNA but differing in the composition of its "backbone" in that is composed of repeating glycerol units linked by phosphodiester bonds:



(R) - GNA

The thermally destabilizing modification of the duplex can be mismatches (i.e., noncomplementary base pairs) between the thermally destabilizing nucleotide and the opposing nucleotide in the opposite strand within the dsRNA duplex. Exemplary mismatch base pairs include G:G, G:A, G:U, G:T, A:A, A:C, C:C, C:U, C:T, U:U, T:T, U:T, or a combination thereof. Other mismatch base pairings known in the art are also amenable to the present invention. A mismatch can occur between nucleotides that are either naturally occurring nucleotides or modified nucleotides, i.e., the mismatch base pairing can occur between the nucleobases from respective nucleotides independent of the modifications on the ribose sugars of the nucleotides. In certain embodiments, the dsRNA molecule contains at least one nucleobase in the mismatch pairing that is a 2'-deoxy nucleobase; *e.g.*, the 2'-deoxy nucleobase is in the sense strand.

In some embodiments, the thermally destabilizing modification of the duplex in the seed region of the antisense strand includes nucleotides with impaired W-C H-bonding to complementary base on the target mRNA, such as:

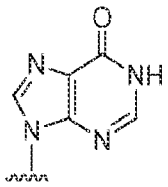


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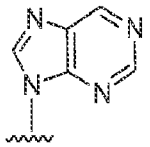
More examples of abasic nucleotide, acyclic nucleotide modifications (including UNA and GNA), and mismatch modifications have been described in detail in WO 2011/133876, which is herein incorporated by reference in its entirety.

The thermally destabilizing modifications may also include universal base with reduced or abolished capability to form hydrogen bonds with the opposing bases, and phosphate modifications.

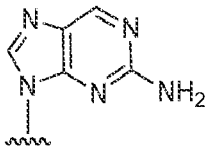
In some embodiments, the thermally destabilizing modification of the duplex includes nucleotides with non-canonical bases such as, but not limited to, nucleobase modifications with impaired or completely abolished capability to form hydrogen bonds with bases in the opposite strand. These nucleobase modifications have been evaluated for destabilization of the central region of the dsRNA duplex as described in WO 2010/0011895, which is herein incorporated by reference in its entirety. Exemplary nucleobase modifications are:



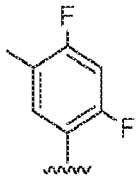
inosine



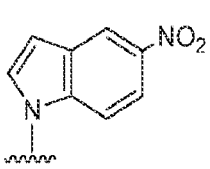
nebularine



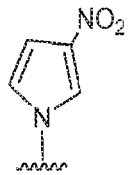
2-aminopurine



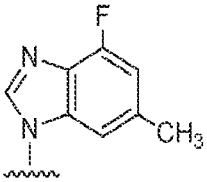
2,4-difluorotoluene



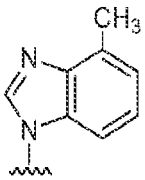
5-nitroindole



3-nitropyrrole

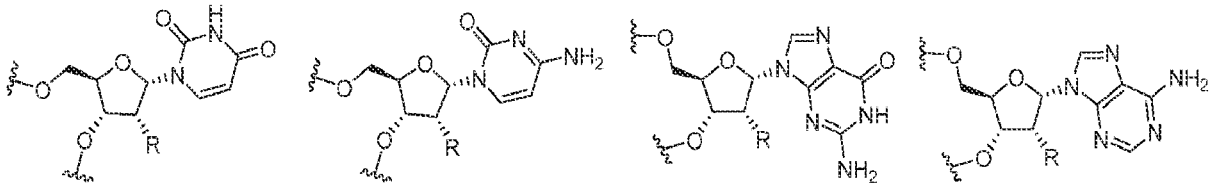


4-Fluoro-6-methylbenzimidazole



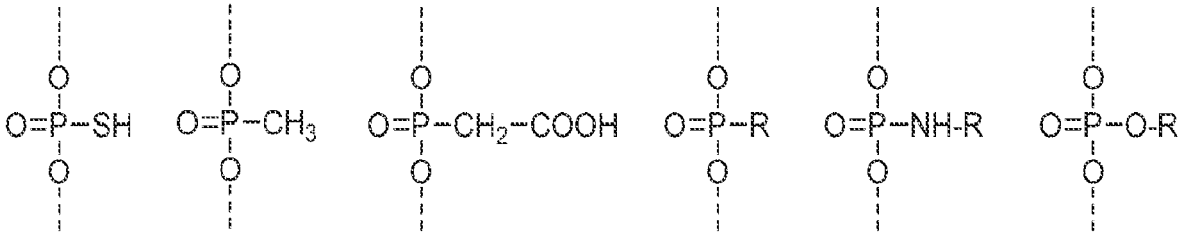
4-Methylbenzimidazole

In some embodiments, the thermally destabilizing modification of the duplex in the seed region of the antisense strand includes one or more α-nucleotide complementary to the base on the target mRNA, such as:



wherein R is H, OH, OCH_3, F, NH_2, NHMe, NMe_2 or O-alkyl.

Exemplary phosphate modifications known to decrease the thermal stability of dsRNA duplexes compared to natural phosphodiester linkages are:



R = alkyl

The alkyl for the R group can be a C_1-C_6alkyl. Specific alkyls for the R group include, but are not limited to methyl, ethyl, propyl, isopropyl, butyl, pentyl and hexyl.

As the skilled artisan will recognize, in view of the functional role of nucleobases is defining specificity of a RNAi agent of the disclosure, while nucleobase modifications can be performed in the various manners as described herein, *e.g.,* to introduce destabilizing modifications into a RNAi agent of the disclosure, *e.g.,* for purpose of enhancing on-target effect

relative to off-target effect, the range of modifications available and, in general, present upon RNAi agents of the disclosure tends to be much greater for non-nucleobase modifications, *e.g.*, modifications to sugar groups or phosphate backbones of polyribonucleotides. Such modifications are described in greater detail in other sections of the instant disclosure and are expressly contemplated for RNAi agents of the disclosure, either possessing native nucleobases or modified nucleobases as described above or elsewhere herein.

In addition to the antisense strand comprising a thermally destabilizing modification, the dsRNA can also comprise one or more stabilizing modifications. For example, the dsRNA can comprise at least two (*e.g.*, two, three, four, five, six, seven, eight, nine, ten, or more) stabilizing modifications. Without limitations, the stabilizing modifications all can be present in one strand. In some embodiments, both the sense and the antisense strands comprise at least two stabilizing modifications. The stabilizing modification can occur on any nucleotide of the sense strand or antisense strand. For instance, the stabilizing modification can occur on every nucleotide on the sense strand or antisense strand; each stabilizing modification can occur in an alternating pattern on the sense strand or antisense strand; or the sense strand or antisense strand comprises both stabilizing modification in an alternating pattern. The alternating pattern of the stabilizing modifications on the sense strand may be the same or different from the antisense strand, and the alternating pattern of the stabilizing modifications on the sense strand can have a shift relative to the alternating pattern of the stabilizing modifications on the antisense strand.

In some embodiments, the antisense strand comprises at least two (*e.g.*, two, three, four, five, six, seven, eight, nine, ten, or more) stabilizing modifications. Without limitations, a stabilizing modification in the antisense strand can be present at any positions.

In some embodiments, the antisense strand comprises stabilizing modifications at positions 2, 6, 8, 9, 14, and 16 from the 5'-end. In some other embodiments, the antisense strand comprises stabilizing modifications at positions 2, 6, 14, and 16 from the 5'-end. In still some other embodiments, the antisense strand comprises stabilizing modifications at positions 2, 14, and 16 from the 5'-end.

In some embodiments, the antisense strand comprises at least one stabilizing modification adjacent to the destabilizing modification. For example, the stabilizing modification can be the nucleotide at the 5'-end or the 3'-end of the destabilizing modification, *i.e.*, at position -1 or +1 from the position of the destabilizing modification. In some embodiments, the antisense strand

comprises a stabilizing modification at each of the 5'-end and the 3'-end of the destabilizing modification, *i.e.*, positions -1 and +1 from the position of the destabilizing modification.

In some embodiments, the antisense strand comprises at least two stabilizing modifications at the 3'-end of the destabilizing modification, *i.e.*, at positions +1 and +2 from the position of the destabilizing modification.

In some embodiments, the sense strand comprises at least two (*e.g.*, two, three, four, five, six, seven, eight, nine, ten or more) stabilizing modifications. Without limitations, a stabilizing modification in the sense strand can be present at any positions. In some embodiments, the sense strand comprises stabilizing modifications at positions 7, 10, and 11 from the 5'-end. In some other embodiments, the sense strand comprises stabilizing modifications at positions 7, 9, 10, and 11 from the 5'-end. In some embodiments, the sense strand comprises stabilizing modifications at positions opposite or complimentary to positions 11, 12, and 15 of the antisense strand, counting from the 5'-end of the antisense strand. In some other embodiments, the sense strand comprises stabilizing modifications at positions opposite or complimentary to positions 11, 12, 13, and 15 of the antisense strand, counting from the 5'-end of the antisense strand. In some embodiments, the sense strand comprises a block of two, three, or four stabilizing modifications.

In some embodiments, the sense strand does not comprise a stabilizing modification in position opposite or complimentary to the thermally destabilizing modification of the duplex in the antisense strand.

Exemplary thermally stabilizing modifications include, but are not limited to, 2'-fluoro modifications. Other thermally stabilizing modifications include, but are not limited to, LNA.

In some embodiments, the dsRNA of the disclosure comprises at least four (*e.g.*, four, five, six, seven, eight, nine, ten, or more) 2'-fluoro nucleotides. Without limitations, the 2'-fluoro nucleotides all can be present in one strand. In some embodiments, both the sense and the antisense strands comprise at least two 2'-fluoro nucleotides. The 2'-fluoro modification can occur on any nucleotide of the sense strand or antisense strand. For instance, the 2'-fluoro modification can occur on every nucleotide on the sense strand or antisense strand; each 2'-fluoro modification can occur in an alternating pattern on the sense strand or antisense strand; or the sense strand or antisense strand comprises both 2'-fluoro modifications in an alternating pattern. The alternating pattern of the 2'-fluoro modifications on the sense strand may be the

same or different from the antisense strand, and the alternating pattern of the 2'-fluoro modifications on the sense strand can have a shift relative to the alternating pattern of the 2'-fluoro modifications on the antisense strand.

In some embodiments, the antisense strand comprises at least two (*e.g.*, two, three, four, five, six, seven, eight, nine, ten, or more) 2'-fluoro nucleotides. Without limitations, a 2'-fluoro modification in the antisense strand can be present at any positions. In some embodiments, the antisense comprises 2'-fluoro nucleotides at positions 2, 6, 8, 9, 14, and 16 from the 5'-end. In some other embodiments, the antisense comprises 2'-fluoro nucleotides at positions 2, 6, 14, and 16 from the 5'-end. In still some other embodiments, the antisense comprises 2'-fluoro nucleotides at positions 2, 14, and 16 from the 5'-end.

In some embodiments, the antisense strand comprises at least one 2'-fluoro nucleotide adjacent to the destabilizing modification. For example, the 2'-fluoro nucleotide can be the nucleotide at the 5'-end or the 3'-end of the destabilizing modification, *i.e.*, at position -1 or +1 from the position of the destabilizing modification. In some embodiments, the antisense strand comprises a 2'-fluoro nucleotide at each of the 5'-end and the 3'-end of the destabilizing modification, *i.e.*, positions -1 and +1 from the position of the destabilizing modification.

In some embodiments, the antisense strand comprises at least two 2'-fluoro nucleotides at the 3'-end of the destabilizing modification, *i.e.*, at positions +1 and +2 from the position of the destabilizing modification.

In some embodiments, the sense strand comprises at least two (*e.g.*, two, three, four, five, six, seven, eight, nine, ten, or more) 2'-fluoro nucleotides. Without limitations, a 2'-fluoro modification in the sense strand can be present at any positions. In some embodiments, the antisense comprises 2'-fluoro nucleotides at positions 7, 10, and 11 from the 5'-end. In some other embodiments, the sense strand comprises 2'-fluoro nucleotides at positions 7, 9, 10, and 11 from the 5'-end. In some embodiments, the sense strand comprises 2'-fluoro nucleotides at positions opposite or complimentary to positions 11, 12, and 15 of the antisense strand, counting from the 5'-end of the antisense strand. In some other embodiments, the sense strand comprises 2'-fluoro nucleotides at positions opposite or complimentary to positions 11, 12, 13, and 15 of the antisense strand, counting from the 5'-end of the antisense strand. In some embodiments, the sense strand comprises a block of two, three, or four 2'-fluoro nucleotides.

In some embodiments, the sense strand does not comprise a 2'-fluoro nucleotide in position opposite or complimentary to the thermally destabilizing modification of the duplex in the antisense strand.

In some embodiments, the dsRNA molecule of the disclosure comprises a 21 nucleotides (nt) sense strand and a 23 nucleotides (nt) antisense, wherein the antisense strand contains at least one thermally destabilizing nucleotide, where the at least one thermally destabilizing nucleotide occurs in the seed region of the antisense strand (*i.e.*, at position 2-9 of the 5'-end of the antisense strand), wherein one end of the dsRNA is blunt, while the other end is comprises a 2 nt overhang, and wherein the dsRNA optionally further has at least one (*e.g.*, one, two, three, four, five, six, or all seven) of the following characteristics: (i) the antisense comprises 2, 3, 4, 5, or 6 2'-fluoro modifications; (ii) the antisense comprises 1, 2, 3, 4, or 5 phosphorothioate internucleotide linkages; (iii) the sense strand is conjugated with a ligand; (iv) the sense strand comprises 2, 3, 4, or 5 2'-fluoro modifications; (v) the sense strand comprises 1, 2, 3, 4, or 5 phosphorothioate internucleotide linkages; (vi) the dsRNA comprises at least four 2'-fluoro modifications; and (vii) the dsRNA comprises a blunt end at 5'-end of the antisense strand. In certain embodiments, the 2 nt overhang is at the 3'-end of the antisense strand.

In some embodiments, every nucleotide in the sense strand and antisense strand of the dsRNA molecule may be modified. Each nucleotide may be modified with the same or different modification which can include one or more alteration of one or both of the non-linking phosphate oxygens or of one or more of the linking phosphate oxygens; alteration of a constituent of the ribose sugar, *e.g.*, of the 2' hydroxyl on the ribose sugar; wholesale replacement of the phosphate moiety with "dephospho" linkers; modification or replacement of a naturally occurring base; and replacement or modification of the ribose-phosphate backbone.

As nucleic acids are polymers of subunits, many of the modifications occur at a position which is repeated within a nucleic acid, *e.g.*, a modification of a base, or a phosphate moiety, or a non-linking O of a phosphate moiety. In some cases, the modification will occur at all of the subject positions in the nucleic acid but in many cases it will not. By way of example, a modification may only occur at a 3' or 5' terminal position, may only occur in a terminal region, *e.g.*, at a position on a terminal nucleotide or in the last 2, 3, 4, 5, or 10 nucleotides of a strand. A modification may occur in a double strand region, a single strand region, or in both. A modification may occur only in the double strand region of an RNA or may only occur in a

single strand region of an RNA. *E.g.*, a phosphorothioate modification at a non-linking O position may only occur at one or both termini, may only occur in a terminal region, *e.g.*, at a position on a terminal nucleotide or in the last 2, 3, 4, 5, or 10 nucleotides of a strand, or may occur in double strand and single strand regions, particularly at termini. The 5' end or ends can be phosphorylated.

It may be possible, *e.g.*, to enhance stability, to include particular bases in overhangs, or to include modified nucleotides or nucleotide surrogates, in single strand overhangs, *e.g.*, in a 5' or 3' overhang, or in both. *E.g.*, it can be desirable to include purine nucleotides in overhangs. In some embodiments all or some of the bases in a 3' or 5' overhang may be modified, *e.g.*, with a modification described herein. Modifications can include, *e.g.*, the use of modifications at the 2' position of the ribose sugar with modifications that are known in the art, *e.g.*, the use of deoxyribonucleotides, 2'-deoxy-2'-fluoro (2'-F) or 2'-O-methyl modified instead of the ribosugar of the nucleobase, and modifications in the phosphate group, *e.g.*, phosphorothioate modifications. Overhangs need not be homologous with the target sequence.

In some embodiments, each residue of the sense strand and antisense strand is independently modified with LNA, HNA, CeNA, 2'-methoxyethyl, 2'- O-methyl, 2'-O-allyl, 2'-C- allyl, 2'-deoxy, or 2'-fluoro. The strands can contain more than one modification. In some embodiments, each residue of the sense strand and antisense strand is independently modified with 2'-O-methyl or 2'-fluoro. It is to be understood that these modifications are in addition to the at least one thermally destabilizing modification of the duplex present in the antisense strand.

At least two different modifications are typically present on the sense strand and antisense strand. Those two modifications may be the 2'-deoxy, 2'- O-methyl, or 2'-fluoro modifications, acyclic nucleotides or others. In some embodiments, the sense strand and antisense strand each comprises two differently modified nucleotides selected from 2'-O-methyl or 2'-deoxy. In some embodiments, each residue of the sense strand and antisense strand is independently modified with 2'-O-methyl nucleotide, 2'-deoxy nucleotide, 2'-deoxy-2'-fluoro nucleotide, 2'-O-N-methylacetamido (2'-O-NMA) nucleotide, a 2'-O-dimethylaminoethoxyethyl (2'-O-DMAEOE) nucleotide, 2'-O-aminopropyl (2'-O-AP) nucleotide, or 2'-ara-F nucleotide. Again, it is to be understood that these modifications are in addition to the at least one thermally destabilizing modification of the duplex present in the antisense strand.

In some embodiments, the dsRNA molecule of the disclosure comprises modifications of an alternating pattern, particular in the B1, B2, B3, B1', B2', B3', B4' regions. The term "alternating motif" or "alternative pattern" as used herein refers to a motif having one or more modifications, each modification occurring on alternating nucleotides of one strand. The alternating nucleotide may refer to one per every other nucleotide or one per every three nucleotides, or a similar pattern. For example, if A, B and C each represent one type of modification to the nucleotide, the alternating motif can be "ABABABABABAB…," "AABBAABBAABB…," "AABAABAABAAB…," "AAABAAABAAAB…," "AAABBBAAABBB…," or "ABCABCABCABC…," etc.

The type of modifications contained in the alternating motif may be the same or different. For example, if A, B, C, D each represent one type of modification on the nucleotide, the alternating pattern, i.e., modifications on every other nucleotide, may be the same, but each of the sense strand or antisense strand can be selected from several possibilities of modifications within the alternating motif such as "ABABAB…", "ACACAC…" "BDBDBD…" or "CDCDCD…," etc.

In some embodiments, the dsRNA molecule of the disclosure comprises the modification pattern for the alternating motif on the sense strand relative to the modification pattern for the alternating motif on the antisense strand is shifted. The shift may be such that the modified group of nucleotides of the sense strand corresponds to a differently modified group of nucleotides of the antisense strand and vice versa. For example, the sense strand when paired with the antisense strand in the dsRNA duplex, the alternating motif in the sense strand may start with "ABABAB" from 5'-3' of the strand and the alternating motif in the antisense strand may start with "BABABA" from 3'-5'of the strand within the duplex region. As another example, the alternating motif in the sense strand may start with "AABBAABB" from 5'-3' of the strand and the alternating motif in the antisense strand may start with "BBAABBAA" from 3'-5'of the strand within the duplex region, so that there is a complete or partial shift of the modification patterns between the sense strand and the antisense strand.

The dsRNA molecule of the disclosure may further comprise at least one phosphorothioate or methylphosphonate internucleotide linkage. The phosphorothioate or methylphosphonate internucleotide linkage modification may occur on any nucleotide of the sense strand or antisense strand or both in any position of the strand. For instance, the

internucleotide linkage modification may occur on every nucleotide on the sense strand or antisense strand; each internucleotide linkage modification may occur in an alternating pattern on the sense strand or antisense strand; or the sense strand or antisense strand comprises both internucleotide linkage modifications in an alternating pattern. The alternating pattern of the internucleotide linkage modification on the sense strand may be the same or different from the antisense strand, and the alternating pattern of the internucleotide linkage modification on the sense strand may have a shift relative to the alternating pattern of the internucleotide linkage modification on the antisense strand.

In some embodiments, the dsRNA molecule comprises the phosphorothioate or methylphosphonate internucleotide linkage modification in the overhang region. For example, the overhang region comprises two nucleotides having a phosphorothioate or methylphosphonate internucleotide linkage between the two nucleotides. Internucleotide linkage modifications also may be made to link the overhang nucleotides with the terminal paired nucleotides within duplex region. For example, at least 2, 3, 4, or all the overhang nucleotides may be linked through phosphorothioate or methylphosphonate internucleotide linkage, and optionally, there may be additional phosphorothioate or methylphosphonate internucleotide linkages linking the overhang nucleotide with a paired nucleotide that is next to the overhang nucleotide. For instance, there may be at least two phosphorothioate internucleotide linkages between the terminal three nucleotides, in which two of the three nucleotides are overhang nucleotides, and the third is a paired nucleotide next to the overhang nucleotide. In certain embodiments, these terminal three nucleotides may be at the 3'-end of the antisense strand.

In some embodiments, the sense strand of the dsRNA molecule comprises 1-10 blocks of two to ten phosphorothioate or methylphosphonate internucleotide linkages separated by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16 phosphate internucleotide linkages, wherein one of the phosphorothioate or methylphosphonate internucleotide linkages is placed at any position in the oligonucleotide sequence and the said sense strand is paired with an antisense strand comprising any combination of phosphorothioate, methylphosphonate, and phosphate internucleotide linkages or an antisense strand comprising either phosphorothioate or methylphosphonate or phosphate linkage.

In some embodiments, the antisense strand of the dsRNA molecule comprises two blocks of two phosphorothioate or methylphosphonate internucleotide linkages separated by 1, 2, 3, 4,

5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 phosphate internucleotide linkages, wherein one of the phosphorothioate or methylphosphonate internucleotide linkages is placed at any position in the oligonucleotide sequence and the said antisense strand is paired with a sense strand comprising any combination of phosphorothioate, methylphosphonate, and phosphate internucleotide linkages or an antisense strand comprising either phosphorothioate or methylphosphonate or phosphate linkage.

In some embodiments, the antisense strand of the dsRNA molecule comprises two blocks of three phosphorothioate or methylphosphonate internucleotide linkages separated by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16 phosphate internucleotide linkages, wherein one of the phosphorothioate or methylphosphonate internucleotide linkages is placed at any position in the oligonucleotide sequence and the said antisense strand is paired with a sense strand comprising any combination of phosphorothioate, methylphosphonate, and phosphate internucleotide linkages or an antisense strand comprising either phosphorothioate or methylphosphonate or phosphate linkage.

In some embodiments, the antisense strand of the dsRNA molecule comprises two blocks of four phosphorothioate or methylphosphonate internucleotide linkages separated by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 phosphate internucleotide linkages, wherein one of the phosphorothioate or methylphosphonate internucleotide linkages is placed at any position in the oligonucleotide sequence and the said antisense strand is paired with a sense strand comprising any combination of phosphorothioate, methylphosphonate, and phosphate internucleotide linkages or an antisense strand comprising either phosphorothioate or methylphosphonate or phosphate linkage.

In some embodiments, the antisense strand of the dsRNA molecule comprises two blocks of five phosphorothioate or methylphosphonate internucleotide linkages separated by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 phosphate internucleotide linkages, wherein one of the phosphorothioate or methylphosphonate internucleotide linkages is placed at any position in the oligonucleotide sequence and the said antisense strand is paired with a sense strand comprising any combination of phosphorothioate, methylphosphonate, and phosphate internucleotide linkages or an antisense strand comprising either phosphorothioate or methylphosphonate or phosphate linkage.

In some embodiments, the antisense strand of the dsRNA molecule comprises two blocks of six phosphorothioate or methylphosphonate internucleotide linkages separated by 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 phosphate internucleotide linkages, wherein one of the phosphorothioate or methylphosphonate internucleotide linkages is placed at any position in the oligonucleotide sequence and the said antisense strand is paired with a sense strand comprising any combination of phosphorothioate, methylphosphonate, and phosphate internucleotide linkages or an antisense strand comprising either phosphorothioate or methylphosphonate or phosphate linkage.

In some embodiments, the antisense strand of the dsRNA molecule comprises two blocks of seven phosphorothioate or methylphosphonate internucleotide linkages separated by 1, 2, 3, 4, 5, 6, 7, or 8 phosphate internucleotide linkages, wherein one of the phosphorothioate or methylphosphonate internucleotide linkages is placed at any position in the oligonucleotide sequence and the said antisense strand is paired with a sense strand comprising any combination of phosphorothioate, methylphosphonate, and phosphate internucleotide linkages or an antisense strand comprising either phosphorothioate or methylphosphonate or phosphate linkage.

In some embodiments, the antisense strand of the dsRNA molecule comprises two blocks of eight phosphorothioate or methylphosphonate internucleotide linkages separated by 1, 2, 3, 4, 5, or 6 phosphate internucleotide linkages, wherein one of the phosphorothioate or methylphosphonate internucleotide linkages is placed at any position in the oligonucleotide sequence and the said antisense strand is paired with a sense strand comprising any combination of phosphorothioate, methylphosphonate, and phosphate internucleotide linkages or an antisense strand comprising either phosphorothioate or methylphosphonate or phosphate linkage.

In some embodiments, the antisense strand of the dsRNA molecule comprises two blocks of nine phosphorothioate or methylphosphonate internucleotide linkages separated by 1, 2, 3, or 4 phosphate internucleotide linkages, wherein one of the phosphorothioate or methylphosphonate internucleotide linkages is placed at any position in the oligonucleotide sequence and the said antisense strand is paired with a sense strand comprising any combination of phosphorothioate, methylphosphonate, and phosphate internucleotide linkages or an antisense strand comprising either phosphorothioate or methylphosphonate or phosphate linkage.

In some embodiments, the dsRNA molecule of the disclosure further comprises one or more phosphorothioate or methylphosphonate internucleotide linkage modification within positions 1-10 of the termini position(s) of the sense or antisense strand. For example, at least 2,

3, 4, 5, 6, 7, 8, 9, or 10 nucleotides may be linked through phosphorothioate or methylphosphonate internucleotide linkage at one end or both ends of the sense or antisense strand.

In some embodiments, the dsRNA molecule of the disclosure further comprises one or more phosphorothioate or methylphosphonate internucleotide linkage modification within positions 1-10 of the internal region of the duplex of each of the sense or antisense strand. For example, at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides may be linked through phosphorothioate methylphosphonate internucleotide linkage at position 8-16 of the duplex region counting from the 5'-end of the sense strand; the dsRNA molecule can optionally further comprise one or more phosphorothioate or methylphosphonate internucleotide linkage modification within positions 1-10 of the termini position(s).

In some embodiments, the dsRNA molecule of the disclosure further comprises one to five phosphorothioate or methylphosphonate internucleotide linkage modification(s) within position 1-5 and one to five phosphorothioate or methylphosphonate internucleotide linkage modification(s) within position 18-23 of the sense strand (counting from the 5'-end), and one to five phosphorothioate or methylphosphonate internucleotide linkage modification at positions 1 and 2 and one to five within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises one phosphorothioate internucleotide linkage modification within position 1-5 and one phosphorothioate or methylphosphonate internucleotide linkage modification within position 18-23 of the sense strand (counting from the 5'-end), and one phosphorothioate internucleotide linkage modification at positions 1 and 2 and two phosphorothioate or methylphosphonate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications within position 1-5 and one phosphorothioate internucleotide linkage modification within position 18-23 of the sense strand (counting from the 5'-end), and one phosphorothioate internucleotide linkage modification at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications within position 1-5 and two phosphorothioate internucleotide linkage modifications within position 18-23 of the sense strand (counting from the 5'-end), and one phosphorothioate internucleotide linkage modification at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications within position 1-5 and two phosphorothioate internucleotide linkage modifications within position 18-23 of the sense strand (counting from the 5'-end), and one phosphorothioate internucleotide linkage modification at positions 1 and 2 and one phosphorothioate internucleotide linkage modification within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises one phosphorothioate internucleotide linkage modification within position 1-5 and one phosphorothioate internucleotide linkage modification within position 18-23 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises one phosphorothioate internucleotide linkage modification within position 1-5 and one within position 18-23 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modification at positions 1 and 2 and one phosphorothioate internucleotide linkage modification within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises one phosphorothioate internucleotide linkage modification within position 1-5 (counting from the 5'-end) of the sense strand, and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and one phosphorothioate internucleotide linkage modification within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications within position 1-5 (counting from the

5'-end) of the sense strand, and one phosphorothioate internucleotide linkage modification at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications within position 1-5 and one within position 18-23 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and one phosphorothioate internucleotide linkage modification within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications within position 1-5 and one phosphorothioate internucleotide linkage modification within position 18-23 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications within position 1-5 and one phosphorothioate internucleotide linkage modification within position 18-23 of the sense strand (counting from the 5'-end), and one phosphorothioate internucleotide linkage modification at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications at position 1 and 2, and two phosphorothioate internucleotide linkage modifications at position 20 and 21 of the sense strand (counting from the 5'-end), and one phosphorothioate internucleotide linkage modification at positions 1 and one at position 21 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises one phosphorothioate internucleotide linkage modification at position 1, and one phosphorothioate internucleotide linkage modification at position 21 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and

two phosphorothioate internucleotide linkage modifications at positions 20 and 21 the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications at position 1 and 2, and two phosphorothioate internucleotide linkage modifications at position 21 and 22 of the sense strand (counting from the 5'-end), and one phosphorothioate internucleotide linkage modification at positions 1 and one phosphorothioate internucleotide linkage modification at position 21 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises one phosphorothioate internucleotide linkage modification at position 1, and one phosphorothioate internucleotide linkage modification at position 21 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications at positions 21 and 22 the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications at position 1 and 2, and two phosphorothioate internucleotide linkage modifications at position 22 and 23 of the sense strand (counting from the 5'-end), and one phosphorothioate internucleotide linkage modification at positions 1 and one phosphorothioate internucleotide linkage modification at position 21 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises one phosphorothioate internucleotide linkage modification at position 1, and one phosphorothioate internucleotide linkage modification at position 21 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications at positions 23 and 23 the antisense strand (counting from the 5'-end).

In some embodiments, compound of the disclosure comprises a pattern of backbone chiral centers. In some embodiments, a common pattern of backbone chiral centers comprises at least 5 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 6 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at

least 7 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 8 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 9 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 10 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 11 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 12 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 13 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 14 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 15 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 16 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 17 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 18 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 19 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises no more than 8 internucleotidic linkages in the Rp configuration. In some embodiments, a common pattern of backbone chiral centers comprises no more than 7 internucleotidic linkages in the Rp configuration. In some embodiments, a common pattern of backbone chiral centers comprises no more than 6 internucleotidic linkages in the Rp configuration. In some embodiments, a common pattern of backbone chiral centers comprises no more than 5 internucleotidic linkages in the Rp configuration. In some embodiments, a common pattern of backbone chiral centers comprises no more than 4 internucleotidic linkages in the Rp configuration. In some embodiments, a common pattern of backbone chiral centers comprises no more than 3 internucleotidic linkages in the Rp configuration. In some embodiments, a common pattern of backbone chiral centers comprises no more than 2 internucleotidic linkages in the Rp configuration. In some embodiments, a common pattern of backbone chiral centers comprises no more than 1 internucleotidic linkages

in the Rp configuration. In some embodiments, a common pattern of backbone chiral centers comprises no more than 8 internucleotidic linkages which are not chiral (as a non-limiting example, a phosphodiester). In some embodiments, a common pattern of backbone chiral centers comprises no more than 7 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises no more than 6 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises no more than 5 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises no more than 4 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises no more than 3 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises no more than 2 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises no more than 1 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises at least 10 internucleotidic linkages in the Sp configuration, and no more than 8 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises at least 11 internucleotidic linkages in the Sp configuration, and no more than 7 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises at least 12 internucleotidic linkages in the Sp configuration, and no more than 6 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises at least 13 internucleotidic linkages in the Sp configuration, and no more than 6 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises at least 14 internucleotidic linkages in the Sp configuration, and no more than 5 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises at least 15 internucleotidic linkages in the Sp configuration, and no more than 4 internucleotidic linkages which are not chiral. In some embodiments, the internucleotidic linkages in the Sp configuration are optionally contiguous or not contiguous. In some embodiments, the internucleotidic linkages in the Rp configuration are optionally contiguous or not contiguous. In some embodiments, the internucleotidic linkages which are not chiral are optionally contiguous or not contiguous.

In some embodiments, compound of the disclosure comprises a block is a stereochemistry block. In some embodiments, a block is an Rp block in that each internucleotidic linkage of the block is Rp. In some embodiments, a 5'-block is an Rp block. In some embodiments, a 3'-block is an Rp block. In some embodiments, a block is an Sp block in that each internucleotidic linkage of the block is Sp. In some embodiments, a 5'-block is an Sp block. In some embodiments, a 3'-block is an Sp block. In some embodiments, provided oligonucleotides comprise both Rp and Sp blocks. In some embodiments, provided oligonucleotides comprise one or more Rp but no Sp blocks. In some embodiments, provided oligonucleotides comprise one or more Sp but no Rp blocks. In some embodiments, provided oligonucleotides comprise one or more PO blocks wherein each internucleotidic linkage in a natural phosphate linkage.

In some embodiments, compound of the disclosure comprises a 5'-block is an Sp block wherein each sugar moiety comprises a 2'-F modification. In some embodiments, a 5'-block is an Sp block wherein each of internucleotidic linkage is a modified internucleotidic linkage and each sugar moiety comprises a 2'-F modification. In some embodiments, a 5'-block is an Sp block wherein each of internucleotidic linkage is a phosphorothioate linkage and each sugar moiety comprises a 2'-F modification. In some embodiments, a 5'-block comprises 4 or more nucleoside units. In some embodiments, a 5'-block comprises 5 or more nucleoside units. In some embodiments, a 5'-block comprises 6 or more nucleoside units. In some embodiments, a 5'-block comprises 7 or more nucleoside units. In some embodiments, a 3'-block is an Sp block wherein each sugar moiety comprises a 2'-F modification. In some embodiments, a 3'-block is an Sp block wherein each of internucleotidic linkage is a modified internucleotidic linkage and each sugar moiety comprises a 2'-F modification. In some embodiments, a 3'-block is an Sp block wherein each of internucleotidic linkage is a phosphorothioate linkage and each sugar moiety comprises a 2'-F modification. In some embodiments, a 3'-block comprises 4 or more nucleoside units. In some embodiments, a 3'-block comprises 5 or more nucleoside units. In some embodiments, a 3'-block comprises 6 or more nucleoside units. In some embodiments, a 3'-block comprises 7 or more nucleoside units.

In some embodiments, compound of the disclosure comprises a type of nucleoside in a region or an oligonucleotide is followed by a specific type of internucleotidic linkage, *e.g.*, natural phosphate linkage, modified internucleotidic linkage, Rp chiral internucleotidic linkage,

Sp chiral internucleotidic linkage, etc. In some embodiments, A is followed by Sp. In some embodiments, A is followed by Rp. In some embodiments, A is followed by natural phosphate linkage (PO). In some embodiments, U is followed by Sp. In some embodiments, U is followed by Rp. In some embodiments, U is followed by natural phosphate linkage (PO). In some embodiments, C is followed by Sp. In some embodiments, C is followed by Rp. In some embodiments, C is followed by natural phosphate linkage (PO). In some embodiments, G is followed by Sp. In some embodiments, G is followed by Rp. In some embodiments, G is followed by natural phosphate linkage (PO). In some embodiments, C and U are followed by Sp. In some embodiments, C and U are followed by Rp. In some embodiments, C and U are followed by natural phosphate linkage (PO). In some embodiments, A and G are followed by Sp. In some embodiments, A and G are followed by Rp.

In some embodiments, the dsRNA molecule of the disclosure comprises mismatch(es) with the target, within the duplex, or combinations thereof. The mismatch can occur in the overhang region or the duplex region. The base pair can be ranked on the basis of their propensity to promote dissociation or melting (*e.g.*, on the free energy of association or dissociation of a particular pairing, the simplest approach is to examine the pairs on an individual pair basis, though next neighbor or similar analysis can also be used). In terms of promoting dissociation: A:U is preferred over G:C; G:U is preferred over G:C; and I:C is preferred over G:C (I=inosine). Mismatches, *e.g.*, non-canonical or other than canonical pairings (as described elsewhere herein) are preferred over canonical (A:T, A:U, G:C) pairings; and pairings which include a universal base are preferred over canonical pairings.

In some embodiments, the dsRNA molecule of the disclosure comprises at least one of the first 1, 2, 3, 4, or 5 base pairs within the duplex regions from the 5'- end of the antisense strand can be chosen independently from the group of: A:U, G:U, I:C, and mismatched pairs, *e.g.*, non-canonical or other than canonical pairings or pairings which include a universal base, to promote the dissociation of the antisense strand at the 5'-end of the duplex.

In some embodiments, the nucleotide at the 1 position within the duplex region from the 5'-end in the antisense strand is selected from the group consisting of A, dA, dU, U, and dT. Alternatively, at least one of the first 1, 2 or 3 base pair within the duplex region from the 5'- end of the antisense strand is an AU base pair. For example, the first base pair within the duplex region from the 5'- end of the antisense strand is an AU base pair.

It was found that introducing 4'-modified or 5'-modified nucleotide to the 3'-end of a phosphodiester (PO), phosphorothioate (PS), or phosphorodithioate (PS2) linkage of a dinucleotide at any position of single stranded or double stranded oligonucleotide can exert steric effect to the internucleotide linkage and, hence, protecting or stabilizing it against nucleases.

In some embodiments, 5'-modified nucleoside is introduced at the 3'-end of a dinucleotide at any position of single stranded or double stranded siRNA. For instance, a 5'-alkylated nucleoside may be introduced at the 3'-end of a dinucleotide at any position of single stranded or double stranded siRNA. The alkyl group at the 5' position of the ribose sugar can be racemic or chirally pure *R* or *S* isomer. An exemplary 5'-alkylated nucleoside is 5'-methyl nucleoside. The 5'-methyl can be either racemic or chirally pure *R* or *S* isomer.

In some embodiments, 4'-modified nucleoside is introduced at the 3'-end of a dinucleotide at any position of single stranded or double stranded siRNA. For instance, a 4'-alkylated nucleoside may be introduced at the 3'-end of a dinucleotide at any position of single stranded or double stranded siRNA. The alkyl group at the 4' position of the ribose sugar can be racemic or chirally pure *R* or *S* isomer. An exemplary 4'-alkylated nucleoside is 4'-methyl nucleoside. The 4'-methyl can be either racemic or chirally pure *R* or *S* isomer. Alternatively, a 4'-*O*-alkylated nucleoside may be introduced at the 3'-end of a dinucleotide at any position of single stranded or double stranded siRNA. The 4'-*O*-alkyl of the ribose sugar can be racemic or chirally pure *R* or *S* isomer. An exemplary 4'-*O*-alkylated nucleoside is 4'-*O*-methyl nucleoside. The 4'-*O*-methyl can be either racemic or chirally pure *R* or *S* isomer.

In some embodiments, 5'-alkylated nucleoside is introduced at any position on the sense strand or antisense strand of a dsRNA, and such modification maintains or improves potency of the dsRNA. The 5'-alkyl can be either racemic or chirally pure *R* or *S* isomer. An exemplary 5'-alkylated nucleoside is 5'-methyl nucleoside. The 5'-methyl can be either racemic or chirally pure *R* or *S* isomer.

In some embodiments, 4'-alkylated nucleoside is introduced at any position on the sense strand or antisense strand of a dsRNA, and such modification maintains or improves potency of the dsRNA. The 4'-alkyl can be either racemic or chirally pure *R* or *S* isomer. An exemplary 4'-alkylated nucleoside is 4'-methyl nucleoside. The 4'-methyl can be either racemic or chirally pure *R* or *S* isomer.

In some embodiments, 4'-*O*-alkylated nucleoside is introduced at any position on the sense strand or antisense strand of a dsRNA, and such modification maintains or improves potency of the dsRNA. The 5'-alkyl can be either racemic or chirally pure *R* or *S* isomer. An exemplary 4'-*O*-alkylated nucleoside is 4'-*O*-methyl nucleoside. The 4'-*O*-methyl can be either racemic or chirally pure *R* or *S* isomer.

In some embodiments, the dsRNA molecule of the disclosure can comprise 2'-5' linkages (with 2'-H, 2'-OH, and 2'-OMe and with P=O or P=S). For example, the 2'-5' linkages modifications can be used to promote nuclease resistance or to inhibit binding of the sense to the antisense strand, or can be used at the 5' end of the sense strand to avoid sense strand activation by RISC.

In another embodiment, the dsRNA molecule of the disclosure can comprise L sugars (*e.g.*, L ribose, L-arabinose with 2'-H, 2'-OH and 2'-OMe). For example, these L sugars modifications can be used to promote nuclease resistance or to inhibit binding of the sense to the antisense strand, or can be used at the 5' end of the sense strand to avoid sense strand activation by RISC.

Various publications describe multimeric siRNA which can all be used with the dsRNA of the disclosure. Such publications include WO2007/091269, US 7858769, WO2010/141511, WO2007/117686, WO2009/014887, and WO2011/031520 which are hereby incorporated by their entirely.

In some embodiments dsRNA molecules of the disclosure are 5' phosphorylated or include a phosphoryl analog at the 5' prime terminus. 5'-phosphate modifications include those which are compatible with RISC mediated gene silencing. Suitable modifications include: 5'-monophosphate ($(HO)_2(O)P$-O-5'); 5'-diphosphate ($(HO)_2(O)P$-O-P(HO)(O)-O-5'); 5'-triphosphate ($(HO)_2(O)P$-O-(HO)(O)P-O-P(HO)(O)-O-5'); 5'-guanosine cap (7-methylated or non-methylated) (7m-G-O-5'-(HO)(O)P-O-(HO)(O)P-O-P(HO)(O)-O-5'); 5'-adenosine cap (Appp), and any modified or unmodified nucleotide cap structure (N-O-5'-(HO)(O)P-O-(HO)(O)P-O-P(HO)(O)-O-5'); 5'-monothiophosphate (phosphorothioate; $(HO)_2(S)P$-O-5'); 5'-monodithiophosphate (phosphorodithioate; (HO)(HS)(S)P-O-5'), 5'-phosphorothiolate ((HO)2(O)P-S-5'); any additional combination of oxygen/sulfur replaced monophosphate, diphosphate and triphosphates (e.g. 5'-alpha-thiotriphosphate, 5'-gamma-thiotriphosphate, etc.), 5'-phosphoramidates ($(HO)_2(O)P$-NH-5', $(HO)(NH_2)(O)P$-O-5'), 5'-alkylphosphonates

(R=alkyl=methyl, ethyl, isopropyl, propyl, etc., e.g. RP(OH)(O)-O-5'-, 5'-alkenylphosphonates (i.e. vinyl, substituted vinyl), $(OH)_2(O)P$-5'-CH_2-), 5'-alkyletherphosphonates (R=alkylether=methoxymethyl (MeOCH_2-), ethoxymethyl, etc., e.g. RP(OH)(O)-O-5'-). In one example, the modification can in placed in the antisense strand of a dsRNA molecule.

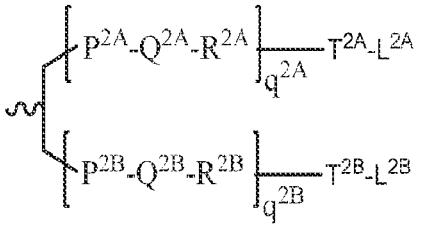
F. Linkers

In some embodiments, the conjugate or ligand described herein can be attached to an iRNA oligonucleotide with various linkers that can be cleavable or non-cleavable.

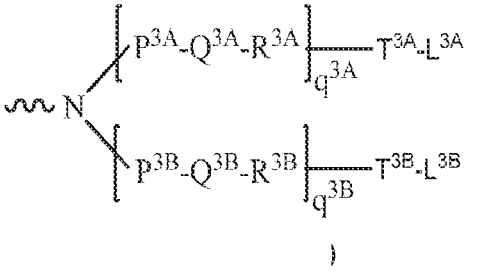
Linkers typically comprise a direct bond or an atom such as oxygen or sulfur, a unit such as NR8, C(O), C(O)NH, SO, SO_2, SO_2NH or a chain of atoms, such as, but not limited to, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkylarylalkyl, alkylarylalkenyl, alkylarylalkynyl, alkenylarylalkyl, alkenylarylalkenyl, alkenylarylalkynyl, alkynylarylalkyl, alkynylarylalkenyl, alkynylarylalkynyl, alkylheteroarylalkyl, alkylheteroarylalkenyl, alkylheteroarylalkynyl, alkenylheteroarylalkyl, alkenylheteroarylalkenyl, alkenylheteroarylalkynyl, alkynylheteroarylalkyl, alkynylheteroarylalkenyl, alkynylheteroarylalkynyl, alkylheterocyclylalkyl, alkylheterocyclylalkenyl, alkylhererocyclylalkynyl, alkenylheterocyclylalkyl, alkenylheterocyclylalkenyl, alkenylheterocyclylalkynyl, alkynylheterocyclylalkyl, alkynylheterocyclylalkenyl, alkynylheterocyclylalkynyl, alkylaryl, alkenylaryl, alkynylaryl, alkylheteroaryl, alkenylheteroaryl, alkynylhereroaryl, which one or more methylenes can be interrupted or terminated by O, S, S(O), SO_2, N(R8), C(O), substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic; where R8 is hydrogen, acyl, aliphatic or substituted aliphatic. In some embodiments, the linker is between about 1-24 atoms, 2-24, 3-24, 4-24, 5-24, 6-24, 6-18, 7-18, 8-18 atoms, 7-17, 8-17, 6-16, 7-16, or 8-16 atoms.

In some embodiments, a dsRNA of the disclosure is conjugated to a bivalent or trivalent branched linker selected from the group of structures shown in any of formula (XXXI) – (XXXIV):

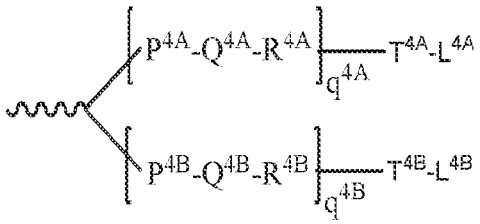
Formula XXXI



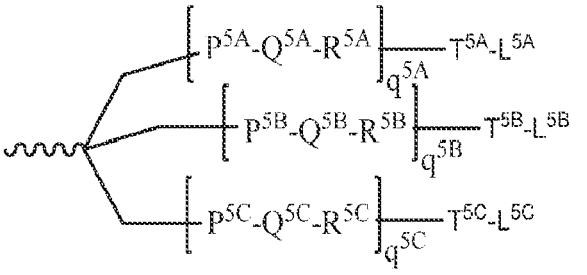
Formula XXXII



Formula XXXIII



Formula XXXIV



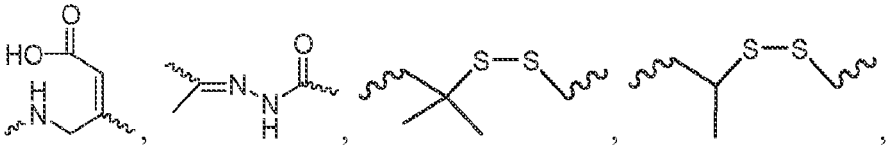
wherein:

q2A, q2B, q3A, q3B, q4A, q4B, q5A, q5B and q5C represent independently for each occurrence 0-20 and wherein the repeating unit can be the same or different;

P^{2A}, P^{2B}, P^{3A}, P^{3B}, P^{4A}, P^{4B}, P^{5A}, P^{5B}, P^{5C}, T^{2A}, T^{2B}, T^{3A}, T^{3B}, T^{4A}, T^{4B}, T^{4A}, T^{5B}, T^{5C} are each independently for each occurrence absent, CO, NH, O, S, OC(O), NHC(O), CH_2, CH_2NH or CH_2O;

Q^{2A}, Q^{2B}, Q^{3A}, Q^{3B}, Q^{4A}, Q^{4B}, Q^{5A}, Q^{5B}, Q^{5C} are independently for each occurrence absent, alkylene, substituted alkylene wherein one or more methylenes can be interrupted or terminated by one or more of O, S, S(O), SO_2, $N(R^N)$, C(R')=C(R''), C≡C or C(O);

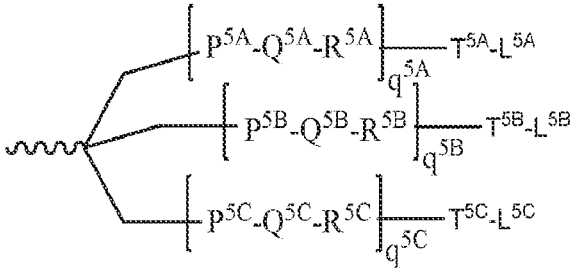
R^{2A}, R^{2B}, R^{3A}, R^{3B}, R^{4A}, R^{4B}, R^{5A}, R^{5B}, R^{5C} are each independently for each occurrence absent, NH, O, S, CH_2, C(O)O, C(O)NH, $NHCH(R^a)C(O)$, -C(O)-$CH(R^a)$-NH-, CO, CH=N-O,




or heterocyclyl;

L^{2A}, L^{2B}, L^{3A}, L^{3B}, L^{4A}, L^{4B}, L^{5A}, L^{5B} and L^{5C} represent the ligand; *i.e.* each independently for each occurrence a monosaccharide (such as GalNAc), disaccharide, trisaccharide, tetrasaccharide, oligosaccharide, or polysaccharide; and R^a is H or amino acid side chain. Trivalent conjugating GalNAc derivatives are particularly useful for use with RNAi agents for inhibiting the expression of a target gene, such as those of formula (XXXV):

Formula XXXV



,

wherein L^{5A}, L^{5B} and L^{5C} represent a monosaccharide, such as GalNAc derivative.

Examples of suitable bivalent and trivalent branched linker groups conjugating GalNAc derivatives include, but are not limited to, the structures recited above as formulas II, VII, XI, X, and XIII.

A cleavable linking group is one which is sufficiently stable outside the cell, but which upon entry into a target cell is cleaved to release the two parts the linker is holding together. In a some embodiments, the cleavable linking group is cleaved at least about 10 times, 20, times, 30 times, 40 times, 50 times, 60 times, 70 times, 80 times, 90 times or more, or at least about 100 times faster in a target cell or under a first reference condition (which can, *e.g.*, be selected to mimic or represent intracellular conditions) than in the blood of a subject, or under a second reference condition (which can, *e.g.*, be selected to mimic or represent conditions found in the blood or serum).

Cleavable linking groups are susceptible to cleavage agents, *e.g.*, pH, redox potential or the presence of degradative molecules. Generally, cleavage agents are more prevalent or found at higher levels or activities inside cells than in serum or blood. Examples of such degradative agents include: redox agents which are selected for particular substrates or which have no substrate specificity, including, *e.g.*, oxidative or reductive enzymes or reductive agents such as mercaptans, present in cells, that can degrade a redox cleavable linking group by reduction; esterases; endosomes or agents that can create an acidic environment, *e.g.*, those that result in a

pH of five or lower; enzymes that can hydrolyze or degrade an acid cleavable linking group by acting as a general acid, peptidases (which can be substrate specific), and phosphatases.

A cleavable linkage group, such as a disulfide bond can be susceptible to pH. The pH of human serum is 7.4, while the average intracellular pH is slightly lower, ranging from about 7.1-7.3. Endosomes have a more acidic pH, in the range of 5.5-6.0, and lysosomes have an even more acidic pH at around 5.0. Some linkers will have a cleavable linking group that is cleaved at a suitable pH, thereby releasing a cationic lipid from the ligand inside the cell, or into the desired compartment of the cell.

A linker can include a cleavable linking group that is cleavable by a particular enzyme. The type of cleavable linking group incorporated into a linker can depend on the cell to be targeted.

In general, the suitability of a candidate cleavable linking group can be evaluated by testing the ability of a degradative agent (or condition) to cleave the candidate linking group. It will also be desirable to also test the candidate cleavable linking group for the ability to resist cleavage in the blood or when in contact with other non-target tissue. Thus, one can determine the relative susceptibility to cleavage between a first and a second condition, where the first is selected to be indicative of cleavage in a target cell and the second is selected to be indicative of cleavage in other tissues or biological fluids, *e.g.*, blood or serum. The evaluations can be carried out in cell free systems, in cells, in cell culture, in organ or tissue culture, or in whole animals. It can be useful to make initial evaluations in cell-free or culture conditions and to confirm by further evaluations in whole animals. In some embodiments, useful candidate compounds are cleaved at least about 2, 4, 10, 20, 30, 40, 50, 60, 70, 80, 90, or about 100 times faster in the cell (or under *in vitro* conditions selected to mimic intracellular conditions) as compared to blood or serum (or under *in vitro* conditions selected to mimic extracellular conditions).

i. Redox cleavable linking groups

In some embodiments, a cleavable linking group is a redox cleavable linking group that is cleaved upon reduction or oxidation. An example of reductively cleavable linking group is a disulphide linking group (-S-S-). To determine if a candidate cleavable linking group is a suitable "reductively cleavable linking group," or for example is suitable for use with a particular

iRNA moiety and particular targeting agent one can look to methods described herein. For example, a candidate can be evaluated by incubation with dithiothreitol (DTT), or other reducing agent using reagents know in the art, which mimic the rate of cleavage which would be observed in a cell, *e.g.*, a target cell. The candidates can also be evaluated under conditions which are selected to mimic blood or serum conditions. In one, candidate compounds are cleaved by at most about 10% in the blood. In other embodiments, useful candidate compounds are degraded at least about 2, 4, 10, 20, 30, 40, 50, 60, 70, 80, 90, or about 100 times faster in the cell (or under *in vitro* conditions selected to mimic intracellular conditions) as compared to blood (or under *in vitro* conditions selected to mimic extracellular conditions). The rate of cleavage of candidate compounds can be determined using standard enzyme kinetics assays under conditions chosen to mimic intracellular media and compared to conditions chosen to mimic extracellular media.

ii. Phosphate-based cleavable linking groups

In some embodiments, a cleavable linker comprises a phosphate-based cleavable linking group. A phosphate-based cleavable linking group is cleaved by agents that degrade or hydrolyze the phosphate group. An example of an agent that cleaves phosphate groups in cells are enzymes such as phosphatases in cells. Examples of phosphate-based linking groups are -O-P(O)(ORk)-O-, -O-P(S)(ORk)-O-, -O-P(S)(SRk)-O-, -S-P(O)(ORk)-O-, -O-P(O)(ORk)-S-, -S-P(O)(ORk)-S-, -O-P(S)(ORk)-S-, -S-P(S)(ORk)-O-, -O-P(O)(Rk)-O-, -O-P(S)(Rk)-O-, -S-P(O)(Rk)-O-, -S-P(S)(Rk)-O-, -S-P(O)(Rk)-S-, -O-P(S)(Rk)-S-. In some embodiments, phosphate-based linking groups are -O-P(O)(OH)-O-, -O-P(S)(OH)-O-, -O-P(S)(SH)-O-, -S-P(O)(OH)-O-, -O-P(O)(OH)-S-, -S-P(O)(OH)-S-, -O-P(S)(OH)-S-, -S-P(S)(OH)-O-, -O-P(O)(H)-O-, -O-P(S)(H)-O-, -S-P(O)(H)-O, -S-P(S)(H)-O-, -S-P(O)(H)-S-, -O-P(S)(H)-S--, wherein Rk at each occurrence can be, independently, C1-C20 alkyl, C1-C20 haloalkyl, C6-C10 aryl, or C7-C12 aralkyl. In some embodiments, a phosphate-based linking group is -O-P(O)(OH)-O-. These candidates can be evaluated using methods analogous to those described above.

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iii. Acid cleavable linking groups

In some embodiments, a cleavable linker comprises an acid cleavable linking group. An acid cleavable linking group is a linking group that is cleaved under acidic conditions. In some embodiments acid cleavable linking groups are cleaved in an acidic environment with a pH of about 6.5 or lower (*e.g.*, about 6.0, 5.75, 5.5, 5.25, 5.0, or lower), or by agents such as enzymes that can act as a general acid. In a cell, specific low pH organelles, such as endosomes and lysosomes can provide a cleaving environment for acid cleavable linking groups. Examples of acid cleavable linking groups include but are not limited to hydrazones, esters, and esters of amino acids. Acid cleavable groups can have the general formula -C=NN-, C(O)O, or -OC(O). In some embodiments, the carbon attached to the oxygen of the ester (the alkoxy group) is an aryl group, substituted alkyl group, or tertiary alkyl group such as dimethyl pentyl or t-butyl. These candidates can be evaluated using methods analogous to those described above.

iv. Ester-based cleavable linking groups

In some embodiments, a cleavable linker comprises an ester-based cleavable linking group. An ester-based cleavable linking group is cleaved by enzymes such as esterases and amidases in cells. Examples of ester-based cleavable linking groups include but are not limited to esters of alkylene, alkenylene and alkynylene groups. Ester cleavable linking groups have the general formula -C(O)O-, or -OC(O)-. These candidates can be evaluated using methods analogous to those described above.

v. Peptide-based cleavable linking groups

In some embodiments, a cleavable linker comprises a peptide-based cleavable linking group. A peptide-based cleavable linking group is cleaved by enzymes such as peptidases and proteases in cells. Peptide-based cleavable linking groups are peptide bonds formed between amino acids to yield oligopeptides (*e.g.*, dipeptides, tripeptides *etc.*) and polypeptides. Peptide-based cleavable groups do not include the amide group (-C(O)NH-). The amide group can be formed between any alkylene, alkenylene or alkynelene. A peptide bond is a special type of amide bond formed between amino acids to yield peptides and proteins. The peptide-based cleavage group is generally limited to the peptide bond (*i.e.*, the amide bond) formed between

amino acids yielding peptides and proteins and does not include the entire amide functional group. Peptide-based cleavable linking groups have the general formula – $NHCHR^{A}C(O)NHCHR^{B}C(O)$-, where R^{A} and R^{B} are the R groups of the two adjacent amino acids. These candidates can be evaluated using methods analogous to those described above.

Representative U.S. patents that teach the preparation of RNA conjugates include, but are not limited to, U.S. Pat. Nos. 4,828,979; 4,948,882; 5,218,105; 5,525,465; 5,541,313; 5,545,730; 5,552,538; 5,578,717, 5,580,731; 5,591,584; 5,109,124; 5,118,802; 5,138,045; 5,414,077; 5,486,603; 5,512,439; 5,578,718; 5,608,046; 4,587,044; 4,605,735; 4,667,025; 4,762,779; 4,789,737; 4,824,941; 4,835,263; 4,876,335; 4,904,582; 4,958,013; 5,082,830; 5,112,963; 5,214,136; 5,082,830; 5,112,963; 5,214,136; 5,245,022; 5,254,469; 5,258,506; 5,262,536; 5,272,250; 5,292,873; 5,317,098; 5,371,241, 5,391,723; 5,416,203, 5,451,463; 5,510,475; 5,512,667; 5,514,785; 5,565,552; 5,567,810; 5,574,142; 5,585,481; 5,587,371; 5,595,726; 5,597,696; 5,599,923; 5,599,928 and 5,688,941; 6,294,664; 6,320,017; 6,576,752; 6,783,931; 6,900,297; 7,037,646; 8,106,022, the entire contents of each of which is herein incorporated by reference.

It is not necessary for all positions in a given compound to be uniformly modified, and in fact more than one of the aforementioned modifications may be incorporated in a single compound or even at a single nucleoside within an iRNA. The present disclosure also includes iRNA compounds that are chimeric compounds.

"Chimeric" iRNA compounds, or "chimeras," in the context of the present disclosure, are iRNA compounds, *e.g.*, dsRNAs, that contain two or more chemically distinct regions, each made up of at least one monomer unit, *i.e.*, a nucleotide in the case of a dsRNA compound. These iRNAs typically contain at least one region wherein the RNA is modified so as to confer upon the iRNA increased resistance to nuclease degradation, increased cellular uptake, and/or increased binding affinity for the target nucleic acid. An additional region of the iRNA may serve as a substrate for enzymes capable of cleaving RNA:DNA or RNA:RNA hybrids. By way of example, RNase H is a cellular endonuclease which cleaves the RNA strand of an RNA:DNA duplex. Activation of RNase H, therefore, results in cleavage of the RNA target, thereby greatly enhancing the efficiency of iRNA inhibition of gene expression. Consequently, comparable results can often be obtained with shorter iRNAs when chimeric dsRNAs are used, compared to phosphorothioate deoxy dsRNAs hybridizing to the same target region. Cleavage of the RNA

target can be routinely detected by gel electrophoresis and, if necessary, associated nucleic acid hybridization techniques known in the art.

In certain instances, the RNA of an iRNA can be modified by a non-ligand group. A number of non-ligand molecules have been conjugated to iRNAs in order to enhance the activity, cellular distribution or cellular uptake of the iRNA, and procedures for performing such conjugations are available in the scientific literature. Such non-ligand moieties have included lipid moieties, such as cholesterol (Kubo, T. *et al.*, *Biochem. Biophys. Res. Comm.*, 2007, 365(1):54-61; Letsinger *et al.*, *Proc. Natl. Acad. Sci. USA*, 1989, 86:6553), cholic acid (Manoharan *et al.*, *Bioorg. Med. Chem. Lett.*, 1994, 4:1053), a thioether, *e.g.*, hexyl-S-tritylthiol (Manoharan *et al.*, *Ann. N.Y. Acad. Sci.*, 1992, 660:306; Manoharan *et al.*, *Bioorg. Med. Chem. Let.*, 1993, 3:2765), a thiocholesterol (Oberhauser *et al.*, *Nucl. Acids Res.*, 1992, 20:533), an aliphatic chain, *e.g.*, dodecandiol or undecyl residues (Saison-Behmoaras *et al.*, *EMBO J.*, 1991, 10:111; Kabanov *et al.*, *FEBS Lett.*, 1990, 259:327; Svinarchuk *et al.*, *Biochimie*, 1993, 75:49), a phospholipid, *e.g.*, di-hexadecyl-rac-glycerol or triethylammonium 1,2-di-O-hexadecyl-rac-glycero-3-H-phosphonate (Manoharan *et al.*, *Tetrahedron Lett.*, 1995, 36:3651; Shea *et al.*, *Nucl. Acids Res.*, 1990, 18:3777), a polyamine or a polyethylene glycol chain (Manoharan *et al.*, Nucleosides & Nucleotides, 1995, 14:969), or adamantane acetic acid (Manoharan *et al.*, Tetrahedron Lett., 1995, 36:3651), a palmityl moiety (Mishra *et al.*, *Biochim. Biophys. Acta*, 1995, 1264:229), or an octadecylamine or hexylamino-carbonyl-oxycholesterol moiety (Crooke *et al.*, *J. Pharmacol. Exp. Ther.*, 1996, 277:923). Representative United States patents that teach the preparation of such RNA conjugates have been listed above. Typical conjugation protocols involve the synthesis of an RNAs bearing an aminolinker at one or more positions of the sequence. The amino group is then reacted with the molecule being conjugated using appropriate coupling or activating reagents. The conjugation reaction may be performed either with the RNA still bound to the solid support or following cleavage of the RNA, in solution phase. Purification of the RNA conjugate by HPLC typically affords the pure conjugate.

V. Delivery of iRNA

The delivery of an iRNA to a subject in need thereof can be achieved in a number of different ways. *In vivo* delivery can be performed directly by administering a composition comprising an iRNA, *e.g.* a dsRNA, to a subject. Alternatively, delivery can be performed

indirectly by administering one or more vectors that encode and direct the expression of the iRNA. These alternatives are discussed further below.

A. Direct delivery

In general, any method of delivering a nucleic acid molecule can be adapted for use with an iRNA (*see e.g.,* Akhtar S. and Julian RL. (1992) *Trends Cell. Biol.* 2(5):139-144 and WO94/02595, which are incorporated herein by reference in their entireties). However, there are three factors that are important to consider in order to successfully deliver an iRNA molecule *in vivo*: (a) biological stability of the delivered molecule, (2) preventing non-specific effects, and (3) accumulation of the delivered molecule in the target tissue. The non-specific effects of an iRNA can be minimized by local administration, for example by direct injection or implantation into a tissue (as a non-limiting example, the eye) or topically administering the preparation. Local administration to a treatment site maximizes local concentration of the agent, limits the exposure of the agent to systemic tissues that may otherwise be harmed by the agent or that may degrade the agent, and permits a lower total dose of the iRNA molecule to be administered. Several studies have shown successful knockdown of gene products when an iRNA is administered locally. For example, intraocular delivery of a dsRNA by intravitreal injection in cynomolgus monkeys (Tolentino, MJ., *et al* (2004) *Retina* 24:132-138) and subretinal injections in mice (Reich, SJ., *et al* (2003) *Mol. Vis.* 9:210-216) were both shown to prevent neovascularization in an experimental model of age-related macular degeneration. In addition, direct intratumoral injection of a dsRNA in mice reduces tumor volume (Pille, J., *et al* (2005) *Mol. Ther.*11:267-274) and can prolong survival of tumor-bearing mice (Kim, WJ., *et al* (2006) *Mol. Ther.* 14:343-350; Li, S., *et al* (2007) *Mol. Ther.* 15:515-523). RNA interference has also shown success with local delivery to the CNS by direct injection (Dorn, G., *et al.* (2004) *Nucleic Acids* 32:e49; Tan, PH., *et al* (2005) *Gene Ther.* 12:59-66; Makimura, H., *et al* (2002) *BMC Neurosci.* 3:18; Shishkina, GT., *et al* (2004) *Neuroscience* 129:521-528; Thakker, ER., *et al* (2004) *Proc. Natl. Acad. Sci. U.S.A.* 101:17270-17275; Akaneya,Y., *et al* (2005) *J. Neurophysiol.* 93:594-602) and to the lungs by intranasal administration (Howard, KA., *et al* (2006) *Mol. Ther.* 14:476-484; Zhang, X., *et al* (2004) *J. Biol. Chem.* 279:10677-10684; Bitko, V., *et al* (2005) *Nat. Med.* 11:50-55). For administering an iRNA systemically for the treatment of a disease, the RNA can be modified or alternatively delivered using a drug delivery system;

both methods act to prevent the rapid degradation of the dsRNA by endo- and exo-nucleases *in vivo*.

Modification of the RNA or the pharmaceutical carrier can also permit targeting of the iRNA composition to the target tissue and avoid undesirable off-target effects. iRNA molecules can be modified by chemical conjugation to other groups, *e.g.*, a lipid or carbohydrate group as described herein. Such conjugates can be used to target iRNA to particular cells, *e.g.*, liver cells, *e.g.*, hepatocytes. For example, GalNAc conjugates or lipid (*e.g.*, LNP) formulations can be used to target iRNA to particular cells, *e.g.*, liver cells, *e.g.*, hepatocytes.

iRNA molecules can also be modified by chemical conjugation to lipophilic groups such as cholesterol to enhance cellular uptake and prevent degradation. For example, an iRNA directed against ApoB conjugated to a lipophilic cholesterol moiety was injected systemically into mice and resulted in knockdown of apoB mRNA in both the liver and jejunum (Soutschek, J., *et al* (2004) *Nature* 432:173-178). Conjugation of an iRNA to an aptamer has been shown to inhibit tumor growth and mediate tumor regression in a mouse model of prostate cancer (McNamara, JO., *et al* (2006) *Nat. Biotechnol.* 24:1005-1015). In an alternative embodiment, the iRNA can be delivered using drug delivery systems such as a nanoparticle, a dendrimer, a polymer, liposomes, or a cationic delivery system. Positively charged cationic delivery systems facilitate binding of an iRNA molecule (negatively charged) and also enhance interactions at the negatively charged cell membrane to permit efficient uptake of an iRNA by the cell. Cationic lipids, dendrimers, or polymers can either be bound to an iRNA, or induced to form a vesicle or micelle (*see e.g.*, Kim SH., *et al* (2008) *Journal of Controlled Release* 129(2):107-116) that encases an iRNA. The formation of vesicles or micelles further prevents degradation of the iRNA when administered systemically. Methods for making and administering cationic- iRNA complexes are well within the abilities of one skilled in the art (*see e.g.*, Sorensen, DR., *et al* (2003) *J. Mol. Biol* 327:761-766; Verma, UN., *et al* (2003) *Clin. Cancer Res.* 9:1291-1300; Arnold, AS *et al* (2007) *J. Hypertens.* 25:197-205, which are incorporated herein by reference in their entirety). Some non-limiting examples of drug delivery systems useful for systemic delivery of iRNAs include DOTAP (Sorensen, DR., *et al* (2003), supra; Verma, UN., *et al* (2003), supra), Oligofectamine, "solid nucleic acid lipid particles" (Zimmermann, TS., *et al* (2006) *Nature* 441:111-114), cardiolipin (Chien, PY., *et al* (2005) Cancer Gene Ther. 12:321-328; Pal, A., *et al* (2005) *Int J. Oncol.* 26:1087-1091), polyethyleneimine (Bonnet ME., *et al*

(2008) *Pharm. Res.* Aug 16 Epub ahead of print; Aigner, A. (2006) *J. Biomed. Biotechnol.* 71659), Arg-Gly-Asp (RGD) peptides (Liu, S. (2006) *Mol. Pharm.* 3:472-487), and polyamidoamines (Tomalia, DA., *et al* (2007) *Biochem. Soc. Trans.* 35:61-67; Yoo, H., *et al* (1999) *Pharm. Res.* 16:1799-1804). In some embodiments, an iRNA forms a complex with cyclodextrin for systemic administration. Methods for administration and pharmaceutical compositions of iRNAs and cyclodextrins can be found in U.S. Patent No. 7,427,605, which is herein incorporated by reference in its entirety.

B. Vector encoded iRNAs

In another aspect, iRNA targeting CA2 can be expressed from transcription units inserted into DNA or RNA vectors (*see*, *e.g.*, Couture, A, *et al.*, *TIG.* (1996), 12:5-10; Skillern, A., *et al.*, International PCT Publication No. WO 00/22113, Conrad, International PCT Publication No. WO 00/22114, and Conrad, U.S. Pat. No. 6,054,299). Expression can be transient (on the order of hours to weeks) or sustained (weeks to months or longer), depending upon the specific construct used and the target tissue or cell type. These transgenes can be introduced as a linear construct, a circular plasmid, or a viral vector, which can be an integrating or non-integrating vector. The transgene can also be constructed to permit it to be inherited as an extrachromosomal plasmid (Gassmann, *et al.*, *Proc. Natl. Acad. Sci. USA* (1995) 92:1292).

The individual strand or strands of an iRNA can be transcribed from a promoter on an expression vector. Where two separate strands are to be expressed to generate, for example, a dsRNA, two separate expression vectors can be co-introduced (*e.g.*, by transfection or infection) into a target cell. Alternatively, each individual strand of a dsRNA can be transcribed by promoters both of which are located on the same expression plasmid. In some embodiments, a dsRNA is expressed as an inverted repeat joined by a linker polynucleotide sequence such that the dsRNA has a stem and loop structure.

An iRNA expression vector is typically a DNA plasmid or viral vector. An expression vector compatible with eukaryotic cells, *e.g.*, with vertebrate cells, can be used to produce recombinant constructs for the expression of an iRNA as described herein. Eukaryotic cell expression vectors are well known in the art and are available from a number of commercial sources. Typically, such vectors contain convenient restriction sites for insertion of the desired nucleic acid segment. Delivery of iRNA expressing vectors can be systemic, such as by

intravenous or intramuscular administration, by administration to target cells ex-planted from the patient followed by reintroduction into the patient, or by any other means that allows for introduction into a desired target cell.

An iRNA expression plasmid can be transfected into a target cell as a complex with a cationic lipid carrier (*e.g.*, Oligofectamine) or a non-cationic lipid-based carrier (*e.g.*, Transit-TKO™). Multiple lipid transfections for iRNA-mediated knockdowns targeting different regions of a target RNA over a period of a week or more are also contemplated by the disclosure. Successful introduction of vectors into host cells can be monitored using various known methods. For example, transient transfection can be signaled with a reporter, such as a fluorescent marker, such as Green Fluorescent Protein (GFP). Stable transfection of cells *ex vivo* can be ensured using markers that provide the transfected cell with resistance to specific environmental factors (*e.g.*, antibiotics and drugs), such as hygromycin B resistance.

Viral vector systems which can be utilized with the methods and compositions described herein include, but are not limited to, (a) adenovirus vectors; (b) retrovirus vectors, including but not limited to lentiviral vectors, moloney murine leukemia virus, *etc.*; (c) adeno- associated virus vectors; (d) herpes simplex virus vectors; (e) SV40 vectors; (f) polyoma virus vectors; (g) papilloma virus vectors; (h) picornavirus vectors; (i) pox virus vectors such as an orthopox, *e.g.*, vaccinia virus vectors or avipox, *e.g.* canary pox or fowl pox; and (j) a helper-dependent or gutless adenovirus. Replication-defective viruses can also be advantageous. Different vectors will or will not become incorporated into the cells' genome. The constructs can include viral sequences for transfection, if desired. Alternatively, the construct may be incorporated into vectors capable of episomal replication, *e.g* EPV and EBV vectors. Constructs for the recombinant expression of an iRNA will generally require regulatory elements, *e.g.*, promoters, enhancers, *etc.*, to ensure the expression of the iRNA in target cells. Other aspects to consider for vectors and constructs are further described below.

Vectors useful for the delivery of an iRNA will include regulatory elements (promoter, enhancer, *etc.*) sufficient for expression of the iRNA in the desired target cell or tissue. The regulatory elements can be chosen to provide either constitutive or regulated/inducible expression.

Expression of the iRNA can be precisely regulated, for example, by using an inducible regulatory sequence that is sensitive to certain physiological regulators, *e.g.*, circulating glucose

levels, or hormones (Docherty *et al.*, 1994, *FASEB J.* 8:20-24). Such inducible expression systems, suitable for the control of dsRNA expression in cells or in mammals include, for example, regulation by ecdysone, by estrogen, progesterone, tetracycline, chemical inducers of dimerization, and isopropyl-β-D1-thiogalactopyranoside (IPTG). A person skilled in the art would be able to choose the appropriate regulatory/promoter sequence based on the intended use of the iRNA transgene.

In a specific embodiment, viral vectors that contain nucleic acid sequences encoding an iRNA can be used. For example, a retroviral vector can be used (see Miller *et al.*, *Meth. Enzymol.* 217:581-599 (1993)). These retroviral vectors contain the components necessary for the correct packaging of the viral genome and integration into the host cell DNA. The nucleic acid sequences encoding an iRNA are cloned into one or more vectors, which facilitates delivery of the nucleic acid into a patient. More detail about retroviral vectors can be found, for example, in Boesen *et al.*, *Biotherapy* 6:291-302 (1994), which describes the use of a retroviral vector to deliver the mdr1 gene to hematopoietic stem cells in order to make the stem cells more resistant to chemotherapy. Other references illustrating the use of retroviral vectors in gene therapy are: Clowes *et al.*, *J. Clin. Invest.* 93:644-651 (1994); Kiem *et al.*, *Blood* 83:1467-1473 (1994); Salmons and Gunzberg, *Human Gene Therapy* 4:129-141 (1993); and Grossman and Wilson, *Curr. Opin. in Genetics and Devel.* 3:110-114 (1993). Lentiviral vectors contemplated for use include, for example, the HIV based vectors described in U.S. Patent Nos. 6,143,520; 5,665,557; and 5,981,276, which are herein incorporated by reference.

Adenoviruses are also contemplated for use in delivery of iRNAs. Adenoviruses are especially attractive vehicles, *e.g.*, for delivering genes to respiratory epithelia. Adenoviruses naturally infect respiratory epithelia where they cause a mild disease. Other targets for adenovirus-based delivery systems are liver, the central nervous system, endothelial cells, and muscle. Adenoviruses have the advantage of being capable of infecting non-dividing cells. Kozarsky and Wilson, *Current Opinion in Genetics and Development* 3:499-503 (1993) present a review of adenovirus-based gene therapy. Bout *et al.*, *Human Gene Therapy* 5:3-10 (1994) demonstrated the use of adenovirus vectors to transfer genes to the respiratory epithelia of rhesus monkeys. Other instances of the use of adenoviruses in gene therapy can be found in Rosenfeld *et al.*, *Science* 252:431-434 (1991); Rosenfeld *et al.*, *Cell* 68:143-155 (1992); Mastrangeli *et al.*, *J. Clin. Invest.* 91:225-234 (1993); PCT Publication WO94/12649; and Wang, *et al.*, *Gene*

Therapy 2:775-783 (1995). A suitable AV vector for expressing an iRNA featured in the disclosure, a method for constructing the recombinant AV vector, and a method for delivering the vector into target cells, are described in Xia H *et al.* (2002), *Nat. Biotech.* 20: 1006-1010.

Use of Adeno-associated virus (AAV) vectors is also contemplated (Walsh *et al.*, *Proc. Soc. Exp. Biol. Med.* 204:289-300 (1993); U.S. Pat. No. 5,436,146). In some embodiments, the iRNA can be expressed as two separate, complementary single-stranded RNA molecules from a recombinant AAV vector having, for example, either the U6 or H1 RNA promoters, or the cytomegalovirus (CMV) promoter. Suitable AAV vectors for expressing the dsRNA featured in the disclosure, methods for constructing the recombinant AV vector, and methods for delivering the vectors into target cells are described in Samulski R *et al.* (1987), *J. Virol.* 61: 3096-3101; Fisher K J *et al.* (1996), *J. Virol.*, 70: 520-532; Samulski R *et al.* (1989), *J. Virol.* 63: 3822-3826; U.S. Pat. No. 5,252,479; U.S. Pat. No. 5,139,941; International Patent Application No. WO 94/13788; and International Patent Application No. WO 93/24641, the entire disclosures of which are herein incorporated by reference.

Another typical viral vector is a pox virus such as a vaccinia virus, for example an attenuated vaccinia such as Modified Virus Ankara (MVA) or NYVAC, an avipox such as fowl pox or canary pox.

The tropism of viral vectors can be modified by pseudotyping the vectors with envelope proteins or other surface antigens from other viruses, or by substituting different viral capsid proteins, as appropriate. For example, lentiviral vectors can be pseudotyped with surface proteins from vesicular stomatitis virus (VSV), rabies, Ebola, Mokola, and the like. AAV vectors can be made to target different cells by engineering the vectors to express different capsid protein serotypes; *see, e.g.,* Rabinowitz J E *et al.* (2002), *J Virol* 76:791-801, the entire disclosure of which is herein incorporated by reference.

The pharmaceutical preparation of a vector can include the vector in an acceptable diluent, or can include a slow release matrix in which the gene delivery vehicle is imbedded. Alternatively, where the complete gene delivery vector can be produced intact from recombinant cells, *e.g.,* retroviral vectors, the pharmaceutical preparation can include one or more cells which produce the gene delivery system.

VI. Pharmaceutical compositions containing iRNA

In some embodiments, the disclosure provides pharmaceutical compositions containing an iRNA, as described herein, and a pharmaceutically acceptable carrier. The pharmaceutical composition containing the iRNA is useful for treating a disease or disorder related to the expression or activity of CA2 (*e.g.*, glaucoma or conditions associated with glaucoma). Such pharmaceutical compositions are formulated based on the mode of delivery. In some embodiments, compositions can be formulated for localized delivery, *e.g.*, by intraocular delivery (*e.g.*, intravitreal administration, e.g., intravitreal injection; transscleral administration, e.g., transscleral injection; subconjunctival administration, e.g., subconjunctival injection; retrobulbar administration, e.g., retrobulbar injection; intracameral administration, e.g., intracameral injection; or subretinal administration, e.g., subretinal injection). In other embodiments, compositions can be formulated for topical delivery. In another example, compositions can be formulated for systemic administration via parenteral delivery, *e.g.*, by intravenous (IV) delivery. In some embodiments, a composition provided herein (*e.g.*, a composition comprising a GalNAc conjugate or an LNP formulation) is formulated for intravenous delivery.

The pharmaceutical compositions featured herein are administered in a dosage sufficient to inhibit expression of CA2. In general, a suitable dose of iRNA will be in the range of 0.01 to 200.0 milligrams per kilogram body weight of the recipient per day. The pharmaceutical composition may be administered once daily, or the iRNA may be administered as two, three, or more sub-doses at appropriate intervals throughout the day or even using continuous infusion or delivery through a controlled release formulation. In that case, the iRNA contained in each sub-dose must be correspondingly smaller in order to achieve the total daily dosage. The dosage unit can also be compounded for delivery over several days, *e.g.*, using a conventional sustained release formulation which provides sustained release of the iRNA over a several day period. Sustained release formulations are well known in the art and are particularly useful for delivery of agents at a particular site, such as can be used with the agents of the present disclosure. In this embodiment, the dosage unit contains a corresponding multiple of the daily dose.

The effect of a single dose on CA2 levels can be long lasting, such that subsequent doses are administered at not more than 3, 4, or 5-day intervals, or at not more than 1, 2, 3, 4, 12, 24, or 36-week intervals.

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The skilled artisan will appreciate that certain factors may influence the dosage and timing required to effectively treat a subject, including but not limited to the severity of the disease or disorder, previous treatments, the general health and/or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically effective amount of a composition can include a single treatment or a series of treatments. Estimates of effective dosages and *in vivo* half-lives for the individual iRNAs encompassed by the disclosure can be made using conventional methodologies or on the basis of *in vivo* testing using a suitable animal model.

A suitable animal model, *e.g.*, a mouse or a cynomolgus monkey, e.g., an animal containing a transgene expressing human CA2, can be used to determine the therapeutically effective dose and/or an effective dosage regimen administration of CA2 siRNA.

The present disclosure also includes pharmaceutical compositions and formulations that include the iRNA compounds featured herein. The pharmaceutical compositions of the present disclosure may be administered in a number of ways depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration may be local (*e.g.*, by intraocular injection), topical (*e.g.*, by an eye drop solution), or parenteral. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal or intramuscular injection or infusion; subdermal, *e.g.*, via an implanted device; or intracranial, *e.g.*, by intraparenchymal, intrathecal, or intraventricular administration.

Pharmaceutical compositions and formulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable. Coated condoms, gloves and the like may also be useful. Suitable topical formulations include those in which the iRNAs featured in the disclosure are in admixture with a topical delivery agent such as lipids, liposomes, fatty acids, fatty acid esters, steroids, chelating agents and surfactants. Suitable lipids and liposomes include neutral (*e.g.*, dioleoylphosphatidyl DOPE ethanolamine, dimyristoylphosphatidyl choline DMPC, distearolyphosphatidyl choline) negative (*e.g.*, dimyristoylphosphatidyl glycerol DMPG) and cationic (*e.g.*, dioleoyltetramethylaminopropyl DOTAP and dioleoylphosphatidyl ethanolamine DOTMA). iRNAs featured in the disclosure may be encapsulated within liposomes or may form complexes thereto, in particular to cationic liposomes. Alternatively, iRNAs may be complexed

to lipids, in particular to cationic lipids. Suitable fatty acids and esters include but are not limited to arachidonic acid, oleic acid, eicosanoic acid, lauric acid, caprylic acid, capric acid, myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, dicaprate, tricaprate, monoolein, dilaurin, glyceryl 1-monocaprate, 1-dodecylazacycloheptan-2-one, an acylcarnitine, an acylcholine, or a C_{1-20} alkyl ester (*e.g.*, isopropylmyristate IPM), monoglyceride, diglyceride or pharmaceutically acceptable salt thereof. Topical formulations are described in detail in U.S. Patent No. 6,747,014, which is incorporated herein by reference.

A. Liposomal formulations

There are many organized surfactant structures besides microemulsions that have been studied and used for the formulation of drugs. These include monolayers, micelles, bilayers and vesicles. Vesicles, such as liposomes, have attracted great interest because of their specificity and the duration of action they offer from the standpoint of drug delivery. As used in the present disclosure, the term "liposome" means a vesicle composed of amphiphilic lipids arranged in a spherical bilayer or bilayers.

Liposomes are unilamellar or multilamellar vesicles which have a membrane formed from a lipophilic material and an aqueous interior. The aqueous portion contains the composition to be delivered. Cationic liposomes possess the advantage of being able to fuse to the cell wall. Non-cationic liposomes, although not able to fuse as efficiently with the cell wall, are taken up by macrophages *in vivo*.

In order to traverse intact mammalian skin, lipid vesicles must pass through a series of fine pores, each with a diameter less than 50 nm, under the influence of a suitable transdermal gradient. Therefore, it is desirable to use a liposome which is highly deformable and able to pass through such fine pores.

Further advantages of liposomes include; liposomes obtained from natural phospholipids are biocompatible and biodegradable; liposomes can incorporate a wide range of water and lipid soluble drugs; liposomes can protect encapsulated drugs in their internal compartments from metabolism and degradation (Rosoff, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 245). Important considerations in the preparation of liposome formulations are the lipid surface charge, vesicle size and the aqueous volume of the liposomes.

Liposomes are useful for the transfer and delivery of active ingredients to the site of action. Because the liposomal membrane is structurally similar to biological membranes, when liposomes are applied to a tissue, the liposomes start to merge with the cellular membranes and as the merging of the liposome and cell progresses, the liposomal contents are emptied into the cell where the active agent may act.

Liposomal formulations have been the focus of extensive investigation as the mode of delivery for many drugs. There is growing evidence that for topical administration, liposomes present several advantages over other formulations. Such advantages include reduced side-effects related to high systemic absorption of the administered drug, increased accumulation of the administered drug at the desired target, and the ability to administer a wide variety of drugs, both hydrophilic and hydrophobic, into the skin.

Several reports have detailed the ability of liposomes to deliver agents including high-molecular weight DNA into the skin. Compounds including analgesics, antibodies, hormones and high-molecular weight DNAs have been administered to the skin. The majority of applications resulted in the targeting of the upper epidermis

Liposomes fall into two broad classes. Cationic liposomes are positively charged liposomes which interact with the negatively charged DNA molecules to form a stable complex. The positively charged DNA/liposome complex binds to the negatively charged cell surface and is internalized in an endosome. Due to the acidic pH within the endosome, the liposomes are ruptured, releasing their contents into the cell cytoplasm (Wang *et al.*, *Biochem. Biophys. Res. Commun.*, 1987, 147, 980-985).

Liposomes which are pH-sensitive or negatively charged, entrap DNA rather than complex with it. Since both the DNA and the lipid are similarly charged, repulsion rather than complex formation occurs. Nevertheless, some DNA is entrapped within the aqueous interior of these liposomes. pH-sensitive liposomes have been used to deliver DNA encoding the thymidine kinase gene to cell monolayers in culture. Expression of the exogenous gene was detected in the target cells (Zhou *et al.*, *Journal of Controlled Release*, 1992, 19, 269-274).

One major type of liposomal composition includes phospholipids other than naturally derived phosphatidylcholine. Neutral liposome compositions, for example, can be formed from dimyristoyl phosphatidylcholine (DMPC) or dipalmitoyl phosphatidylcholine (DPPC). Anionic liposome compositions generally are formed from dimyristoyl phosphatidylglycerol, while

anionic fusogenic liposomes are formed primarily from dioleoyl phosphatidylethanolamine (DOPE). Another type of liposomal composition is formed from phosphatidylcholine (PC) such as, for example, soybean PC, and egg PC. Another type is formed from mixtures of phospholipid and/or phosphatidylcholine and/or cholesterol.

Several studies have assessed the topical delivery of liposomal drug formulations to the skin. Application of liposomes containing interferon to guinea pig skin resulted in a reduction of skin herpes sores while delivery of interferon via other means (*e.g.*, as a solution or as an emulsion) were ineffective (Weiner *et al.*, *Journal of Drug Targeting*, 1992, 2, 405-410). Further, an additional study tested the efficacy of interferon administered as part of a liposomal formulation to the administration of interferon using an aqueous system, and concluded that the liposomal formulation was superior to aqueous administration (du Plessis *et al.*, *Antiviral Research*, 1992, 18, 259-265).

Non-ionic liposomal systems have also been examined to determine their utility in the delivery of drugs to the skin, in particular systems comprising non-ionic surfactant and cholesterol. Non-ionic liposomal formulations comprising Novasome™ I (glyceryl dilaurate/cholesterol/polyoxyethylene-10-stearyl ether) and Novasome™ II (glyceryl distearate/cholesterol/polyoxyethylene-10-stearyl ether) were used to deliver cyclosporin-A into the dermis of mouse skin. Results indicated that such non-ionic liposomal systems were effective in facilitating the deposition of cyclosporin-A into different layers of the skin (Hu *et al.* S.T.P. *Pharma. Sci.*, 1994, 4, 6, 466).

Liposomes also include "sterically stabilized" liposomes, a term which, as used herein, refers to liposomes comprising one or more specialized lipids that, when incorporated into liposomes, result in enhanced circulation lifetimes relative to liposomes lacking such specialized lipids. Examples of sterically stabilized liposomes are those in which part of the vesicle-forming lipid portion of the liposome (A) comprises one or more glycolipids, such as monosialoganglioside G_{M1}, or (B) is derivatized with one or more hydrophilic polymers, such as a polyethylene glycol (PEG) moiety. While not wishing to be bound by any particular theory, it is thought in the art that, at least for sterically stabilized liposomes containing gangliosides, sphingomyelin, or PEG-derivatized lipids, the enhanced circulation half-life of these sterically stabilized liposomes derives from a reduced uptake into cells of the reticuloendothelial system (RES) (Allen *et al.*, *FEBS Letters*, 1987, 223, 42; Wu *et al.*, *Cancer Research*, 1993, 53, 3765).

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Various liposomes comprising one or more glycolipids are known in the art. Papahadjopoulos *et al.* (*Ann. N.Y. Acad. Sci.*, 1987, 507, 64) reported the ability of monosialoganglioside G_{M1}, galactocerebroside sulfate and phosphatidylinositol to improve blood half-lives of liposomes. These findings were expounded upon by Gabizon *et al.* (*Proc. Natl. Acad. Sci. U.S.A.*, 1988, 85, 6949). U.S. Pat. No. 4,837,028 and WO 88/04924, both to Allen *et al.*, disclose liposomes comprising (1) sphingomyelin and (2) the ganglioside G_{M1} or a galactocerebroside sulfate ester. U.S. Pat. No. 5,543,152 (Webb *et al.*) discloses liposomes comprising sphingomyelin. Liposomes comprising 1,2-sn-dimyristoylphosphatidylcholine are disclosed in WO 97/13499 (Lim *et al*).

Many liposomes comprising lipids derivatized with one or more hydrophilic polymers, and methods of preparation thereof, are known in the art. Sunamoto *et al.* (Bull. *Chem. Soc. Jpn.*, 1980, 53, 2778) described liposomes comprising a nonionic detergent, $2C_{1215G}$, that contains a PEG moiety. Illum *et al.* (*FEBS Lett.*, 1984, 167, 79) noted that hydrophilic coating of polystyrene particles with polymeric glycols results in significantly enhanced blood half-lives. Synthetic phospholipids modified by the attachment of carboxylic groups of polyalkylene glycols (*e.g.*, PEG) are described by Sears (U.S. Pat. Nos. 4,426,330 and 4,534,899). Klibanov *et al.* (*FEBS Lett.*, 1990, 268, 235) described experiments demonstrating that liposomes comprising phosphatidylethanolamine (PE) derivatized with PEG or PEG stearate have significant increases in blood circulation half-lives. Blume *et al.* (*Biochimica et Biophysica Acta*, 1990, 1029, 91) extended such observations to other PEG-derivatized phospholipids, *e.g.*, DSPE-PEG, formed from the combination of distearoylphosphatidylethanolamine (DSPE) and PEG. Liposomes having covalently bound PEG moieties on their external surface are described in European Patent No. EP 0 445 131 B1 and WO 90/04384 to Fisher. Liposome compositions containing 1-20 mole percent of PE derivatized with PEG, and methods of use thereof, are described by Woodle *et al.* (U.S. Pat. Nos. 5,013,556 and 5,356,633) and Martin *et al.* (U.S. Pat. No. 5,213,804 and European Patent No. EP 0 496 813 B1). Liposomes comprising a number of other lipid-polymer conjugates are disclosed in WO 91/05545 and U.S. Pat. No. 5,225,212 (both to Martin *et al.*) and in WO 94/20073 (Zalipsky *et al.*). Liposomes comprising PEG-modified ceramide lipids are described in WO 96/10391 (Choi *et al*). U.S. Pat. No. 5,540,935 (Miyazaki *et al.*) and U.S. Pat. No. 5,556,948 (Tagawa *et al.*) describe PEG-containing liposomes that can be further derivatized with functional moieties on their surfaces.

A number of liposomes comprising nucleic acids are known in the art. WO 96/40062 to Thierry *et al.* discloses methods for encapsulating high molecular weight nucleic acids in liposomes. U.S. Pat. No. 5,264,221 to Tagawa *et al.* discloses protein-bonded liposomes and asserts that the contents of such liposomes may include a dsRNA. U.S. Pat. No. 5,665,710 to Rahman *et al.* describes certain methods of encapsulating oligodeoxynucleotides in liposomes. WO 97/04787 to Love *et al.* discloses liposomes comprising dsRNAs targeted to the raf gene.

Transfersomes are yet another type of liposomes, and are highly deformable lipid aggregates which are attractive candidates for drug delivery vehicles. Transfersomes may be described as lipid droplets which are so highly deformable that they are easily able to penetrate through pores which are smaller than the droplet. Transfersomes are adaptable to the environment in which they are used, *e.g.*, they are self-optimizing (adaptive to the shape of pores in the skin), self-repairing, frequently reach their targets without fragmenting, and often self-loading. To make transfersomes it is possible to add surface edge-activators, usually surfactants, to a standard liposomal composition. Transfersomes have been used to deliver serum albumin to the skin. The transfersome-mediated delivery of serum albumin has been shown to be as effective as subcutaneous injection of a solution containing serum albumin.

Surfactants find wide application in formulations such as emulsions (including microemulsions) and liposomes. The most common way of classifying and ranking the properties of the many different types of surfactants, both natural and synthetic, is by the use of the hydrophile/lipophile balance (HLB). The nature of the hydrophilic group (also known as the "head") provides the most useful means for categorizing the different surfactants used in formulations (Rieger, in *Pharmaceutical Dosage Forms*, Marcel Dekker, Inc., New York, N.Y., 1988, p. 285).

If the surfactant molecule is not ionized, it is classified as a nonionic surfactant. Nonionic surfactants find wide application in pharmaceutical and cosmetic products and are usable over a wide range of pH values. In general, their HLB values range from 2 to about 18 depending on their structure. Nonionic surfactants include nonionic esters such as ethylene glycol esters, propylene glycol esters, glyceryl esters, polyglyceryl esters, sorbitan esters, sucrose esters, and ethoxylated esters. Nonionic alkanolamides and ethers such as fatty alcohol ethoxylates, propoxylated alcohols, and ethoxylated/propoxylated block polymers are also included in this

class. The polyoxyethylene surfactants are the most popular members of the nonionic surfactant class.

If the surfactant molecule carries a negative charge when it is dissolved or dispersed in water, the surfactant is classified as anionic. Anionic surfactants include carboxylates such as soaps, acyl lactylates, acyl amides of amino acids, esters of sulfuric acid such as alkyl sulfates and ethoxylated alkyl sulfates, sulfonates such as alkyl benzene sulfonates, acyl isethionates, acyl taurates and sulfosuccinates, and phosphates. The most important members of the anionic surfactant class are the alkyl sulfates and the soaps.

If the surfactant molecule carries a positive charge when it is dissolved or dispersed in water, the surfactant is classified as cationic. Cationic surfactants include quaternary ammonium salts and ethoxylated amines. The quaternary ammonium salts are the most used members of this class.

If the surfactant molecule has the ability to carry either a positive or negative charge, the surfactant is classified as amphoteric. Amphoteric surfactants include acrylic acid derivatives, substituted alkylamides, N-alkylbetaines and phosphatides.

The use of surfactants in drug products, formulations and in emulsions has been reviewed (Rieger, in *Pharmaceutical Dosage Forms*, Marcel Dekker, Inc., New York, N.Y., 1988, p. 285).

B. Nucleic acid lipid particles

In some embodiments, a CA2 dsRNA featured in the disclosure is fully encapsulated in the lipid formulation, *e.g.*, to form a SPLP, pSPLP, SNALP, or other nucleic acid-lipid particle. SNALPs and SPLPs typically contain a cationic lipid, a non-cationic lipid, and a lipid that prevents aggregation of the particle (*e.g.*, a PEG-lipid conjugate). SNALPs and SPLPs are extremely useful for systemic applications, as they exhibit extended circulation lifetimes following intravenous (i.v.) injection and accumulate at distal sites (*e.g.*, sites physically separated from the administration site). SPLPs include "pSPLP," which include an encapsulated condensing agent-nucleic acid complex as set forth in PCT Publication No. WO 00/03683. The particles of the present disclosure typically have a mean diameter of about 50 nm to about 150 nm, more typically about 60 nm to about 130 nm, more typically about 70 nm to about 110 nm, most typically about 70 nm to about 90 nm, and are substantially nontoxic. In addition, the nucleic acids when present in the nucleic acid- lipid particles of the present disclosure are

resistant in aqueous solution to degradation with a nuclease. Nucleic acid-lipid particles and their method of preparation are disclosed in, *e.g.*, U.S. Patent Nos. 5,976,567; 5,981,501; 6,534,484; 6,586,410; 6,815,432; and PCT Publication No. WO 96/40964.

In some embodiments, the lipid to drug ratio (mass/mass ratio) (*e.g.*, lipid to dsRNA ratio) will be in the range of from about 1:1 to about 50:1, from about 1:1 to about 25:1, from about 3:1 to about 15:1, from about 4:1 to about 10:1, from about 5:1 to about 9:1, or about 6:1 to about 9:1.

The cationic lipid may be, for example, N,N-dioleyl-N,N-dimethylammonium chloride (DODAC), N,N-distearyl-N,N-dimethylammonium bromide (DDAB), N-(I -(2,3-dioleoyloxy)propyl)-N,N,N-trimethylammonium chloride (DOTAP), N-(I -(2,3-dioleyloxy)propyl)-N,N,N-trimethylammonium chloride (DOTMA), N,N-dimethyl-2,3-dioleyloxy)propylamine (DODMA), 1,2-DiLinoleyloxy-N,N-dimethylaminopropane (DLinDMA), l,2-Dilinolenyloxy-N,N-dimethylaminopropane (DLenDMA), 1,2-Dilinoleylcarbamoyloxy-3-dimethylaminopropane (DLin-C-DAP), 1,2-Dilinoleyoxy-3-(dimethylamino)acetoxypropane (DLin-DAC), 1,2-Dilinoleyoxy-3-morpholinopropane (DLin-MA), 1,2-Dilinoleoyl-3-dimethylaminopropane (DLinDAP), 1,2-Dilinoleylthio-3-dimethylaminopropane (DLin-S-DMA), 1-Linoleoyl-2-linoleyloxy-3-dimethylaminopropane (DLin-2-DMAP), 1,2-Dilinoleyloxy-3-trimethylaminopropane chloride salt (DLin-TMA.Cl), 1,2-Dilinoleoyl-3-trimethylaminopropane chloride salt (DLin-TAP.Cl), 1,2-Dilinoleyloxy-3-(N-methylpiperazino)propane (DLin-MPZ), or 3-(N,N-Dilinoleylamino)-1,2-propanediol (DLinAP), 3-(N,N-Dioleylamino)-1,2-propanedio (DOAP), 1,2-Dilinoleyloxo-3-(2-N,N-dimethylamino)ethoxypropane (DLin-EG-DMA), l,2-Dilinolenyloxy-N,N-dimethylaminopropane (DLinDMA), 2,2-Dilinoleyl-4-dimethylaminomethyl-[1,3]-dioxolane (DLin-K-DMA) or analogs thereof, (3aR,5s,6aS)-N,N-dimethyl-2,2-di((9Z,12Z)-octadeca-9,12-dienyl)tetrahydro-3aH-cyclopenta[d][1,3]dioxol-5-amine (ALN100), (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate (MC3), 1,1'-(2-(4-(2-((2-(bis(2-hydroxydodecyl)amino)ethyl)(2-hydroxydodecyl)amino)ethyl)piperazin-1-yl)ethylazanediyl)didodecan-2-ol (Tech G1), or a mixture thereof. The cationic lipid may comprise from about 20 mol % to about 50 mol % or about 40 mol % of the total lipid present in the particle.

In some embodiments, the compound 2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane can be used to prepare lipid-siRNA nanoparticles. Synthesis of 2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane is described in United States provisional patent application number 61/107,998 filed on October 23, 2008, which is herein incorporated by reference.

In some embodiments, the lipid-siRNA particle includes 40% 2, 2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane: 10% DSPC: 40% Cholesterol: 10% PEG-C-DOMG (mole percent) with a particle size of 63.0 ± 20 nm and a 0.027 siRNA/Lipid Ratio.

The non-cationic lipid may be an anionic lipid or a neutral lipid including, but not limited to, distearoylphosphatidylcholine (DSPC), dioleoylphosphatidylcholine (DOPC), dipalmitoylphosphatidylcholine (DPPC), dioleoylphosphatidylglycerol (DOPG), dipalmitoylphosphatidylglycerol (DPPG), dioleoyl-phosphatidylethanolamine (DOPE), palmitoyloleoylphosphatidylcholine (POPC), palmitoyloleoylphosphatidylethanolamine (POPE), dioleoyl- phosphatidylethanolamine 4-(N-maleimidomethyl)-cyclohexane-l- carboxylate (DOPE-mal), dipalmitoyl phosphatidyl ethanolamine (DPPE), dimyristoylphosphoethanolamine (DMPE), distearoyl-phosphatidyl-ethanolamine (DSPE), 16-O-monomethyl PE, 16-O-dimethyl PE, 18-1 -trans PE, 1 -stearoyl-2-oleoyl- phosphatidyethanolamine (SOPE), cholesterol, or a mixture thereof. The non-cationic lipid may be from about 5 mol % to about 90 mol %, about 10 mol %, or about 58 mol % if cholesterol is included, of the total lipid present in the particle.

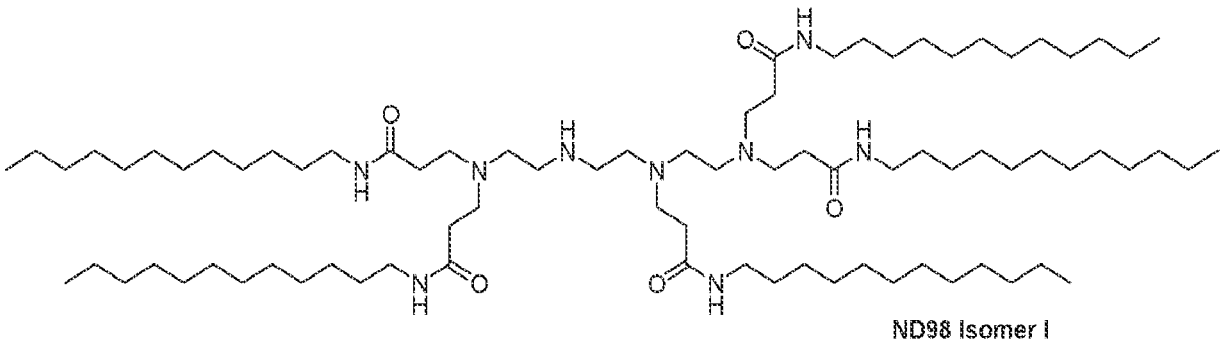
The conjugated lipid that inhibits aggregation of particles may be, for example, a polyethyleneglycol (PEG)-lipid including, without limitation, a PEG-diacylglycerol (DAG), a PEG-dialkyloxypropyl (DAA), a PEG-phospholipid, a PEG-ceramide (Cer), or a mixture thereof. The PEG-DAA conjugate may be, for example, a PEG-dilauryloxypropyl (C_{12}), a PEG-dimyristyloxypropyl (C_{14}), a PEG-dipalmityloxypropyl (C_{16}), or a PEG- distearyloxypropyl (C_{18}). The conjugated lipid that prevents aggregation of particles may be from 0 mol % to about 20 mol % or about 2 mol % of the total lipid present in the particle.

In some embodiments, the nucleic acid-lipid particle further includes cholesterol at, *e.g.*, about 10 mol % to about 60 mol % or about 48 mol % of the total lipid present in the particle.

In some embodiments, the iRNA is formulated in a lipid nanoparticle (LNP).

LNP01

In some embodiments, the lipidoid ND98·4HCl (MW 1487) (see U.S. Patent Application No. 12/056,230, filed 3/26/2008, which is herein incorporated by reference), Cholesterol (Sigma-Aldrich), and PEG-Ceramide C16 (Avanti Polar Lipids) can be used to prepare lipid-dsRNA nanoparticles (*e.g.*, LNP01 particles). Stock solutions of each in ethanol can be prepared as follows: ND98, 133 mg/ml; Cholesterol, 25 mg/ml, PEG-Ceramide C16, 100 mg/ml. The ND98, Cholesterol, and PEG-Ceramide C16 stock solutions can then be combined in a, *e.g.*, 42:48:10 molar ratio. The combined lipid solution can be mixed with aqueous dsRNA (*e.g.*, in sodium acetate pH 5) such that the final ethanol concentration is about 35-45% and the final sodium acetate concentration is about 100-300 mM. Lipid-dsRNA nanoparticles typically form spontaneously upon mixing. Depending on the desired particle size distribution, the resultant nanoparticle mixture can be extruded through a polycarbonate membrane (*e.g.*, 100 nm cut-off) using, for example, a thermobarrel extruder, such as Lipex Extruder (Northern Lipids, Inc). In some cases, the extrusion step can be omitted. Ethanol removal and simultaneous buffer exchange can be accomplished by, for example, dialysis or tangential flow filtration. Buffer can be exchanged with, for example, phosphate buffered saline (PBS) at about pH 7, *e.g.*, about pH 6.9, about pH 7.0, about pH 7.1, about pH 7.2, about pH 7.3, or about pH 7.4.



Formula I

LNP01 formulations are described, *e.g.*, in International Application Publication No. WO 2008/042973, which is hereby incorporated by reference.

Additional exemplary lipid-dsRNA formulations are provided in the following Table 1.

Table 1: Exemplary lipid formulations

	Cationic Lipid	cationic lipid/non-cationic lipid/cholesterol/PEG-lipid conjugate Lipid:siRNA ratio
SNALP	1,2-Dilinolenyloxy-N,N-dimethylaminopropane (DLinDMA)	DLinDMA/DPPC/Cholesterol/PEG-cDMA (57.1/7.1/34.4/1.4) lipid:siRNA ~ 7:1
S-XTC	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DPPC/Cholesterol/PEG-cDMA 57.1/7.1/34.4/1.4 lipid:siRNA ~ 7:1
LNP05	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DSPC/Cholesterol/PEG-DMG 57.5/7.5/31.5/3.5 lipid:siRNA ~ 6:1
LNP06	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DSPC/Cholesterol/PEG-DMG 57.5/7.5/31.5/3.5 lipid:siRNA ~ 11:1
LNP07	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DSPC/Cholesterol/PEG-DMG 60/7.5/31/1.5, lipid:siRNA ~ 6:1
LNP08	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DSPC/Cholesterol/PEG-DMG 60/7.5/31/1.5, lipid:siRNA ~ 11:1
LNP09	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DSPC/Cholesterol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA 10:1
LNP10	(3aR,5s,6aS)-N,N-dimethyl-2,2-di((9Z,12Z)-octadeca-9,12-dienyl)tetrahydro-3aH-cyclopenta[d][1,3]dioxol-5-amine (ALN100)	ALN100/DSPC/Cholesterol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA 10:1
LNP11	(6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate (MC3)	MC-3/DSPC/Cholesterol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA 10:1

LNP12	1,1'-(2-(4-(2-((2-(bis(2-hydroxydodecyl)amino)ethyl)(2-hydroxydodecyl)amino)ethyl)piperazin-1-yl)ethylazanediyl)didodecan-2-ol (C12-200)	C12-200/DSPC/Cholesterol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA 10:1
LNP13	XTC	XTC/DSPC/Chol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA: 33:1
LNP14	MC3	MC3/DSPC/Chol/PEG-DMG 40/15/40/5 Lipid:siRNA: 11:1
LNP15	MC3	MC3/DSPC/Chol/PEG-DSG/GalNAc-PEG-DSG 50/10/35/4.5/0.5 Lipid:siRNA: 11:1
LNP16	MC3	MC3/DSPC/Chol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA: 7:1
LNP17	MC3	MC3/DSPC/Chol/PEG-DSG 50/10/38.5/1.5 Lipid:siRNA: 10:1
LNP18	MC3	MC3/DSPC/Chol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA: 12:1
LNP19	MC3	MC3/DSPC/Chol/PEG-DMG 50/10/35/5 Lipid:siRNA: 8:1
LNP20	MC3	MC3/DSPC/Chol/PEG-DPG 50/10/38.5/1.5 Lipid:siRNA: 10:1
LNP21	C12-200	C12-200/DSPC/Chol/PEG-DSG 50/10/38.5/1.5 Lipid:siRNA: 7:1
LNP22	XTC	XTC/DSPC/Chol/PEG-DSG 50/10/38.5/1.5 Lipid:siRNA: 10:1

DSPC: distearoylphosphatidylcholine

DPPC: dipalmitoylphosphatidylcholine

PEG-DMG: PEG-didimyristoyl glycerol (C14-PEG, or PEG-C14) (PEG with avg mol wt of 2000)

PEG-DSG: PEG-distyryl glycerol (C18-PEG, or PEG-C18) (PEG with avg mol wt of 2000)

PEG-cDMA: PEG-carbamoyl-1,2-dimyristyloxypropylamine (PEG with avg mol wt of 2000)

SNALP (l,2-Dilinolenyloxy-N,N-dimethylaminopropane (DLinDMA)) comprising formulations are described in International Publication No. WO2009/127060, filed April 15, 2009, which is hereby incorporated by reference.

XTC comprising formulations are described, *e.g.*, in U.S. Provisional Serial No. 61/148,366, filed January 29, 2009; U.S. Provisional Serial No. 61/156,851, filed March 2, 2009; U.S. Provisional Serial No. 61/185,712, filed June 10, 2009; U.S. Provisional Serial No. 61/228,373, filed July 24, 2009; U.S. Provisional Serial No. 61/239,686, filed September 3, 2009, and International Application No. PCT/US2010/022614, filed January 29, 2010, which are hereby incorporated by reference.

MC3 comprising formulations are described, *e.g.*, in U.S. Provisional Serial No. 61/244,834, filed September 22, 2009, U.S. Provisional Serial No. 61/185,800, filed June 10, 2009, and International Application No. PCT/US10/28224, filed June 10, 2010, which are hereby incorporated by reference.

ALNY-100 comprising formulations are described, *e.g.*, International patent application number PCT/US09/63933, filed on November 10, 2009, which is hereby incorporated by reference.

C12-200 comprising formulations are described in U.S. Provisional Serial No. 61/175,770, filed May 5, 2009 and International Application No. PCT/US10/33777, filed May 5, 2010, which are hereby incorporated by reference.

C. Synthesis of cationic lipids

Any of the compounds, *e.g.*, cationic lipids and the like, used in the nucleic acid-lipid particles featured in the disclosure may be prepared by known organic synthesis techniques. All substituents are as defined below unless indicated otherwise.

"Alkyl" means a straight chain or branched, noncyclic or cyclic, saturated aliphatic hydrocarbon containing from 1 to 24 carbon atoms. Representative saturated straight chain alkyls include methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, and the like; while saturated branched alkyls include isopropyl, *sec*-butyl, isobutyl, *tert*-butyl, isopentyl, and the like. Representative saturated cyclic alkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like; while unsaturated cyclic alkyls include cyclopentenyl and cyclohexenyl, and the like.

"Alkenyl" means an alkyl, as defined above, containing at least one double bond between adjacent carbon atoms. Alkenyls include both cis and trans isomers. Representative straight chain and branched alkenyls include ethylenyl, propylenyl, 1-butenyl, 2-butenyl, isobutylenyl, 1-pentenyl, 2-pentenyl, 3-methyl-1-butenyl, 2-methyl-2-butenyl, 2,3-dimethyl-2-butenyl, and the like.

"Alkynyl" means any alkyl or alkenyl, as defined above, which additionally contains at least one triple bond between adjacent carbons. Representative straight chain and branched alkynyls include acetylenyl, propynyl, 1-butynyl, 2-butynyl, 1-pentynyl, 2-pentynyl, 3-methyl-1 butynyl, and the like.

"Acyl" means any alkyl, alkenyl, or alkynyl wherein the carbon at the point of attachment is substituted with an oxo group, as defined below. For example, -C(=O)alkyl, -C(=O)alkenyl, and -C(=O)alkynyl are acyl groups.

"Heterocycle" means a 5- to 7-membered monocyclic, or 7- to 10-membered bicyclic, heterocyclic ring which is either saturated, unsaturated, or aromatic, and which contains from 1 or 2 heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the nitrogen and sulfur heteroatoms may be optionally oxidized, and the nitrogen heteroatom may be optionally quaternized, including bicyclic rings in which any of the above heterocycles are fused to a benzene ring. The heterocycle may be attached via any heteroatom or carbon atom. Heterocycles include heteroaryls as defined below. Heterocycles include morpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperizynyl, hydantoinyl, valerolactamyl, oxiranyl,

oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydroprimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like.

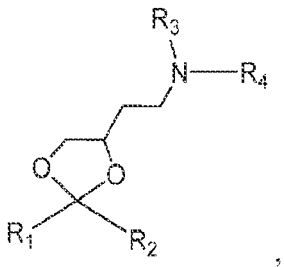
The terms "optionally substituted alkyl", "optionally substituted alkenyl", "optionally substituted alkynyl", "optionally substituted acyl", and "optionally substituted heterocycle" means that, when substituted, at least one hydrogen atom is replaced with a substituent. In the case of an oxo substituent (=O) two hydrogen atoms are replaced. In this regard, substituents include oxo, halogen, heterocycle, -CN, -OR^x, -NR^xR^y, -$NR^xC(=O)R^y$, -$NR^xSO_2R^y$, -$C(=O)R^x$, -$C(=O)OR^x$, -$C(=O)NR^xR^y$, –SO_nR^x and -$SO_nNR^xR^y$, wherein n is 0, 1 or 2, R^x and R^y are the same or different and independently hydrogen, alkyl or heterocycle, and each of said alkyl and heterocycle substituents may be further substituted with one or more of oxo, halogen, -OH, -CN, alkyl, -OR^x, heterocycle, -NR^xR^y, -$NR^xC(=O)R^y$, -$NR^xSO_2R^y$, -$C(=O)R^x$, -$C(=O)OR^x$, -$C(=O)NR^xR^y$, -SO_nR^x and -$SO_nNR^xR^y$.

"Halogen" means fluoro, chloro, bromo and iodo.

In some embodiments, the methods featured in the disclosure may require the use of protecting groups. Protecting group methodology is well known to those skilled in the art (*see, for example*, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS, Green, T.W. *et al.*, Wiley-Interscience, New York City, 1999). Briefly, protecting groups within the context of this disclosure are any group that reduces or eliminates unwanted reactivity of a functional group. A protecting group can be added to a functional group to mask its reactivity during certain reactions and then removed to reveal the original functional group. In some embodiments an "alcohol protecting group" is used. An "alcohol protecting group" is any group which decreases or eliminates unwanted reactivity of an alcohol functional group. Protecting groups can be added and removed using techniques well known in the art.

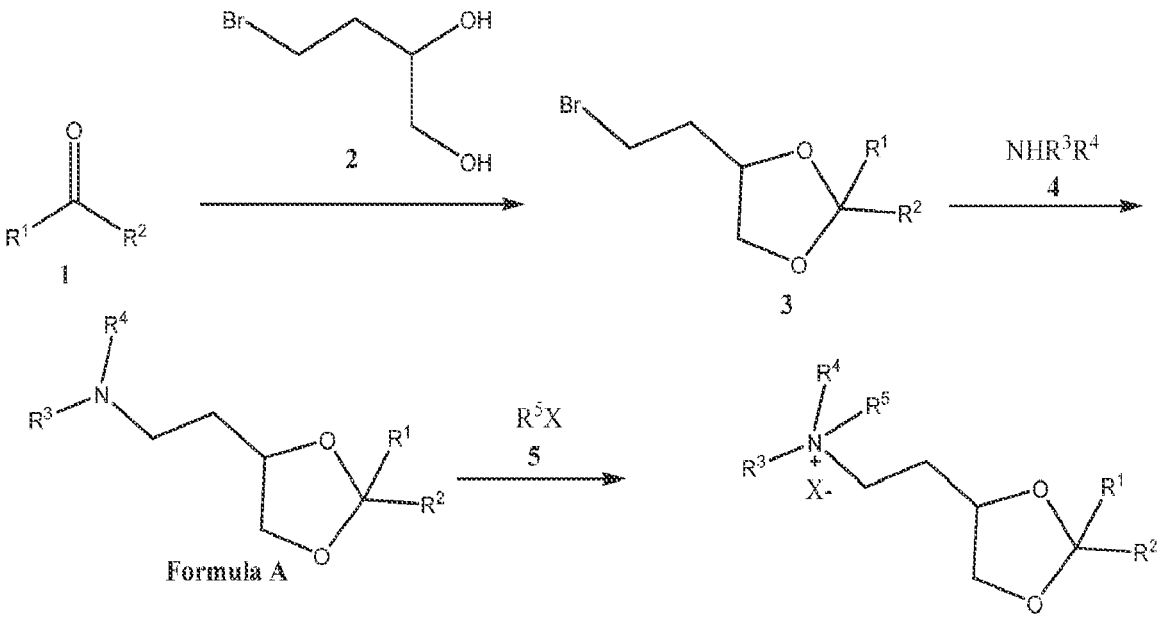
Synthesis of Formula A

In some embodiments, nucleic acid-lipid particles featured in the disclosure are formulated using a cationic lipid of formula A:



where R1 and R2 are independently alkyl, alkenyl or alkynyl, each can be optionally substituted, and R3 and R4 are independently lower alkyl or R3 and R4 can be taken together to form an optionally substituted heterocyclic ring. In some embodiments, the cationic lipid is XTC (2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane). In general, the lipid of formula A above may be made by the following Reaction Schemes 1 or 2, wherein all substituents are as defined above unless indicated otherwise.

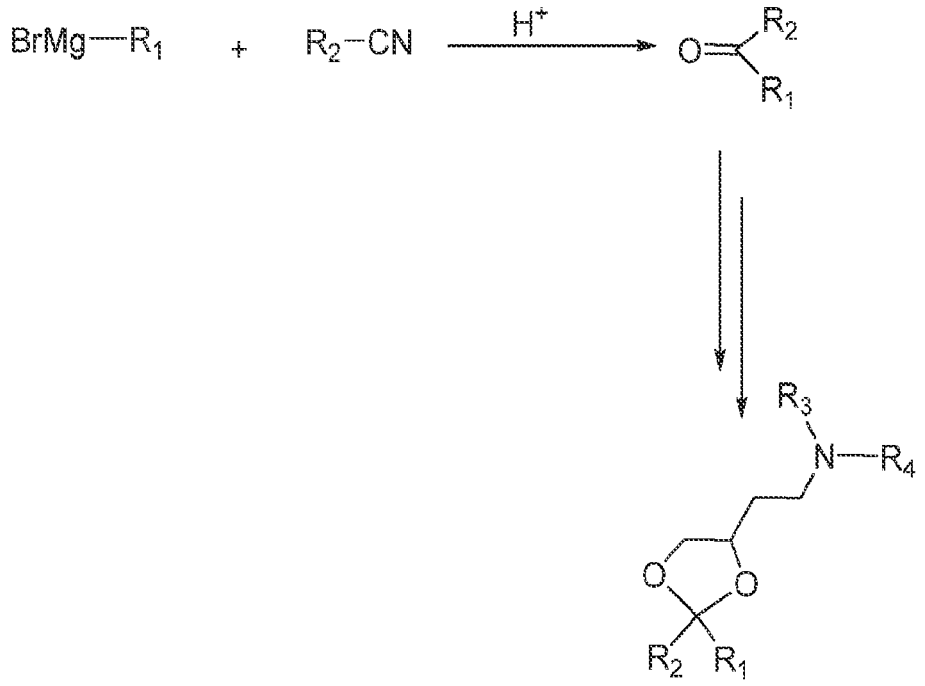
Scheme 1



Lipid A, where R_1 and R_2 are independently alkyl, alkenyl or alkynyl, each can be optionally substituted, and R_3 and R_4 are independently lower alkyl or R_3 and R_4 can be taken together to form an optionally substituted heterocyclic ring, can be prepared according to Scheme 1. Ketone 1 and bromide 2 can be purchased or prepared according to methods known to those of ordinary skill in the art. Reaction of 1 and 2 yields ketal 3. Treatment of ketal 3 with amine 4 yields lipids of formula A. The lipids of formula A can be converted to the

corresponding ammonium salt with an organic salt of formula 5, where X is anion counter ion selected from halogen, hydroxide, phosphate, sulfate, or the like.

Scheme 2



Alternatively, the ketone 1 starting material can be prepared according to Scheme 2. Grignard reagent 6 and cyanide 7 can be purchased or prepared according to methods known to those of ordinary skill in the art. Reaction of 6 and 7 yields ketone 1. Conversion of ketone 1 to the corresponding lipids of formula A is as described in Scheme 1.

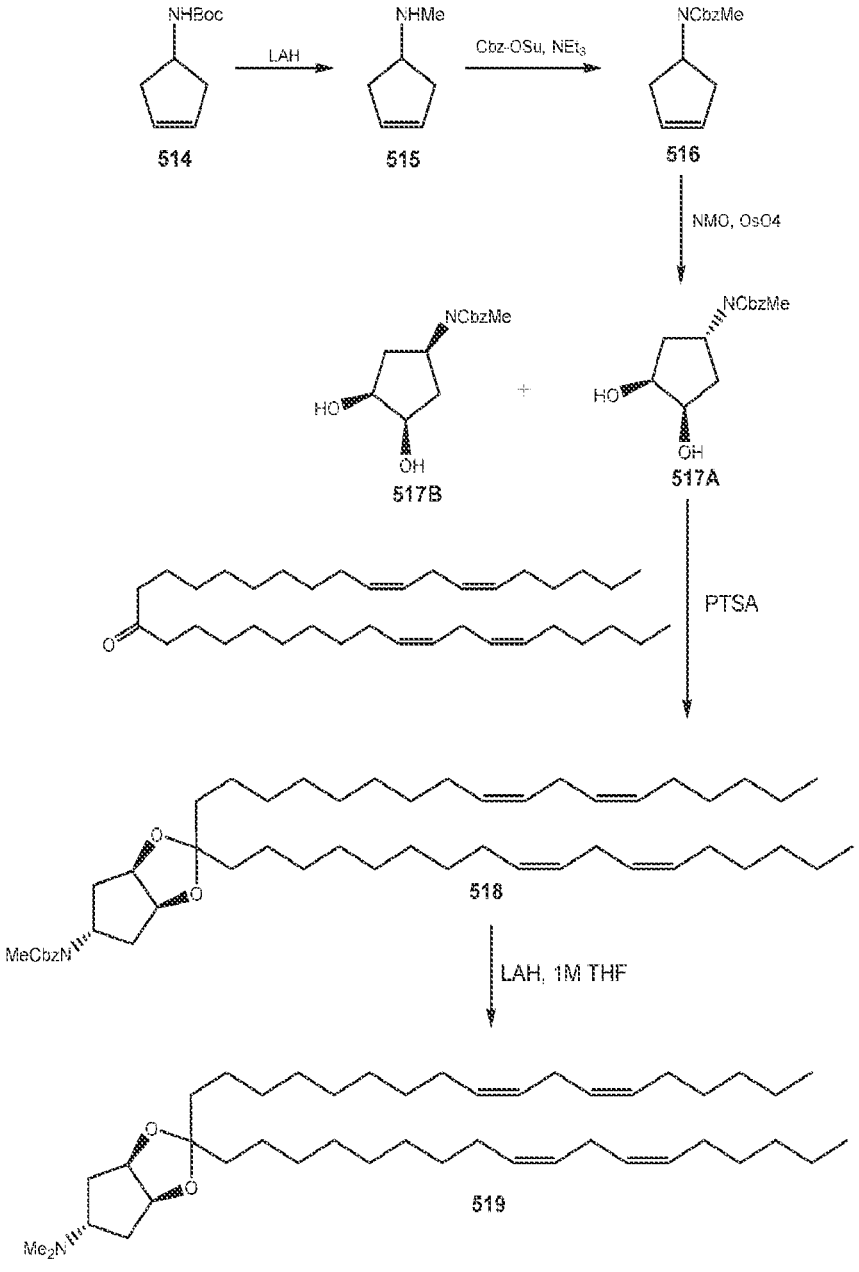
Synthesis of MC3:

Preparation of DLin-M-C3-DMA (*i.e.*, (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate) was as follows. A solution of (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-ol (0.53 g), 4-N,N-dimethylaminobutyric acid hydrochloride (0.51 g), 4-N,N-dimethylaminopyridine (0.61g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.53 g) in dichloromethane (5 mL) was stirred at room temperature overnight. The solution was washed with dilute hydrochloric acid followed by dilute aqueous sodium bicarbonate. The organic fractions were dried over anhydrous magnesium sulphate, filtered and the solvent removed on a rotovap. The residue was passed down a silica gel column (20 g) using a 1-5% methanol/dichloromethane elution gradient.

Fractions containing the purified product were combined and the solvent removed, yielding a colorless oil (0.54 g).

Synthesis of ALNY-100:

Synthesis of ketal 519 [ALNY-100] was performed using the following scheme 3:



Synthesis of 515:

To a stirred suspension of LiAlH4 (3.74 g, 0.09852 mol) in 200 ml anhydrous THF in a two neck RBF (1L), was added a solution of 514 (10g, 0.04926mol) in 70 mL of THF slowly at 0

0C under nitrogen atmosphere. After complete addition, reaction mixture was warmed to room temperature and then heated to reflux for 4 h. Progress of the reaction was monitored by TLC. After completion of reaction (by TLC) the mixture was cooled to 0 0C and quenched with careful addition of saturated Na2SO4 solution. Reaction mixture was stirred for 4 h at room temperature and filtered off. Residue was washed well with THF. The filtrate and washings were mixed and diluted with 400 mL dioxane and 26 mL conc. HCl and stirred for 20 minutes at room temperature. The volatilities were stripped off under vacuum to furnish the hydrochloride salt of 515 as a white solid. Yield: 7.12 g 1H-NMR (DMSO, 400MHz): δ= 9.34 (broad, 2H), 5.68 (s, 2H), 3.74 (m, 1H), 2.66-2.60 (m, 2H), 2.50-2.45 (m, 5H).

Synthesis of 516:

To a stirred solution of compound 515 in 100 mL dry DCM in a 250 mL two neck RBF, was added NEt3 (37.2 mL, 0.2669 mol) and cooled to 0 0C under nitrogen atmosphere. After a slow addition of N-(benzyloxy-carbonyloxy)-succinimide (20 g, 0.08007 mol) in 50 mL dry DCM, reaction mixture was allowed to warm to room temperature. After completion of the reaction (2-3 h by TLC) mixture was washed successively with 1N HCl solution (1 x 100 mL) and saturated NaHCO3 solution (1 x 50 mL). The organic layer was then dried over anhyd. Na2SO4 and the solvent was evaporated to give crude material which was purified by silica gel column chromatography to get 516 as sticky mass. Yield: 11g (89%). 1H-NMR (CDCl3, 400MHz): δ = 7.36-7.27(m, 5H), 5.69 (s, 2H), 5.12 (s, 2H), 4.96 (br., 1H) 2.74 (s, 3H), 2.60(m, 2H), 2.30-2.25(m, 2H). LC-MS [M+H] -232.3 (96.94%).

Synthesis of 517A and 517B:

The cyclopentene 516 (5 g, 0.02164 mol) was dissolved in a solution of 220 mL acetone and water (10:1) in a single neck 500 mL RBF and to it was added N-methyl morpholine-N-oxide (7.6 g, 0.06492 mol) followed by 4.2 mL of 7.6% solution of OsO4 (0.275 g, 0.00108 mol) in tert-butanol at room temperature. After completion of the reaction (~ 3 h), the mixture was quenched with addition of solid Na2SO3 and resulting mixture was stirred for 1.5 h at room temperature. Reaction mixture was diluted with DCM (300 mL) and washed with water (2 x 100 mL) followed by saturated NaHCO3 (1 x 50 mL) solution, water (1 x 30 mL) and finally with brine (1x 50 mL). Organic phase was dried over an.Na2SO4 and solvent was removed in

vacuum. Silica gel column chromatographic purification of the crude material was afforded a mixture of diastereomers, which were separated by prep HPLC. Yield: - 6 g crude

517A - Peak-1 (white solid), 5.13 g (96%). 1H-NMR (DMSO, 400MHz): δ= 7.39-7.31(m, 5H), 5.04(s, 2H), 4.78-4.73 (m, 1H), 4.48-4.47(d, 2H), 3.94-3.93(m, 2H), 2.71(s, 3H), 1.72- 1.67(m, 4H). LC-MS - [M+H]-266.3, [M+NH4 +]-283.5 present, HPLC-97.86%. Stereochemistry confirmed by X-ray.

Synthesis of 518:

Using a procedure analogous to that described for the synthesis of compound 505, compound 518 (1.2 g, 41%) was obtained as a colorless oil. 1H-NMR (CDCl3, 400MHz): δ= 7.35-7.33(m, 4H), 7.30-7.27(m, 1H), 5.37-5.27(m, 8H), 5.12(s, 2H), 4.75(m,1H), 4.58-4.57(m,2H), 2.78-2.74(m,7H), 2.06-2.00(m,8H), 1.96-1.91(m, 2H), 1.62(m, 4H), 1.48(m, 2H), 1.37-1.25(br m, 36H), 0.87(m, 6H). HPLC-98.65%.

General Procedure for the Synthesis of Compound 519:

A solution of compound 518 (1 eq) in hexane (15 mL) was added in a drop-wise fashion to an ice-cold solution of LAH in THF (1 M, 2 eq). After complete addition, the mixture was heated at 40°C over 0.5 h then cooled again on an ice bath. The mixture was carefully hydrolyzed with saturated aqueous Na2SO4 then filtered through celite and reduced to an oil. Column chromatography provided the pure 519 (1.3 g, 68%) which was obtained as a colorless oil. 13C NMR = 130.2, 130.1 (x2), 127.9 (x3), 112.3, 79.3, 64.4, 44.7, 38.3, 35.4, 31.5, 29.9 (x2), 29.7, 29.6 (x2), 29.5 (x3), 29.3 (x2), 27.2 (x3), 25.6, 24.5, 23.3, 226, 14.1; Electrospray MS (+ve): Molecular weight for C44H80NO2 (M + H)+ Calc. 654.6, Found 654.6.

Formulations prepared by either the standard or extrusion-free method can be characterized in similar manners. For example, formulations are typically characterized by visual inspection. They should be whitish translucent solutions free from aggregates or sediment. Particle size and particle size distribution of lipid-nanoparticles can be measured by light scattering using, for example, a Malvern Zetasizer Nano ZS (Malvern, USA). Particles should be about 20-300 nm, such as 40-100 nm in size. The particle size distribution should be unimodal. The total dsRNA concentration in the formulation, as well as the entrapped fraction, is estimated using a dye exclusion assay. A sample of the formulated dsRNA can be incubated with an RNA-binding dye, such as Ribogreen (Molecular Probes) in the presence or absence of a

formulation disrupting surfactant, *e.g.*, 0.5% Triton-X100. The total dsRNA in the formulation can be determined by the signal from the sample containing the surfactant, relative to a standard curve. The entrapped fraction is determined by subtracting the "free" dsRNA content (as measured by the signal in the absence of surfactant) from the total dsRNA content. Percent entrapped dsRNA is typically >85%. For SNALP formulation, the particle size is at least 30 nm, at least 40 nm, at least 50 nm, at least 60 nm, at least 70 nm, at least 80 nm, at least 90 nm, at least 100 nm, at least 110 nm, and at least 120 nm. The suitable range is typically about at least 50 nm to about at least 110 nm, about at least 60 nm to about at least 100 nm, or about at least 80 nm to about at least 90 nm.

Compositions and formulations for oral administration include powders or granules, microparticulates, nanoparticulates, suspensions or solutions in water or non-aqueous media, capsules, gel capsules, sachets, tablets or minitablets. Thickeners, flavoring agents, diluents, emulsifiers, dispersing aids or binders may be desirable. In some embodiments, oral formulations are those in which dsRNAs featured in the disclosure are administered in conjunction with one or more penetration enhancers surfactants and chelators. Suitable surfactants include fatty acids and/or esters or salts thereof, bile acids and/or salts thereof. Suitable bile acids/salts include chenodeoxycholic acid (CDCA) and ursodeoxychenodeoxycholic acid (UDCA), cholic acid, dehydrocholic acid, deoxycholic acid, glucholic acid, glycholic acid, glycodeoxycholic acid, taurocholic acid, taurodeoxycholic acid, sodium tauro-24,25-dihydro-fusidate and sodium glycodihydrofusidate. Suitable fatty acids include arachidonic acid, undecanoic acid, oleic acid, lauric acid, caprylic acid, capric acid, myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, dicaprate, tricaprate, monoolein, dilaurin, glyceryl 1-monocaprate, 1-dodecylazacycloheptan-2-one, an acylcarnitine, an acylcholine, or a monoglyceride, a diglyceride or a pharmaceutically acceptable salt thereof (*e.g.*, sodium). In some embodiments, combinations of penetration enhancers are used, for example, fatty acids/salts in combination with bile acids/salts. One exemplary combination is the sodium salt of lauric acid, capric acid and UDCA. Further penetration enhancers include polyoxyethylene-9-lauryl ether, polyoxyethylene-20-cetyl ether. DsRNAs featured in the disclosure may be delivered orally, in granular form including sprayed dried particles, or complexed to form micro or nanoparticles. DsRNA complexing agents include poly-amino acids; polyimines; polyacrylates; polyalkylacrylates, polyoxethanes, polyalkylcyanoacrylates;

cationized gelatins, albumins, starches, acrylates, polyethyleneglycols (PEG) and starches; polyalkylcyanoacrylates; DEAE-derivatized polyimines, pollulans, celluloses and starches. Suitable complexing agents include chitosan, N-trimethylchitosan, poly-L-lysine, polyhistidine, polyornithine, polyspermines, protamine, polyvinylpyridine, polythiodiethylaminomethylethylene P(TDAE), polyaminostyrene (*e.g.*, p-amino), poly(methylcyanoacrylate), poly(ethylcyanoacrylate), poly(butylcyanoacrylate), poly(isobutylcyanoacrylate), poly(isohexylcynaoacrylate), DEAE-methacrylate, DEAE-hexylacrylate, DEAE-acrylamide, DEAE-albumin and DEAE-dextran, polymethylacrylate, polyhexylacrylate, poly(D,L-lactic acid), poly(DL-lactic-co-glycolic acid (PLGA), alginate, and polyethyleneglycol (PEG). Oral formulations for dsRNAs and their preparation are described in detail in U.S. Patent 6,887,906, US Publn. No. 20030027780, and U.S. Patent No. 6,747,014, each of which is incorporated herein by reference.

Compositions and formulations for parenteral, intraparenchymal (into the brain), intrathecal, intravitreal, subretinal, transscleral, subconjunctival, retrobulbar, intracameral, intraventricular, or intrahepatic administration may include sterile aqueous solutions which may 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.

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.

The pharmaceutical formulations featured in the present disclosure, which may conveniently be presented in unit dosage form, may be prepared according to conventional techniques well known in the pharmaceutical industry. Such techniques include the step of bringing into association the active ingredients with the pharmaceutical carrier(s) or excipient(s). In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

The compositions featured in the present disclosure may be formulated into any of many possible dosage forms such as, but not limited to, tablets, capsules, gel capsules, liquid syrups, soft gels, suppositories, and enemas. The compositions may also be formulated as suspensions

in aqueous, non-aqueous or mixed media. Aqueous suspensions may further contain substances which increase the viscosity of the suspension including, for example, sodium carboxymethylcellulose, sorbitol and/or dextran. The suspension may also contain stabilizers.

D. Additional Formulations

i. Emulsions

The compositions of the present disclosure may be prepared and formulated as emulsions. Emulsions are typically heterogeneous systems of one liquid dispersed in another in the form of droplets usually exceeding 0.1μm in diameter (*see e.g.*, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Idson, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199; Rosoff, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., Volume 1, p. 245; Block in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 2, p. 335; Higuchi *et al.*, in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa., 1985, p. 301). Emulsions are often biphasic systems comprising two immiscible liquid phases intimately mixed and dispersed with each other. In general, emulsions may be of either the water-in-oil (w/o) or the oil-in-water (o/w) variety. When an aqueous phase is finely divided into and dispersed as minute droplets into a bulk oily phase, the resulting composition is called a water-in-oil (w/o) emulsion. Alternatively, when an oily phase is finely divided into and dispersed as minute droplets into a bulk aqueous phase, the resulting composition is called an oil-in-water (o/w) emulsion. Emulsions may contain additional components in addition to the dispersed phases, and the active drug which may be present as a solution in either the aqueous phase, oily phase or itself as a separate phase. Pharmaceutical excipients such as emulsifiers, stabilizers, dyes, and anti-oxidants may also be present in emulsions as needed. Pharmaceutical emulsions may also be multiple emulsions that are comprised of more than two phases such as, for example, in the case of oil-in-water-in-oil (o/w/o) and water-in-oil-in-water (w/o/w) emulsions. Such complex formulations often provide certain advantages that simple binary emulsions do not. Multiple emulsions in which individual oil droplets of an o/w emulsion enclose small water droplets constitute a w/o/w emulsion.

Likewise, a system of oil droplets enclosed in globules of water stabilized in an oily continuous phase provides an o/w/o emulsion.

Emulsions are characterized by little or no thermodynamic stability. Often, the dispersed or discontinuous phase of the emulsion is well dispersed into the external or continuous phase and maintained in this form through the means of emulsifiers or the viscosity of the formulation. Either of the phases of the emulsion may be a semisolid or a solid, as is the case of emulsion-style ointment bases and creams. Other means of stabilizing emulsions entail the use of emulsifiers that may be incorporated into either phase of the emulsion. Emulsifiers may broadly be classified into four categories: synthetic surfactants, naturally occurring emulsifiers, absorption bases, and finely dispersed solids (*see e.g.,* Ansel's *Pharmaceutical Dosage Forms and Drug Delivery Systems,* Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Idson, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199).

Synthetic surfactants, also known as surface active agents, have found wide applicability in the formulation of emulsions and have been reviewed in the literature (*see e.g.,* Ansel's *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Rieger, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 285; Idson, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), Marcel Dekker, Inc., New York, N.Y., 1988, volume 1, p. 199). Surfactants are typically amphiphilic and comprise a hydrophilic and a hydrophobic portion. The ratio of the hydrophilic to the hydrophobic nature of the surfactant has been termed the hydrophile/lipophile balance (HLB) and is a valuable tool in categorizing and selecting surfactants in the preparation of formulations. Surfactants may be classified into different classes based on the nature of the hydrophilic group: nonionic, anionic, cationic and amphoteric (*see e.g.,* Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY Rieger, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 285).

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Naturally occurring emulsifiers used in emulsion formulations include lanolin, beeswax, phosphatides, lecithin and acacia. Absorption bases possess hydrophilic properties such that they can soak up water to form w/o emulsions yet retain their semisolid consistencies, such as anhydrous lanolin and hydrophilic petrolatum. Finely divided solids have also been used as good emulsifiers especially in combination with surfactants and in viscous preparations. These include polar inorganic solids, such as heavy metal hydroxides, nonswelling clays such as bentonite, attapulgite, hectorite, kaolin, montmorillonite, colloidal aluminum silicate and colloidal magnesium aluminum silicate, pigments and nonpolar solids such as carbon or glyceryl tristearate.

A large variety of non-emulsifying materials are also included in emulsion formulations and contribute to the properties of emulsions. These include fats, oils, waxes, fatty acids, fatty alcohols, fatty esters, humectants, hydrophilic colloids, preservatives and antioxidants (Block, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 335; Idson, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199).

Hydrophilic colloids or hydrocolloids include naturally occurring gums and synthetic polymers such as polysaccharides (for example, acacia, agar, alginic acid, carrageenan, guar gum, karaya gum, and tragacanth), cellulose derivatives (for example, carboxymethylcellulose and carboxypropylcellulose), and synthetic polymers (for example, carbomers, cellulose ethers, and carboxyvinyl polymers). These disperse or swell in water to form colloidal solutions that stabilize emulsions by forming strong interfacial films around the dispersed-phase droplets and by increasing the viscosity of the external phase.

Since emulsions often contain a number of ingredients such as carbohydrates, proteins, sterols and phosphatides that may readily support the growth of microbes, these formulations often incorporate preservatives. Commonly used preservatives included in emulsion formulations include methyl paraben, propyl paraben, quaternary ammonium salts, benzalkonium chloride, esters of p-hydroxybenzoic acid, and boric acid. Antioxidants are also commonly added to emulsion formulations to prevent deterioration of the formulation. Antioxidants used may be free radical scavengers such as tocopherols, alkyl gallates, butylated hydroxyanisole, butylated hydroxytoluene, or reducing agents such as ascorbic acid and sodium metabisulfite, and antioxidant synergists such as citric acid, tartaric acid, and lecithin.

The application of emulsion formulations via dermatological, oral and parenteral routes and methods for their manufacture have been reviewed in the literature (*see e.g.,* Ansel's *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Idson, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199). Emulsion formulations for oral delivery have been very widely used because of ease of formulation, as well as efficacy from an absorption and bioavailability standpoint (*see e.g.,* Ansel's *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Rosoff, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 245; Idson, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199). Mineral-oil base laxatives, oil-soluble vitamins and high fat nutritive preparations are among the materials that have commonly been administered orally as o/w emulsions.

ii. Microemulsions

In some embodiments of the present disclosure, the compositions of iRNAs and nucleic acids are formulated as microemulsions. A microemulsion may be defined as a system of water, oil and amphiphile which is a single optically isotropic and thermodynamically stable liquid solution (*see e.g.,* Ansel's *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Rosoff, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 245). Typically, microemulsions are systems that are prepared by first dispersing an oil in an aqueous surfactant solution and then adding a sufficient amount of a fourth component, generally an intermediate chain-length alcohol to form a transparent system. Therefore, microemulsions have also been described as thermodynamically stable, isotopically clear dispersions of two immiscible liquids that are stabilized by interfacial films of surface-active molecules (Leung and Shah, in: *Controlled Release of Drugs: Polymers and Aggregate Systems*, Rosoff, M., Ed., 1989, VCH Publishers, New York, pages 185-215). Microemulsions commonly are prepared via a combination of three to five components that include oil, water, surfactant, cosurfactant and electrolyte. Whether the

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microemulsion is of the water-in-oil (w/o) or an oil-in-water (o/w) type is dependent on the properties of the oil and surfactant used and on the structure and geometric packing of the polar heads and hydrocarbon tails of the surfactant molecules (Schott, in Remington's *Pharmaceutical Sciences*, Mack Publishing Co., Easton, Pa., 1985, p. 271).

The phenomenological approach utilizing phase diagrams has been extensively studied and has yielded a comprehensive knowledge, to one skilled in the art, of how to formulate microemulsions (*see e.g.*, Ansel's *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Rosoff, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 245; Block, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 335). Compared to conventional emulsions, microemulsions offer the advantage of solubilizing water-insoluble drugs in a formulation of thermodynamically stable droplets that are formed spontaneously.

Surfactants used in the preparation of microemulsions include, but are not limited to, ionic surfactants, non-ionic surfactants, Brij 96, polyoxyethylene oleyl ethers, polyglycerol fatty acid esters, tetraglycerol monolaurate (ML310), tetraglycerol monooleate (MO310), hexaglycerol monooleate (PO310), hexaglycerol pentaoleate (PO500), decaglycerol monocaprate (MCA750), decaglycerol monooleate (MO750), decaglycerol sequioleate (SO750), decaglycerol decaoleate (DAO750), alone or in combination with cosurfactants. The cosurfactant, usually a short-chain alcohol such as ethanol, 1-propanol, and 1-butanol, serves to increase the interfacial fluidity by penetrating into the surfactant film and consequently creating a disordered film because of the void space generated among surfactant molecules. Microemulsions may, however, be prepared without the use of cosurfactants and alcohol-free self-emulsifying microemulsion systems are known in the art. The aqueous phase may typically be, but is not limited to, water, an aqueous solution of the drug, glycerol, PEG300, PEG400, polyglycerols, propylene glycols, and derivatives of ethylene glycol. The oil phase may include, but is not limited to, materials such as Captex 300, Captex 355, Capmul MCM, fatty acid esters, medium chain (C8-C12) mono, di, and tri-glycerides, polyoxyethylated glyceryl fatty acid esters, fatty alcohols, polyglycolized glycerides, saturated polyglycolized C8-C10 glycerides, vegetable oils and silicone oil.

Microemulsions are particularly of interest from the standpoint of drug solubilization and the enhanced absorption of drugs. Lipid based microemulsions (both o/w and w/o) have been proposed to enhance the oral bioavailability of drugs, including peptides (*see e.g.,* U.S. Patent Nos. 6,191,105; 7,063,860; 7,070,802; 7,157,099; Constantinides *et al., Pharmaceutical Research*, 1994, 11, 1385-1390; Ritschel, *Meth. Find. Exp. Clin. Pharmacol.*, 1993, 13, 205). Microemulsions afford advantages of improved drug solubilization, protection of drug from enzymatic hydrolysis, possible enhancement of drug absorption due to surfactant-induced alterations in membrane fluidity and permeability, ease of preparation, ease of oral administration over solid dosage forms, improved clinical potency, and decreased toxicity (*see e.g.*, U.S. Patent Nos. 6,191,105; 7,063,860; 7,070,802; 7,157,099; Constantinides *et al., Pharmaceutical Research*, 1994, 11, 1385; Ho *et al., J. Pharm. Sci.*, 1996, 85, 138-143). Often microemulsions may form spontaneously when their components are brought together at ambient temperature. This may be particularly advantageous when formulating thermolabile drugs, peptides or iRNAs. Microemulsions have also been effective in the transdermal delivery of active components in both cosmetic and pharmaceutical applications. It is expected that the microemulsion compositions and formulations of the present disclosure will facilitate the increased systemic absorption of iRNAs and nucleic acids from the gastrointestinal tract, as well as improve the local cellular uptake of iRNAs and nucleic acids.

Microemulsions of the present disclosure may also contain additional components and additives such as sorbitan monostearate (Grill 3), Labrasol, and penetration enhancers to improve the properties of the formulation and to enhance the absorption of the iRNAs and nucleic acids of the present disclosure. Penetration enhancers used in the microemulsions of the present disclosure may be classified as belonging to one of five broad categories--surfactants, fatty acids, bile salts, chelating agents, and non-chelating non-surfactants (Lee *et al., Critical Reviews in Therapeutic Drug Carrier Systems*, 1991, p. 92). Each of these classes has been discussed above.

iii. Penetration Enhancers

In some embodiments, the present disclosure employs various penetration enhancers to effect the efficient delivery of nucleic acids, particularly iRNAs, to the skin of animals. Most drugs are present in solution in both ionized and nonionized forms. However, usually only lipid

soluble or lipophilic drugs readily cross cell membranes. It has been discovered that even non-lipophilic drugs may cross cell membranes if the membrane to be crossed is treated with a penetration enhancer. In addition to aiding the diffusion of non-lipophilic drugs across cell membranes, penetration enhancers also enhance the permeability of lipophilic drugs.

Penetration enhancers may be classified as belonging to one of five broad categories, *i.e.*, surfactants, fatty acids, bile salts, chelating agents, and non-chelating non-surfactants (*see e.g.*, Malmsten, M. Surfactants and polymers in drug delivery, *Informa Health Care*, New York, NY, 2002; Lee *et al.*, *Critical Reviews in Therapeutic Drug Carrier Systems*, 1991, p.92). Each of the above-mentioned classes of penetration enhancers are described below in greater detail.

Surfactants: In connection with the present disclosure, surfactants (or "surface-active agents") are chemical entities which, when dissolved in an aqueous solution, reduce the surface tension of the solution or the interfacial tension between the aqueous solution and another liquid, with the result that absorption of iRNAs through the mucosa is enhanced. In addition to bile salts and fatty acids, these penetration enhancers include, for example, sodium lauryl sulfate, polyoxyethylene-9-lauryl ether and polyoxyethylene-20-cetyl ether) (*see e.g.*, Malmsten, M. Surfactants and polymers in drug delivery, Informa Health Care, New York, NY, 2002; Lee *et al.*, *Critical Reviews in Therapeutic Drug Carrier Systems*, 1991, p.92); and perfluorochemical emulsions, such as FC-43. Takahashi *et al.*, *J. Pharm. Pharmacol.*, 1988, 40, 252).

Fatty acids: Various fatty acids and their derivatives which act as penetration enhancers include, for example, oleic acid, lauric acid, capric acid (n-decanoic acid), myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, dicaprate, tricaprate, monoolein (1-monooleoyl-rac-glycerol), dilaurin, caprylic acid, arachidonic acid, glycerol 1-monocaprate, 1-dodecylazacycloheptan-2-one, acylcarnitines, acylcholines, C_{1-20} alkyl esters thereof (*e.g.*, methyl, isopropyl and t-butyl), and mono- and di-glycerides thereof (*i.e.*, oleate, laurate, caprate, myristate, palmitate, stearate, linoleate, *etc.*) (*see e.g.*, Touitou, E., *et al. Enhancement in Drug Delivery*, CRC Press, Danvers, MA, 2006; Lee *et al.*, *Critical Reviews in Therapeutic Drug Carrier Systems*, 1991, p.92; Muranishi, *Critical Reviews in Therapeutic Drug Carrier Systems*, 1990, 7, 1-33; El Hariri *et al.*, *J. Pharm. Pharmacol.*, 1992, 44, 651-654).

Bile salts: The physiological role of bile includes the facilitation of dispersion and absorption of lipids and fat-soluble vitamins (*see e.g.*, Malmsten, M. Surfactants and polymers in drug delivery, *Informa Health Care*, New York, NY, 2002; Brunton, Chapter 38 in: Goodman &

Gilman's *The Pharmacological Basis of Therapeutics*, 9th Ed., Hardman *et al.* Eds., McGraw-Hill, New York, 1996, pp. 934-935). Various natural bile salts, and their synthetic derivatives, act as penetration enhancers. Thus, the term "bile salts" includes any of the naturally occurring components of bile as well as any of their synthetic derivatives. Suitable bile salts include, for example, cholic acid (or its pharmaceutically acceptable sodium salt, sodium cholate), dehydrocholic acid (sodium dehydrocholate), deoxycholic acid (sodium deoxycholate), glucholic acid (sodium glucholate), glycholic acid (sodium glycocholate), glycodeoxycholic acid (sodium glycodeoxycholate), taurocholic acid (sodium taurocholate), taurodeoxycholic acid (sodium taurodeoxycholate), chenodeoxycholic acid (sodium chenodeoxycholate), ursodeoxycholic acid (UDCA), sodium tauro-24,25-dihydro-fusidate (STDHF), sodium glycodihydrofusidate and polyoxyethylene-9-lauryl ether (POE) (*see e.g.*, Malmsten, M. Surfactants and polymers in drug delivery, *Informa Health Care*, New York, NY, 2002; Lee *et al.*, *Critical Reviews in Therapeutic Drug Carrier Systems*, 1991, page 92; Swinyard, Chapter 39 In: *Remington's Pharmaceutical Sciences*, 18th Ed., Gennaro, ed., Mack Publishing Co., Easton, Pa., 1990, pages 782-783; Muranishi, *Critical Reviews in Therapeutic Drug Carrier Systems*, 1990, 7, 1-33; Yamamoto *et al.*, *J. Pharm. Exp. Ther.*, 1992, 263, 25; Yamashita *et al.*, *J. Pharm. Sci.*, 1990, 79, 579-583).

Chelating Agents: Chelating agents, as used in connection with the present disclosure, can be defined as compounds that remove metallic ions from solution by forming complexes therewith, with the result that absorption of iRNAs through the mucosa is enhanced. With regards to their use as penetration enhancers in the present disclosure, chelating agents have the added advantage of also serving as DNase inhibitors, as most characterized DNA nucleases require a divalent metal ion for catalysis and are thus inhibited by chelating agents (Jarrett, *J. Chromatogr.*, 1993, 618, 315-339). Suitable chelating agents include but are not limited to disodium ethylenediaminetetraacetate (EDTA), citric acid, salicylates (*e.g.*, sodium salicylate, 5-methoxysalicylate and homovanilate), N-acyl derivatives of collagen, laureth-9 and N-amino acyl derivatives of β-diketones (enamines)(*see e.g.*, Katdare, A. *et al.*, *Excipient development for pharmaceutical, biotechnology, and drug delivery*, CRC Press, Danvers, MA, 2006; Lee *et al.*, *Critical Reviews in Therapeutic Drug Carrier Systems*, 1991, page 92; Muranishi, *Critical Reviews in Therapeutic Drug Carrier Systems*, 1990, 7, 1-33; Buur *et al.*, *J. Control Rel.*, 1990, 14, 43-51).

Non-chelating non-surfactants: As used herein, non-chelating non-surfactant penetration enhancing compounds can be defined as compounds that demonstrate insignificant activity as chelating agents or as surfactants but that nonetheless enhance absorption of iRNAs through the alimentary mucosa (*see e.g.*, Muranishi, *Critical Reviews in Therapeutic Drug Carrier Systems*, 1990, 7, 1-33). This class of penetration enhancers include, for example, unsaturated cyclic ureas, 1-alkyl- and 1-alkenylazacyclo-alkanone derivatives (Lee *et al.*, *Critical Reviews in Therapeutic Drug Carrier Systems*, 1991, page 92); and non-steroidal anti-inflammatory agents such as diclofenac sodium, indomethacin and phenylbutazone (Yamashita *et al.*, *J. Pharm. Pharmacol.*, 1987, 39, 621-626).

Agents that enhance uptake of iRNAs at the cellular level may also be added to the pharmaceutical and other compositions of the present disclosure. For example, cationic lipids, such as lipofectin (Junichi *et al*, U.S. Pat. No. 5,705,188), cationic glycerol derivatives, and polycationic molecules, such as polylysine (Lollo *et al.*, PCT Application WO 97/30731), are also known to enhance the cellular uptake of dsRNAs. Examples of commercially available transfection reagents include, for example Lipofectamine™ (Invitrogen; Carlsbad, CA), Lipofectamine 2000™ (Invitrogen; Carlsbad, CA), 293fectin™ (Invitrogen; Carlsbad, CA), Cellfectin™ (Invitrogen; Carlsbad, CA), DMRIE-C™ (Invitrogen; Carlsbad, CA), FreeStyle™ MAX (Invitrogen; Carlsbad, CA), Lipofectamine™ 2000 CD (Invitrogen; Carlsbad, CA), Lipofectamine™ (Invitrogen; Carlsbad, CA), RNAiMAX (Invitrogen; Carlsbad, CA), Oligofectamine™ (Invitrogen; Carlsbad, CA), Optifect™ (Invitrogen; Carlsbad, CA), X-tremeGENE Q2 Transfection Reagent (Roche; Grenzacherstrasse, Switzerland), DOTAP Liposomal Transfection Reagent (Grenzacherstrasse, Switzerland), DOSPER Liposomal Transfection Reagent (Grenzacherstrasse, Switzerland), or Fugene (Grenzacherstrasse, Switzerland), Transfectam® Reagent (Promega; Madison, WI), TransFast™ Transfection Reagent (Promega; Madison, WI), Tfx™-20 Reagent (Promega; Madison, WI), Tfx™-50 Reagent (Promega; Madison, WI), DreamFect™ (OZ Biosciences; Marseille, France), EcoTransfect (OZ Biosciences; Marseille, France), TransPass® D1 Transfection Reagent (New England Biolabs; Ipswich, MA, USA), LyoVec™/LipoGen™ (Invivogen; San Diego, CA, USA), PerFectin Transfection Reagent (Genlantis; San Diego, CA, USA), NeuroPORTER Transfection Reagent (Genlantis; San Diego, CA, USA), GenePORTER Transfection reagent (Genlantis; San Diego, CA, USA), GenePORTER 2 Transfection reagent (Genlantis; San Diego,

CA, USA), Cytofectin Transfection Reagent (Genlantis; San Diego, CA, USA), BaculoPORTER Transfection Reagent (Genlantis; San Diego, CA, USA), TroganPORTER™ transfection Reagent (Genlantis; San Diego, CA, USA), RiboFect (Bioline; Taunton, MA, USA), PlasFect (Bioline; Taunton, MA, USA), UniFECTOR (B-Bridge International; Mountain View, CA, USA), SureFECTOR (B-Bridge International; Mountain View, CA, USA), or HiFect™ (B-Bridge International, Mountain View, CA, USA), among others.

Other agents may be utilized to enhance the penetration of the administered nucleic acids, including glycols such as ethylene glycol and propylene glycol, pyrrols such as 2-pyrrol, azones, and terpenes such as limonene and menthone.

iv. Carriers

Certain compositions of the present disclosure also incorporate carrier compounds in the formulation. As used herein, "carrier compound" can refer to a nucleic acid, or analog thereof, which is inert (*i.e.*, does not possess biological activity per se) but is recognized as a nucleic acid by *in vivo* processes that reduce the bioavailability of a nucleic acid having biological activity by, for example, degrading the biologically active nucleic acid or promoting its removal from circulation. The coadministration of a nucleic acid and a carrier compound, typically with an excess of the latter substance, can result in a substantial reduction of the amount of nucleic acid recovered in the liver, kidney or other extracirculatory reservoirs, presumably due to competition between the carrier compound and the nucleic acid for a common receptor. For example, the recovery of a partially phosphorothioate dsRNA in hepatic tissue can be reduced when it is coadministered with polyinosinic acid, dextran sulfate, polycytidic acid or 4-acetamido-4'isothiocyano-stilbene-2,2'-disulfonic acid (Miyao *et al.*, *DsRNA Res. Dev.*, 1995, 5, 115-121; Takakura *et al.*, *DsRNA & Nucl. Acid Drug Dev.*, 1996, 6, 177-183).

v. Excipients

In contrast to a carrier compound, a pharmaceutical carrier or excipient may comprise, *e.g.*, a pharmaceutically acceptable solvent, suspending agent or any other pharmacologically inert vehicle for delivering one or more nucleic acids to an animal. The excipient may be liquid or solid and is selected, with the planned manner of administration in mind, so as to provide for the desired bulk, consistency, *etc.*, when combined with a nucleic acid and the other components

of a given pharmaceutical composition. Typical pharmaceutical carriers include, but are not limited to, binding agents (*e.g.*, pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose, *etc.*); fillers (*e.g.*, lactose and other sugars, microcrystalline cellulose, pectin, gelatin, calcium sulfate, ethyl cellulose, polyacrylates or calcium hydrogen phosphate, *etc.*); lubricants (*e.g.*, magnesium stearate, talc, silica, colloidal silicon dioxide, stearic acid, metallic stearates, hydrogenated vegetable oils, corn starch, polyethylene glycols, sodium benzoate, sodium acetate, *etc.*); disintegrants (*e.g.*, starch, sodium starch glycolate, *etc.*); and wetting agents (*e.g.*, sodium lauryl sulphate, *etc*).

Pharmaceutically acceptable organic or inorganic excipients suitable for non-parenteral administration which do not deleteriously react with nucleic acids can also be used to formulate the compositions of the present disclosure. Suitable pharmaceutically acceptable carriers include, but are not limited to, water, salt solutions, alcohols, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, hydroxymethylcellulose, polyvinylpyrrolidone and the like.

Formulations for topical administration of nucleic acids may include sterile and non-sterile aqueous solutions, non-aqueous solutions in common solvents such as alcohols, or solutions of the nucleic acids in liquid or solid oil bases. The solutions may also contain buffers, diluents and other suitable additives. Pharmaceutically acceptable organic or inorganic excipients suitable for non-parenteral administration which do not deleteriously react with nucleic acids can be used.

Suitable pharmaceutically acceptable excipients include, but are not limited to, water, salt solutions, alcohol, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, hydroxymethylcellulose, polyvinylpyrrolidone and the like.

vi. Other Components

The compositions of the present disclosure may additionally contain other adjunct components conventionally found in pharmaceutical compositions, *e.g.*, at their art-established usage levels. Thus, for example, the compositions may contain additional, compatible, pharmaceutically-active materials such as, for example, antipruritics, astringents, local anesthetics or anti-inflammatory agents, or may contain additional materials useful in physically formulating various dosage forms of the compositions of the present disclosure, such as dyes,

flavoring agents, preservatives, antioxidants, opacifiers, thickening agents and stabilizers. However, such materials, when added, should not unduly interfere with the biological activities of the components of the compositions of the present disclosure. The formulations can be sterilized and, if desired, mixed with auxiliary agents, *e.g.*, lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, colorings, flavorings and/or aromatic substances and the like which do not deleteriously interact with the nucleic acid(s) of the formulation.

Aqueous suspensions may contain substances that increase the viscosity of the suspension including, for example, sodium carboxymethylcellulose, sorbitol and/or dextran. The suspension may also contain stabilizers.

In some embodiments, pharmaceutical compositions featured in the disclosure include (a) one or more iRNA compounds and (b) one or more biologic agents which function by a non-RNAi mechanism. Examples of such biologic agents include agents that interfere with an interaction of CA2 and at least one CA2 binding partner.

Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD50/ED50. Compounds that exhibit high therapeutic indices are typical.

The data obtained from cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of compositions featured in the disclosure lies generally within a range of circulating concentrations that include the ED50 with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the methods featured in the disclosure, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range of the compound or, when appropriate, of the polypeptide product of a target sequence (*e.g.*, achieving a decreased concentration of the polypeptide) that includes the IC50 (*i.e.*, the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful

doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography.

In addition to their administration, as discussed above, the iRNAs featured in the disclosure can be administered in combination with other known agents effective in treatment of diseases or disorders related to CA2 expression (*e.g.*, glaucoma or conditions associated with glaucoma). In any event, the administering physician can adjust the amount and timing of iRNA administration on the basis of results observed using standard measures of efficacy known in the art or described herein.

VII. Methods of treating disorders related to expression of CA2

The present disclosure relates to the use of an iRNA targeting CA2 to inhibit CA2 expression and/or to treat a disease, disorder, or pathological process that is related to CA2 expression (*e.g.*, glaucoma or conditions associated with glaucoma).

In some aspects, a method of treatment of a disorder related to expression of CA2 is provided, the method comprising administering an iRNA (*e.g.*, a dsRNA) disclosed herein to a subject in need thereof. In some embodiments, the iRNA inhibits (decreases) CA2 expression.

In some embodiments, the subject is an animal that serves as a model for a disorder related to CA2 expression, *e.g.*, glaucoma or conditions associated with glaucoma.

A. Glaucoma or Conditions Associated with Glaucoma

In some embodiments, the disorder related to CA2 expression is glaucoma or conditions associated with glaucoma. Non-limiting examples of glaucoma or conditions associated with glaucoma that are treatable using the methods described herein include glaucoma, open-angle glaucoma, angle-closure glaucoma, ocular inflammation, systemic inflammation, anterior uveitis, acute retinal necrosis, Sturge-Weber syndrome, Axenfeld-Rieger syndrome, Marfan syndrome, homocystinuria, Weill-Marchesani syndrome, and autoimmune diseases, such as juvenile rheumatoid arthritis and Marie-Strumpell ankylosing spondylitis.

Clinical and pathological features of glaucoma or conditions associated with glaucoma include, but are not limited to, intraocular pressure, vision loss, a reduction in visual acuity (*e.g.*, characterized by floating spots, blurriness around the edges or center of field of vision (*e.g.*, scotoma), ocular inflammation, and/or optic nerve damage.

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In some embodiments, the subject with glaucoma or conditions associated with glaucoma is less than 18 years old. In some embodiments, the subject with glaucoma or conditions associated with glaucoma is an adult. In some embodiments, the subject has, or is identified as having, elevated levels of CA2 mRNA or protein relative to a reference level (e.g., a level of CA2 that is greater than a reference level).

In some embodiments, the glaucoma or conditions associated with glaucoma is diagnosed using analysis of a sample from the subject (*e.g.*, a ciliary epithelium sample). In some embodiments, the sample is analyzed using a method selected from one or more of: fluorescent in situ hybridization (FISH), immunohistochemistry, CA2 immunoassay, electron microscopy, laser microdissection, and mass spectrometry. In some embodiments, glaucoma or conditions associated with glaucoma is diagnosed using any suitable diagnostic test or technique, *e.g.*, tonometry, pachymetry, evaluation of the retina, gonioscopy, angiography (*e.g.*, fluorescein angiography or indocyanine green angiography), electroretinography, ultrasonography, optical coherence tomography (OCT), computed tomography (CT) and magnetic resonance imaging (MRI), color vision testing, visual field testing, slit-lamp examination, ophthalmoscopy, and physical examination (*e.g.*, to assess visual acuity (e.g., by fundoscopy or optical coherence tomography (OCT)).

B. Combination Therapies

In some embodiments, an iRNA (*e.g.*, a dsRNA) disclosed herein is administered in combination with a second therapy (*e.g.*, one or more additional therapies) known to be effective in treating a disorder related to CA2 expression (*e.g.*, glaucoma) or a symptom of such a disorder. The iRNA may be administered before, after, or concurrent with the second therapy. In some embodiments, the iRNA is administered before the second therapy. In some embodiments, the iRNA is administered after the second therapy. In some embodiments, the iRNA is administered concurrent with the second therapy.

The second therapy may be an additional therapeutic agent. The iRNA and the additional therapeutic agent can be administered in combination in the same composition or the additional therapeutic agent can be administered as part of a separate composition.

In some embodiments, the second therapy is a non-iRNA therapeutic agent that is effective to treat the disorder or symptoms of the disorder.

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In some embodiments, the iRNA is administered in conjunction with a therapy. Exemplary combination therapies include, but are not limited to, medication to reduce intraocular pressure, laser treatment, surgery or trabeculectomy. In some embodiments, the additional therapeutic agent comprises a prostaglandin analog, a beta blocker, an alpha-adrenergic agonist, a carbonic anhydrase inhibitor, or an anti-CA2 agent.

In some embodiments, the additional therapeutic is a prostaglandin analog. In some embodiments, the prostaglandin analog comprises Bimatoprost (Lumigan®), Latanoprost (Xalatan®), Tafluprost (Zioptan™), latanoprostene bunod (Vyzulta™) or Travoprost (Travatan Z®).

In some embodiments, the additional therapeutic agent is a beta blocker. In some embodiments, the beta blocker comprises Betaxolol (Betoptic S®) or Timolol (Betimol®, Timoptic).

In some embodiments, the additional therapeutic agent is an alpha-adrenergic agonist. In some embodiments, the alpha-adrenergic agonist comprises brimonidine (Alphagan®P) or apraclonidine (Iopidine®).

In some embodiments, the additional therapeutic agent is a carbonic anhydrase inhibitor. In some embodiments, the carbonic anhydrase inhibitor comprises dorzolamide (Trusopt®), brinzolamide (Azopt®), acetazolamide (Diamox) or methazolamide (Neptazane®).

In some embodiments, the anti-CA2 agent is an antibody molecule. In some embodiments the antibody is a monoclonal antibody.

C. Administration dosages, routes, and timing

A subject (*e.g.*, a human subject, *e.g.*, a patient) can be administered a therapeutic amount of iRNA. The therapeutic amount can be, *e.g.*, 0.05-50 mg/kg.

In some embodiments, the iRNA is formulated for delivery to a target organ, *e.g.*, to the eye.

In some embodiments, the iRNA is formulated as a lipid formulation, *e.g.*, an LNP formulation as described herein. In some such embodiments, the therapeutic amount is 0.05-5 mg/kg dsRNA. In some embodiments, the lipid formulation, *e.g.*, LNP formulation, is administered intravenously.

In some embodiments, the iRNA is in the form of a GalNAc conjugate *e.g.*, as described herein. In some such embodiments, the therapeutic amount is 0.5-50 mg dsRNA. In some embodiments, the *e.g.*, GalNAc conjugate is administered subcutaneously.

In some embodiments, the iRNA is in the form of a C16 conjugate *e.g.*, as described herein.

In certain embodiments, subjects can be administered a therapeutic amount of dsRNA, such as about 0.01 mg/kg to about 200 mg/kg. In other embodiments, subjects can be administered a therapeutic amount of dsRNA, such as about 0.01 mg/kg to about 500 mg/kg. In yet other embodiments, subjects can be administered a therapeutic amount of dsRNA of about 500 mg/kg or more.

In some embodiments, the administration is repeated, for example, on a regular basis, such as, daily, biweekly (*i.e.*, every two weeks) for one month, two months, three months, four months, six months or longer. After an initial treatment regimen, the treatments can be administered on a less frequent basis. For example, after administration biweekly for three months, administration can be repeated once per month, for six months or a year or longer.

In some embodiments, the iRNA agent is administered in two or more doses. In some embodiments, the number or amount of subsequent doses is dependent on the achievement of a desired effect, *e.g.*, to (a) inhibit or reduce intraocular pressure; (b) inhibit or reduce the expression or activity of CA2; (c) decrease the amount of aqueous humor; (d) inhibit or reduce optic nerve damage; or (e) inhibit or reduce retinal ganglion cell death, or the achievement of a therapeutic or prophylactic effect, *e.g.*, reduction or prevention of one or more symptoms associated with the disorder.

In some embodiments, the iRNA agent is administered according to a schedule. For example, the iRNA agent may be administered once per week, twice per week, three times per week, four times per week, or five times per week. In some embodiments, the schedule involves regularly spaced administrations, *e.g.*, hourly, every four hours, every six hours, every eight hours, every twelve hours, daily, every 2 days, every 3 days, every 4 days, every 5 days, weekly, biweekly, or monthly. In some embodiments, the iRNA agent is administered at the frequency required to achieve a desired effect.

In some embodiments, the schedule involves closely spaced administrations followed by a longer period of time during which the agent is not administered. For example, the schedule

may involve an initial set of doses that are administered in a relatively short period of time (*e.g.*, about every 6 hours, about every 12 hours, about every 24 hours, about every 48 hours, or about every 72 hours) followed by a longer time period (*e.g.*, about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, or about 8 weeks) during which the iRNA agent is not administered. In some embodiments, the iRNA agent is initially administered hourly and is later administered at a longer interval (*e.g.*, daily, weekly, biweekly, or monthly). In some embodiments, the iRNA agent is initially administered daily and is later administered at a longer interval (*e.g.*, weekly, biweekly, or monthly). In certain embodiments, the longer interval increases over time or is determined based on the achievement of a desired effect.

Before administration of a full dose of the iRNA, patients can be administered a smaller dose, such as a 5% infusion dose, and monitored for adverse effects, such as an allergic reaction, or for elevated lipid levels or blood pressure. In another example, the patient can be monitored for unwanted effects.

VIII. Methods for modulating expression of CA2

In some aspects, the disclosure provides a method for modulating (*e.g.*, inhibiting or activating) the expression of CA2, *e.g.*, in a cell, in a tissue, or in a subject. In some embodiments, the cell or tissue is *ex vivo*, *in vitro*, or *in vivo*. In some embodiments, the cell or tissue is in the eye (*e.g.*, a ciliary epithelium cell, an optic nerve cell, a trabecular meshwork cell, a Schlemm's canal cell (e.g., including an endothelial cell), a juxtacanalicular tissue cell, a ciliary muscle cell, a retinal cell, an astrocyte, a pericyte, a Müller cell, a ganglion cell (e.g., including a retinal ganglion cell), an endothelial cell, a photoreceptor cell, a retinal blood vessel (e.g., including endothelial cells and vascular smooth muscle cells), episcleral veins or choroid tissue, e.g., a choroid vessel). In some embodiments, the cell or tissue is in a subject (*e.g.*, a mammal, such as, for example, a human). In some embodiments, the subject (*e.g.*, the human) is at risk, or is diagnosed with a disorder related to expression of CA2 expression, as described herein.

In some embodiments, the method includes contacting the cell with an iRNA as described herein, in an amount effective to decrease the expression of CA2 in the cell. In some embodiments, contacting a cell with an RNAi agent includes contacting a cell *in vitro* with the

RNAi agent or contacting a cell *in vivo* with the RNAi agent. In some embodiments, the RNAi agent is put into physical contact with the cell by the individual performing the method, or the RNAi agent may be put into a situation that will permit or cause it to subsequently come into contact with the cell. Contacting a cell in vitro may be done, for example, by incubating the cell with the RNAi agent. Contacting a cell in vivo may be done, for example, by injecting the RNAi agent into or near the tissue where the cell is located, or by injecting the RNAi agent into another area, *e.g.*, ocular tissue. For example, the RNAi agent may contain or be coupled to a ligand, *e.g.*, a lipophilic moiety or moieties as described below and further detailed, *e.g.*, in PCT/US2019/031170 which is incorporated herein by reference in its entirety, including the passages therein describing lipophilic moieties, that directs or otherwise stabilizes the RNAi agent at a site of interest. Combinations of in vitro and in vivo methods of contacting are also possible. For example, a cell may also be contacted in vitro with an RNAi agent and subsequently transplanted into a subject.

The expression of CA2 may be assessed based on the level of expression of CA2 mRNA, CA2 protein, or the level of another parameter functionally linked to the level of expression of CA2. In some embodiments, the expression of CA2 is inhibited by 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 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95%. In some embodiments, the iRNA has an IC_{50} in the range of 0.001-0.01 nM, 0.001-0.10 nM, 0.001-1.0 nM, 0.001-10 nM, 0.01-0.05 nM, 0.01-0.50 nM, 0.02-0.60 nM, 0.01-1.0 nM, 0.01-1.5 nM, 0.01-10 nM. The IC_{50} value may be normalized relative to an appropriate control value, *e.g.*, the IC_{50} of a non-targeting iRNA.

In some embodiments, the method includes introducing into the cell or tissue an iRNA as described herein and maintaining the cell or tissue for a time sufficient to obtain degradation of the mRNA transcript of CA2, thereby inhibiting the expression of CA2 in the cell or tissue.

In some embodiments, the method includes administering a composition described herein, *e.g.*, a composition comprising an iRNA that binds CA2, to the mammal such that expression of the target CA2 is decreased, such as for an extended duration, *e.g.*, at least two, three, four days or more, *e.g.*, one week, two weeks, three weeks, or four weeks or longer. In some embodiments, the decrease in expression of CA2 is detectable within 1 hour, 2 hours, 4 hours, 8 hours, 12 hours, or 24 hours of the first administration.

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In some embodiments, the method includes administering a composition as described herein to a mammal such that expression of the target CA2 is increased by e.g., at least 10% compared to an untreated animal. In some embodiments, the activation of CA2 occurs over an extended duration, e.g., at least two, three, four days or more, e.g., one week, two weeks, three weeks, four weeks, or more. Without wishing to be bound by theory, an iRNA can activate CA2 expression by stabilizing the CA2 mRNA transcript, interacting with a promoter in the genome, or inhibiting an inhibitor of CA2 expression.

The iRNAs useful for the methods and compositions featured in the disclosure specifically target RNAs (primary or processed) of CA2. Compositions and methods for inhibiting the expression of CA2 using iRNAs can be prepared and performed as described elsewhere herein.

In some embodiments, the method includes administering a composition containing an iRNA, where the iRNA includes a nucleotide sequence that is complementary to at least a part of an RNA transcript of CA2 of the subject, *e.g.*, the mammal, *e.g.*, the human, to be treated. The composition may be administered by any appropriate means known in the art including, but not limited to ocular (*e.g.*, intraocular), topical, and intravenous administration.

In certain embodiments, the composition is administered intraocularly (*e.g.*, by intravitreal administration, e.g., intravitreal injection; transscleral administration, e.g., transscleral injection; subconjunctival administration, e.g., subconjunctival injection; retrobulbar administration, e.g., retrobulbar injection; intracameral administration, e.g., intracameral injection; or subretinal administration, e.g., subretinal injection. In other embodiments, the composition is administered topically. In other embodiments, the composition is administered by intravenous infusion or injection.

In certain embodiments, the composition is administered by intravenous infusion or injection. In some such embodiments, the composition comprises a lipid formulated siRNA (*e.g.*, an LNP formulation, such as an LNP11 formulation) for intravenous infusion.

Unless otherwise defined, 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 belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the iRNAs and methods featured in the disclosure, suitable methods and materials are described below. All publications, patent applications, patents, and

other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

Specific Embodiments

In an embodiment the disclosure provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of carbonic anhydrase 2 (CA2), wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, of a portion of a coding strand of human CA2 and the antisense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, of the corresponding portion of a non-coding strand of human CA2 such that the sense strand is complementary to the at least 15 contiguous nucleotides in the antisense strand.

In some embodiments the disclosure provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of carbonic anhydrase 2 (CA2), wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, of a portion of a coding strand of human CA2 and the antisense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, of the corresponding portion of a non-coding strand of human CA2 such that the sense strand is complementary to the at least 15 contiguous nucleotides in the antisense strand wherein the dsRNA agent comprises at least one modified nucleotide.

In some embodiments the coding strand of human CA2 comprises the sequence SEQ ID NO: 1. In some embodiments the non-coding strand of human CA2 comprises the sequence of SEQ ID NO: 2

In some embodiments the double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of CA2 comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, of a portion of nucleotide sequence of

SEQ ID NO: 2 such that the sense strand is complementary to the at least 15 contiguous nucleotides in the antisense strand.

In some embodiments the double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of CA2 comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides, with 0, or 1, 2, or 3 mismatches, of the corresponding portion of the nucleotide sequence of SEQ ID NO: 1.

In some embodiments the dsRNA agent comprises a sense strand and an antisense strand, wherein the antisense strand comprises a nucleotide sequence comprising at least 17 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, of a portion of nucleotide sequence of SEQ ID NO: 2 such that the sense strand is complementary to the at least 17 contiguous nucleotides in the antisense strand.

In some embodiments the dsRNA agent comprises a sense strand and an antisense strand, wherein the sense strand comprises a nucleotide sequence comprising at least 17 contiguous nucleotides, with 0, or 1, 2, or 3 mismatches, of the corresponding portion of the nucleotide sequence of SEQ ID NO: 1.

In some embodiments the dsRNA agent comprises a sense strand and an antisense strand, wherein the antisense strand comprises a nucleotide sequence comprising at least 19 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, of a portion of nucleotide sequence of SEQ ID NO: 2 such that the sense strand is complementary to the at least 19 contiguous nucleotides in the antisense strand.

In some embodiments the sense strand comprises a nucleotide sequence comprising at least 19 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, of the corresponding portion of the nucleotide sequence of SEQ ID NO: 1.

In some embodiments the dsRNA agent comprises a sense strand and an antisense strand, wherein the antisense strand comprises a nucleotide sequence comprising at least 21 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, of a portion of nucleotide sequence of SEQ ID NO: 2 such that the sense strand is complementary to the at least 21 contiguous nucleotides in the antisense strand.

In some embodiments the sense strand of the dsRNA agent comprises a nucleotide sequence comprising at least 21 contiguous nucleotides, with 0, or 1, 2, or 3 mismatches, of the corresponding portion of the nucleotide sequence of SEQ ID NO: 1.

In some embodiments the portion of the sense strand of the dsRNA agent is a portion within a sense strand in any one of Tables 3-10. In some embodiments the portion of the antisense strand of the dsRNA agent is a portion within an antisense strand in any one of Tables 3-10.

In some embodiments the antisense strand of the dsRNA agent comprises a nucleotide sequence comprising at least 15 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, from one of the antisense sequences listed in any one of Tables 3-10.

In some embodiments the sense strand of the dsRNA agent comprises a nucleotide sequence comprising at least 15 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, from a sense sequence listed in any one of Tables 3-10 that corresponds to the antisense sequence.

In some embodiments the antisense strand of the dsRNA agent comprises a nucleotide sequence comprising at least 17 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, from one of the antisense sequences listed in any one of Tables 3-10.

In some embodiments the sense strand of the dsRNA agent comprises a nucleotide sequence comprising at least 17 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, from a sense sequence listed in any one of Tables 3-10 that corresponds to the antisense sequence.

In some embodiments the antisense strand of the dsRNA agent comprises a nucleotide sequence comprising at least 19 contiguous nucleotides, with 0,1, 2, or 3 mismatches, from one of the antisense sequences listed in any one of Tables 3-10.

In some embodiments the sense strand of the dsRNA agent comprises a nucleotide sequence comprising at least 19 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, from a sense sequence listed in any one of Tables 3-10 that corresponds to the antisense sequence.

In some embodiments the antisense strand of the dsRNA agent comprises a nucleotide sequence comprising at least 21 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, from one of the antisense sequences listed in any one of Tables 3-10.

In some embodiments the sense strand of the dsRNA agent comprises a nucleotide sequence comprising at least 21 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, from a sense sequence listed in any one of Tables 3-10 that corresponds to the antisense sequence.

In some embodiments the sense strand of the dsRNA agent is at least 23 nucleotides in length, e.g., 23-30 nucleotides in length.

In some embodiments at least one of the sense strand and the antisense strand of the dsRNA agent is conjugated to one or more lipophilic moieties.

In some embodiments the lipophilic moiety is conjugated to one or more positions in the double stranded region of the dsRNA agent. In some embodiments the lipophilic moiety is conjugated via a linker or carrier.

In some embodiments the lipophilicity of the lipophilic moiety, measured by logKow, exceeds 0.

In some embodiments the hydrophobicity of the double-stranded RNAi agent, measured by the unbound fraction in a plasma protein binding assay of the double-stranded RNAi agent, exceeds 0.2.

In an embodiment the plasma protein binding assay is an electrophoretic mobility shift assay using human serum albumin protein.

In a particular embodiment the dsRNA agent comprises at least one modified nucleotide.

In some embodiments no more than five of the sense strand nucleotides and not more than five of the nucleotides of the antisense strand of the dsRNA agent are unmodified nucleotides.

In some embodiments all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand of the dsRNA agent comprise a modification.

In some embodiments at least one of the modified nucleotides of the dsRNA agent is selected from the group consisting of a deoxy-nucleotide, a 3'-terminal deoxythimidine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5'-phosphate, a nucleotide comprising a 5'-phosphate mimic, a glycol

modified nucleotide, and a 2-O-(N-methylacetamide) modified nucleotide; and combinations thereof.

In some embodiments no more than five of the sense strand nucleotides and not more than five of the nucleotides of the antisense strand of the dsRNA agent include modifications other than 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, unlocked nucleic acids (UNA) or glycerol nucleic acid (GNA).

In some embodiments the dsRNA agent comprises a non-nucleotide spacer (wherein optionally the non-nucleotide spacer comprises a C3-C6 alkyl) between two of the contiguous nucleotides of the sense strand or between two of the contiguous nucleotides of the antisense strand.

In some embodiments each strand of the dsRNA agent is no more than 30 nucleotides in length.

In some embodiments at least one strand of the dsRNA agent comprises a 3' overhang of at least 1 nucleotide.

In some embodiments at least one strand of the dsRNA agent comprises a 3' overhang of at least 2 nucleotides.

In some embodiments the double stranded region of the dsRNA agent is 15-30 nucleotide pairs in length. In some embodiments the double stranded region of the dsRNA agent is 17-23 nucleotide pairs in length. In some embodiments the double stranded region of the dsRNA agent is 17-25 nucleotide pairs in length. In some embodiments the double stranded region of the dsRNA agent is 23-27 nucleotide pairs in length. In some embodiments the double stranded region of the dsRNA agent is 19-21 nucleotide pairs in length. In some embodiments the double stranded region is 21-23 nucleotide pairs in length. In some embodiments the positions in the double stranded region exclude a cleavage site region of the sense strand of the dsRNA agent.

In some embodiments each strand of the dsRNA agent has 19-30 nucleotides. In some embodiments each strand of the dsRNA agent has 19-23 nucleotides. In some embodiments each strand of the dsRNA agent has 21-23 nucleotides.

In some embodiments the dsRNA agent comprises at least one phosphorothioate or methylphosphonate internucleotide linkage. In some embodiments the phosphorothioate or methylphosphonate internucleotide linkage is at the 3'-terminus of one strand of the dsRNA

agent. In some embodiments the phosphorothioate or methylphosphonate internucleotide linkage is at the 3'-terminus of the antisense strand of the dsRNA agent. In some embodiments the phosphorothioate or methylphosphonate internucleotide linkage is at the 3'-terminus of the sense strand of the dsRNA agent. In some embodiments the phosphorothioate or methylphosphonate internucleotide linkage is at the 5'-terminus of one strand of the dsRNA agent. In some embodiments the phosphorothioate or methylphosphonate internucleotide linkage is at the 5'-terminus of the antisense strand of the dsRNA agent. In some embodiments the phosphorothioate or methylphosphonate internucleotide linkage is at the 5'-terminus of the sense strand of the dsRNA agent. In some embodiments the 5'- and 3'-terminus of one strand of the dsRNA agent comprises a phosphorothioate or methylphosphonate internucleotide linkage.

In some embodiments the 5'- and 3'-terminus of the antisense strand of the dsRNA agent comprises a phosphorothioate or methylphosphonate internucleotide linkage.

In some embodiments the base pair at the 1 position of the 5′-end of the antisense strand of the duplex is an AU base pair.

In some embodiments the sense strand of the dsRNA agent has a total of 21 nucleotides and the antisense strand has a total of 23 nucleotides.

In some embodiments one or more lipophilic moieties are conjugated to one or more internal positions on at least one strand of the dsRNA agent. In some embodiments one or more lipophilic moieties are conjugated to one or more internal positions on at least one strand of the dsRNA agent via a linker or carrier. In some embodiments the internal positions include all positions except the terminal two positions from each end of at least one strand of the dsRNA agent. In some embodiments the internal positions include all positions except the terminal three positions from each end of the at least one strand of the dsRNA agent. In some embodiments the internal positions exclude a cleavage site region of the sense strand of the dsRNA agent.

In some embodiments the internal positions include all positions except positions 9-12, counting from the 5'-end of the sense strand of the dsRNA agent.

In some embodiments the internal positions include all positions except positions 11-13, counting from the 3'-end of the sense strand of the dsRNA agent.

In some embodiments the internal positions exclude a cleavage site region of the antisense strand of the dsRNA agent.

In some embodiments the internal positions include all positions except positions 12-14, counting from the 5'-end of the antisense strand of the dsRNA agent.

In some embodiments the internal positions include all positions except positions 11-13 on the sense strand of the dsRNA agent, counting from the 3'-end, and positions 12-14 on the antisense strand of the dsRNA agent, counting from the 5'-end.

In some embodiments the lipophilic moieties are conjugated to one or more of the internal positions selected from the group consisting of positions 4-8 and 13-18 on the sense strand, and positions 6-10 and 15-18 on the antisense strand, counting from the 5'end of each strand of the dsRNA agent.

In some embodiments the lipophilic moieties are conjugated to one or more of the internal positions selected from the group consisting of positions 5, 6, 7, 15, and 17 on the sense strand, and positions 15 and 17 on the antisense strand, counting from the 5'-end of each strand of the dsRNA agent.

In some embodiments the sense strand is 21 nucleotides in length, the antisense strand is 23 nucleotides in length, and the lipophilic moiety is conjugated to position 21, position 20, position 15, position 1, position 7, position 6, or position 2 of the sense strand or position 16 of the antisense strand of the dsRNA agent.

In some embodiments the lipophilic moiety is conjugated to position 21, position 20, position 15, position 1, or position 7 of the sense strand of the dsRNA agent.

In some embodiments the lipophilic moiety is conjugated to position 21, position 20, or position 15 of the sense strand of the dsRNA agent.

In some embodiments the lipophilic moiety is conjugated to position 20 or position 15 of the sense strand of the dsRNA agent.

In some embodiments the lipophilic moiety is conjugated to position 16 of the antisense strand of the dsRNA agent.

In some embodiments the lipophilic moiety is conjugated to position 6, counting from the 5'-end of the sense strand of the dsRNA agent.

In some embodiments the lipophilic moiety is an aliphatic, alicyclic, or polyalicyclic compound.

In some embodiments the lipophilic moiety is selected from the group consisting of lipid, cholesterol, retinoic acid, cholic acid, adamantane acetic acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-bis-O(hexadecyl)glycerol, geranyloxyhexyanol, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl group, palmitic acid, myristic acid, O3-(oleoyl)lithocholic acid, O3-(oleoyl)cholenic acid, dimethoxytrityl, or phenoxazine.

In some embodiments the lipophilic moiety contains a saturated or unsaturated C4-C30 hydrocarbon chain, and an optional functional group selected from the group consisting of hydroxyl, amine, carboxylic acid, sulfonate, phosphate, thiol, azide, and alkyne.

In some embodiments the lipophilic moiety contains a saturated or unsaturated C6-C18 hydrocarbon chain.

In some embodiments the lipophilic moiety contains a saturated or unsaturated C16 hydrocarbon chain.

In some embodiments the lipophilic moiety is conjugated via a carrier that replaces one or more nucleotide(s) in the internal position(s) or the double stranded region.

In some embodiments the carrier is a cyclic group selected from the group consisting of pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, [1,3]dioxolanyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl, tetrahydrofuranyl, and decalinyl; or is an acyclic moiety based on a serinol backbone or a diethanolamine backbone.

In some embodiments the lipophilic moiety is conjugated to the double-stranded iRNA agent via a linker containing an ether, thioether, urea, carbonate, amine, amide, maleimide-thioether, disulfide, phosphodiester, sulfonamide linkage, a product of a click reaction, or carbamate.

In some embodiments the lipophilic moiety is conjugated to a nucleobase, sugar moiety, or internucleosidic linkage.

In some embodiments the lipophilic moiety is conjugated via a bio-cleavable linker selected from the group consisting of DNA, RNA, disulfide, amide, functionalized monosaccharides or oligosaccharides of galactosamine, glucosamine, glucose, galactose, mannose, and combinations thereof.

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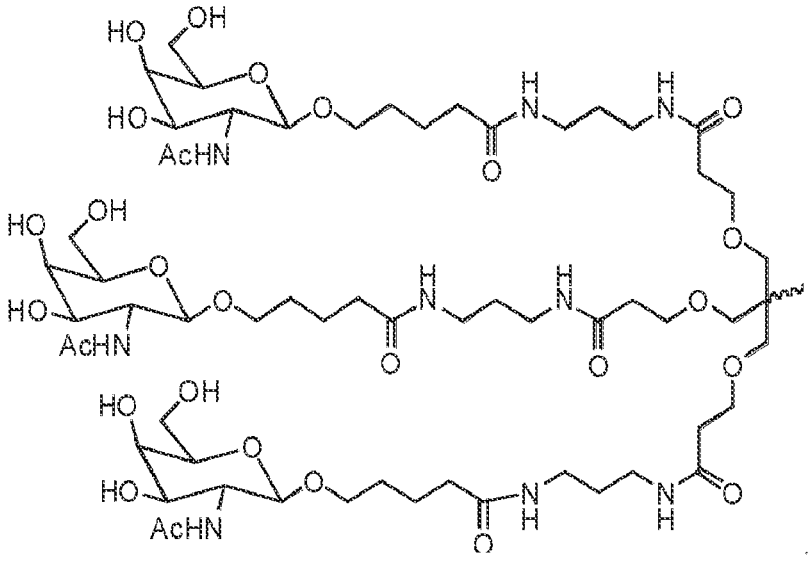
In some embodiments the 3' end of the sense strand of the dsRNA agent is protected via an end cap which is a cyclic group having an amine, said cyclic group being selected from the group consisting of pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, [1,3]dioxolanyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl, tetrahydrofuranyl, and decalinyl.

In some embodiments the dsRNA agent further comprising a targeting ligand, e.g., a ligand that targets an ocular tissue or a liver tissue. In some embodiments the ligand is conjugated to the sense strand of the dsRNA agent. In some embodiments the ligand is conjugated to the 3' end or the 5' end of the sense strand of the dsRNA agent. In some embodiments the ligand is conjugated to the 3' end of the sense strand of the dsRNA agent.

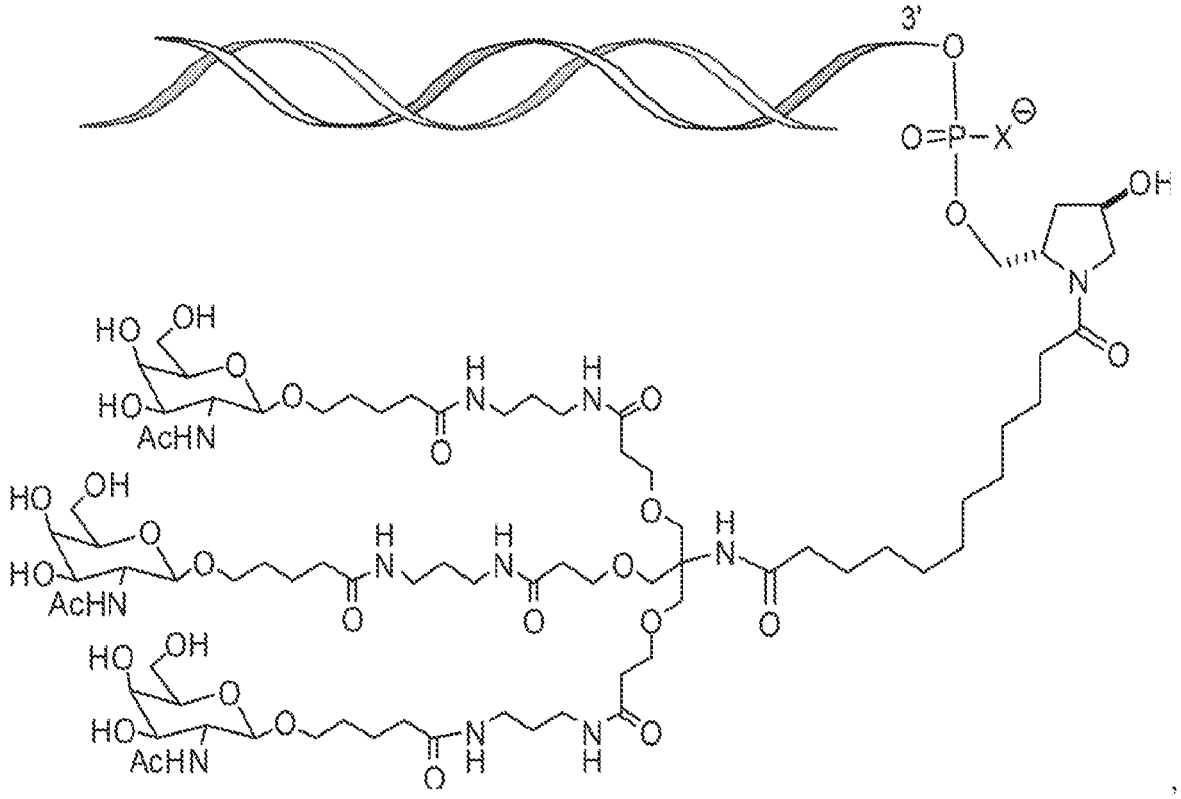
In some embodiments the dsRNA agent further comprising a ligand that targets an ocular tissue wherein the ocular tissue is ciliary epithelium, an optic nerve, a trabecular meshwork, a juxtacanalicular tissue, a ganglion (e.g., including a retinal ganglion), episcleral veins or a Schlemm's canal (e.g., including an endothelial cell).

In some embodiments the targeting ligand of the dsRNA agent comprises N-acetylgalactosamine (GalNAc). In some embodiments the targeting ligand of the dsRNA agent is one or more GalNAc conjugates or one or more or GalNAc derivatives. In some embodiments the GalNAc conjugates or one or more GalNAc derivatives are attached through a monovalent linker, or a bivalent, trivalent, or tetravalent branched linker.

In some embodiments the targeting ligand of the dsRNA agent is



In some embodiments the dsRNA agent is conjugated to the ligand as shown in the following schematic



wherein X is O or S.

In some embodiments the dsRNA agent further comprises a terminal, chiral modification occurring at the first internucleotide linkage at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration, a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration, and a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp configuration or Sp configuration.

In some embodiments the dsRNA agent further comprises a terminal, chiral modification occurring at the first and second internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration; a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration; and a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp or Sp configuration.

In some embodiments the dsRNA agent further comprises a terminal, chiral modification occurring at the first, second and third internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration; a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration; and a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp or Sp configuration.

In some embodiments the dsRNA agent further comprises a terminal, chiral modification occurring at the first, and second internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration; a terminal, chiral modification occurring at the third internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Rp configuration; a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration; and a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp or Sp configuration.

In some embodiments the dsRNA agent further comprises a terminal, chiral modification occurring at the first, and second internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration; a terminal, chiral modification occurring at the first, and second internucleotide linkages at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration; and a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp or Sp configuration.

In some embodiments the dsRNA agent further comprises a phosphate or phosphate mimic at the 5'-end of the antisense strand. In some embodiments the phosphate mimic is a 5'-vinyl phosphonate (VP).

In some embodiments the disclosure provides a cell containing the dsRNA agent of any one of the preceding embodiments.

In some embodiments the cell containing the dsRNA agent is a human ocular cell, e.g., (a ciliary epithelium cell, an optic nerve cell, a trabecular meshwork cell, a Schlemm's canal cell (e.g., including an endothelial cell), a juxtacanalicular tissue cell, a ciliary muscle cell, a retinal

cell, an astrocyte, a pericyte, a Müller cell, a ganglion cell (e.g., including a retinal ganglion cell), an endothelial cell, a photoreceptor cell, a retinal blood vessel (e.g., including endothelial cells and vascular smooth muscle cells), episcleral veins or choroid tissue, e.g., a choroid vessel) comprising a reduced level of CA2 mRNA or a level of CA2 protein as compared to an otherwise similar untreated cell, wherein optionally the level is reduced by at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%.

In some embodiments the human cell containing the dsRNA agent is produced by a process comprising contacting a human cell with the dsRNA agent of any one of preceding embodiments.

In some embodiments the disclosure provides a pharmaceutical composition for inhibiting expression of CA2, comprising the dsRNA agent of any one of preceding embodiments.

In a particular embodiment the disclosure provides a pharmaceutical composition comprising the dsRNA agent of any one of preceding embodiments and a lipid formulation.

In some embodiments the disclosure provides a method of inhibiting expression of CA2 in a cell, the method comprising:

(a) contacting the cell with the dsRNA agent of any one of preceding embodiments or a pharmaceutical composition comprising the dsRNA agent of any one of preceding embodiments; and

(b) maintaining the cell produced in step (a) for a time sufficient to obtain degradation of the mRNA transcript of CA2, thereby inhibiting expression of CA2 in the cell.

In other embodiments the disclosure provides a method of inhibiting expression of CA2 in a cell, the method comprising:

(a) contacting the cell with the dsRNA agent of any one of preceding embodiments or a pharmaceutical composition comprising the dsRNA agent of any one of preceding embodiments; and

(b) maintaining the cell produced in step (a) for a time sufficient to reduce levels of CA2 mRNA, CA2 protein, or both of CA2 mRNA and protein, thereby inhibiting expression of CA2 in the cell.

In some embodiments the disclosure provides a method of inhibiting expression of CA2 in a cell wherein the cell is within a subject.

In some embodiments the disclosure provides a method of inhibiting expression of CA2 in a cell, wherein the cell is within a human subject.

In some embodiments the disclosure provides a method of inhibiting expression of CA2 in a cell wherein the level of CA2 mRNA is inhibited by at least 50%.

In some embodiments the disclosure provides a method of inhibiting expression of CA2 in a cell wherein the level of CA2 protein is inhibited by at least 50%.

In some embodiments the disclosure provides a method of inhibiting expression of CA2 in a cell wherein inhibiting expression of CA2 decreases a CA2 protein level in a biological sample (*e.g.*, a ciliary epithelium sample) from the subject by at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 95%.

In particular embodiments the disclosure provides a method of inhibiting expression of CA2 in a cell wherein the subject has been diagnosed with a CA2-associated disorder, *e.g.*, glaucoma.

In some embodiments the method of inhibiting expression of CA2 in an ocular cell or tissue comprises

(a) contacting the cell or tissue with a dsRNA agent that binds CA2; and

(b) maintaining the cell or tissue produced in step (a) for a time sufficient to reduce levels of CA2 mRNA, CA2 protein, or both of CA2 mRNA and protein, thereby inhibiting expression of CA2 in the cell or tissue. In some embodiments the ocular cell or tissue comprises a ciliary epithelium cell, an optic nerve cell, a trabecular meshwork cell, a Schlemm's canal cell (e.g., including an endothelial cell), a juxtacanalicular tissue cell, a ciliary muscle cell, a retinal cell, an astrocyte, a pericyte, a Müller cell, a ganglion cell (e.g., including a retinal ganglion cell), an endothelial cell, a photoreceptor cell, a retinal blood vessel (e.g., including endothelial cells and vascular smooth muscle cells), episcleral veins or choroid tissue, e.g., a choroid vessel.

In some embodiments the disclosure provides a method of treating a subject diagnosed with a CA2-associated disorder comprising administering to the subject a therapeutically effective amount of the dsRNA agent of any one of preceding embodiments or a pharmaceutical composition thereof, thereby treating the disorder. In some embodiments the disclosure provides

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a method of treating a subject diagnosed with a CA2-associated disorder wherein the CA2-associated disorder is glaucoma or a glaucoma associated condition.

In particular embodiments the disclosure provides a method of treating a subject diagnosed with a CA2-associated disorder wherein treating comprises amelioration of at least one sign or symptom of the disorder. In particular embodiments the disclosure provides a method of treating a subject diagnosed with a CA2-associated disorder where treating comprises prevention of progression of the disorder. In some embodiments the treating comprises one or more of (a) inhibiting or reducing intraocular pressure; (b) inhibiting or reducing the expression or activity of CA2; (c) decreasing the amount of aqueous humor; (d) inhibiting or reducing optic nerve damage; (e) inhibiting or reducing retinal ganglion cell death; (f) medication to reduce intraocular pressure; (g) laser treatment; (h) surgery; (i) or trabeculectomy.

In some embodiments the disclosure provides a method of treating a subject diagnosed with glaucoma wherein at least one sign or symptom of glaucoma comprises a measure of one or more of intraocular pressure, vision loss, optic nerve damage, ocular inflammation, visual acuity, or presence, level, or activity of CA2 (*e.g.*, CA2 gene, CA2 mRNA, or CA2 protein).

In particular embodiments the disclosure provides a method of treating a subject diagnosed with a CA2-associated disorder wherein the treating results in at least a 30% mean reduction from baseline of CA2 mRNA in a ciliary epithelium cell, an optic nerve cell, a trabecular meshwork cell, a Schlemm's canal cell (e.g., including an endothelial cell), a juxtacanalicular tissue cell, a ciliary muscle cell, retinal pigment epithelium (RPE), a retinal cell, an astrocyte, a pericyte, a Müller cell, a ganglion cell (e.g., including a retinal ganglion cell), an endothelial cell, a photoreceptor cell, a retinal blood vessel (e.g., including endothelial cells and vascular smooth muscle cells), episcleral veins or choroid tissue, e.g., a choroid vessel.

In some embodiments the disclosure provides a method of treating a subject diagnosed with a CA2-associated disorder wherein the treating results in at least a 60% mean reduction from baseline of CA2 mRNA in the ciliary epithelium cell, optic nerve cell, trabecular meshwork cell, Schlemm's canal cell (e.g., including an endothelial cell), juxtacanalicular tissue cell, ciliary muscle cell, retinal pigment epithelium (RPE), retinal cell, astrocyte, pericyte, Müller cell, ganglion cell (e.g., including retinal ganglion cell), endothelial cell, photoreceptor cell, retinal

blood vessel (e.g., including endothelial cells and vascular smooth muscle cells), episcleral veins or choroid tissue, e.g., choroid vessel.

In other embodiments the disclosure provides a method of treating a subject diagnosed with a CA2-associated disorder wherein the treating results in at least a 90% mean reduction from baseline of CA2 mRNA in the ciliary epithelium cell, optic nerve cell, trabecular meshwork cell, Schlemm's canal cell (e.g., including an endothelial cell), juxtacanalicular tissue cell, ciliary muscle cell, retinal pigment epithelium (RPE), retinal cell, astrocyte, pericyte, Müller cell, ganglion cell (e.g., including retinal ganglion cell), endothelial cell, photoreceptor cell, retinal blood vessel (e.g., including endothelial cells and vascular smooth muscle cells), episcleral veins or choroid tissue, e.g., choroid vessel.

In some embodiments the disclosure provides a method of treating a subject diagnosed with a CA2-associated disorder wherein after treatment the subject experiences at least an 8-week duration of knockdown following a single dose of dsRNA as assessed by CA2 protein in the ciliary epithelium.

In particular embodiments the disclosure provides a method of treating a subject diagnosed with a CA2-associated disorder wherein treating results in at least a 12-week duration of knockdown following a single dose of dsRNA as assessed by CA2 protein in the ciliary epithelium.

In particular embodiments the disclosure provides a method of treating a subject diagnosed with a CA2-associated disorder wherein treating results in at least a 16-week duration of knockdown following a single dose of dsRNA as assessed by CA2 protein in the ciliary epithelium.

In some embodiments the disclosure provides a method of treating a subject diagnosed with a CA2-associated disorder wherein the subject is human.

In some embodiments the disclosure provides a method of treating a subject diagnosed with a CA2-associated disorder wherein the dsRNA agent is administered at a dose of about 0.01 mg/kg to about 50 mg/kg. In some embodiments the disclosure provides a method of treating a subject diagnosed with a CA2-associated disorder wherein the dsRNA agent is administered to the subject intraocularly, intravenously, or topically. In some embodiments the intraocular administration comprises intravitreal administration (e.g., intravitreal injection),

transscleral administration (e.g., transscleral injection), subconjunctival administration (e.g., subconjunctival injection), retrobulbar administration (e.g., retrobulbar injection), intracameral administration (e.g., intracameral injection), or subretinal administration (e.g., subretinal injection).

In some embodiments the method of treating a subject diagnosed with a CA2-associated disorder further comprising measuring level of CA2 (*e.g.*, CA2 gene, CA2 mRNA, or CA2 protein) in the subject.

In some embodiments measuring the level of CA2 in the subject comprises measuring the level of CA2 gene, CA2 protein or CA2 mRNA in a biological sample from the subject (*e.g.*, a ciliary epithelium sample). In some embodiments measuring level of CA2 (*e.g.*, CA2 gene, CA2 mRNA, or CA2 protein) in the subject is performed prior to treatment with the dsRNA agent or the pharmaceutical composition. In other embodiments measuring level of CA2 (*e.g.*, CA2 gene, CA2 mRNA, or CA2 protein) in the subject is performed after treatment with the dsRNA agent or the pharmaceutical composition. In some embodiments upon determination that a subject has a level of CA2 (*e.g.*, CA2 gene, CA2 mRNA, or CA2 protein) that is greater than a reference level, the dsRNA agent or the pharmaceutical composition is administered to the subject. In some embodiments, measuring level of CA2 (*e.g.*, CA2 gene, CA2 mRNA, or CA2 protein) in the subject is performed after treatment with the dsRNA agent or the pharmaceutical composition.

In some embodiments the disclosure provides a method of treating a subject diagnosed with a CA2-associated disorder further comprising performing a blood test, an imaging test, a tonometry test or a ciliary epithelium biopsy.

In some embodiments the disclosure provides a method of treating a subject diagnosed with a CA2-associated disorder, the method further comprising administering to the subject an additional agent and/or therapy suitable for treatment or prevention of an CA2-associated disorder. In some embodiments the additional agent and/or therapy comprises one or more of a prostaglandin analog, a beta blocker, an alpha-adrenergic agonist, a carbonic anhydrase inhibitor, or an anti-CA2 agent.

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EXAMPLES

Example 1. CA2 siRNA

Nucleic acid sequences provided herein are represented using standard nomenclature. *See* the abbreviations of Table 2.

Table 2. Abbreviations of nucleotide monomers used in nucleic acid sequence representation

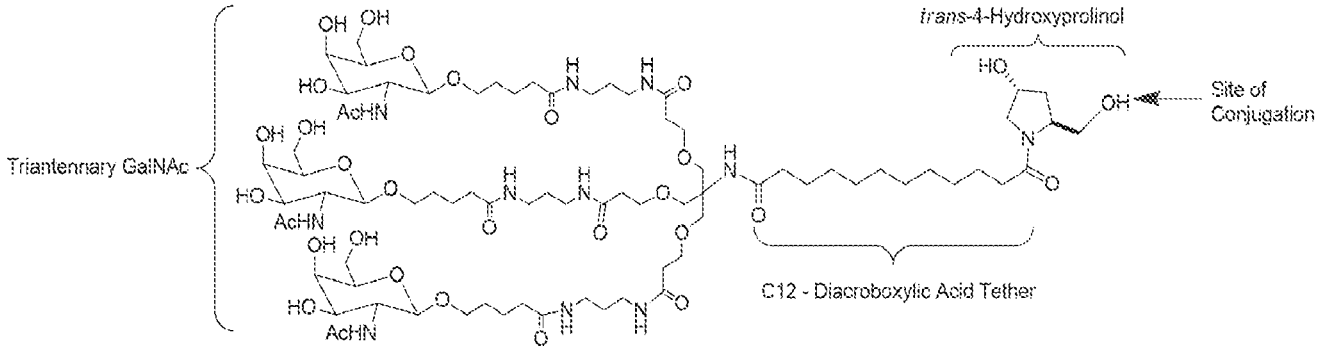
It will be understood that these monomers, when present in an oligonucleotide, are mutually linked by 5'-3'-phosphodiester bonds.

Abbreviation	Nucleotide(s)
A	Adenosine-3'-phosphate
Ab	beta-L-adenosine-3`-phosphate
Abs	beta-L-adenosine-3`-phosphorothioate
Af	2'-fluoroadenosine-3'-phosphate
Afs	2'-fluoroadenosine-3'-phosphorothioate
(Ahd)	2'-O-hexadecyl-adenosine-3'-phosphate
(Ahds)	2'-O-hexadecyl-adenosine-3'-phosphorothioate
As	adenosine-3'-phosphorothioate
(A2p)	adenosine-2`-phosphate
(A2ps)	adenosine-2`-phosphorothioate
C	cytidine-3'-phosphate
Cb	beta-L-cytidine-3'-phosphate
Cbs	beta-L-cytidine-3'-phosphorothioate
Cf	2'-fluorocytidine-3'-phosphate
Cfs	2'-fluorocytidine-3'-phosphorothioate
(Chd)	2'-O-hexadecyl-cytidine-3'-phosphate
(Chds)	2'-O-hexadecyl-cytidine-3'-phosphorothioate
Cs	cytidine-3'-phosphorothioate
(C2p)	cytidine-2`-phosphate
(C2ps)	cytidine-2`-phosphorothioate
G	guanosine-3'-phosphate
Gb	beta-L-guanosine-3`-phosphate
Gbs	beta-L-guanosine-3`-phosphorothioate
Gf	2'-fluoroguanosine-3'-phosphate
Gfs	2'-fluoroguanosine-3'-phosphorothioate
(Ghd)	2'-O-hexadecyl-guanosine-3'-phosphate
(Ghds)	2'-O-hexadecyl-guanosine-3'-phosphorothioate
Gs	guanosine-3'-phosphorothioate
(G2p)	guanosine-2`-phosphate
(G2ps)	guanosine-2`-phosphorothioate
T	5`-methyluridine-3'-phosphate

Tb	beta-L-thymidine-3'-phosphate
Tbs	beta-L-thymidine-3'-phosphorothioate
Tf	2'-fluoro-5-methyluridine-3'-phosphate
Tfs	2'-fluoro-5-methyluridine-3'-phosphorothioate
Tgn	thymidine-glycol nucleic acid (GNA) S-Isomer
Agn	adenosine- glycol nucleic acid (GNA) S-Isomer
Cgn	cytidine-glycol nucleic acid (GNA) S-Isomer
Ggn	guanosine-glycol nucleic acid (GNA) S-Isomer
Ts	5-methyluridine-3'-phosphorothioate
U	Uridine-3'-phosphate
Ub	beta-L-uridine-3`-phosphate
Ubs	beta-L-uridine-3`-phosphorothioate
Uf	2'-fluorouridine-3'-phosphate
Ufs	2'-fluorouridine -3'-phosphorothioate
(Uhd)	2'-O-hexadecyl-uridine-3'-phosphate
(Uhds)	2'-O-hexadecyl-uridine-3'-phosphorothioate
Us	uridine -3'-phosphorothioate
(U2p)	uridine-2`-phosphate
(U2ps)	uridine-2`-phosphorothioate
N	any nucleotide (G, A, C, T or U)
VP	Vinyl phosphonate
a	2'-O-methyladenosine-3'-phosphate
as	2'-O-methyladenosine-3'- phosphorothioate
c	2'-O-methylcytidine-3'-phosphate
cs	2'-O-methylcytidine-3'- phosphorothioate
g	2'-O-methylguanosine-3'-phosphate
gs	2'-O-methylguanosine-3'- phosphorothioate
t	2'-O-methyl-5-methyluridine-3'-phosphate
ts	2'-O-methyl-5-methyluridine-3'-phosphorothioate
u	2'-O-methyluridine-3'-phosphate
us	2'-O-methyluridine-3'-phosphorothioate
dA	2`-deoxyadenosine-3`-phosphate
dAs	2`-deoxyadenosine-3`-phosphorothioate
dC	2`-deoxycytidine-3`-phosphate
dCs	2`-deoxycytidine-3`-phosphorothioate
dG	2`-deoxyguanosine-3`-phosphate
dGs	2`-deoxyguanosine-3`-phosphorothioate
dT	2'-deoxythymidine
dTs	2`-deoxythymidine-3`-phosphorothioate
dU	2`-deoxyuridine
s	phosphorothioate linkage
L96[1]	N-[tris(GalNAc-alkyl)-amidodecanoyl)]-4-hydroxyprolinol Hyp-(GalNAc-alkyl)3
(Aeo)	2'-O-methoxyethyladenosine-3'-phosphate
(Aeos)	2'-O-methoxyethyladenosine-3'-phosphorothioate

(Geo)	2'-O-methoxyethylguanosine-3'-phosphate
(Geos)	2'-O-methoxyethylguanosine-3'- phosphorothioate
(Teo)	2'-O-methoxyethyl-5-methyluridine-3'-phosphate
(Teos)	2'-O-methoxyethyl-5-methyluridine-3'- phosphorothioate
(m5Ceo)	2'-O-methoxyethyl-5-methylcytidine-3'-phosphate
(m5Ceos)	2'-O-methoxyethyl-5-methylcytidine-3'- phosphorothioate

[1]The chemical structure of L96 is as follows:



Experimental Methods

Bioinformatics

Transcripts

siRNAs targeting the human CA2, "carbonic anhydrase 2" (human: NCBI refseqID NM_000067.3; NCBI GeneID: 760) were generated. The human NM_000067.3 REFSEQ mRNA, version 1, has a length of 1562 bases. Pairs of oligos were generated using bioinformatic methods and ranked, and exemplary pairs of oligos are shown in Tables 3 and 4, Tables 7 and 8, and Tables 9 and 10. Modified sequences are presented in Tables 5, 6, 8, and 10. Unmodified sequences are presented in Tables 3, 4, 7, and 9. The oligos in Tables 3, 5, and 9 were designed for C16 modification and the oligos in Tables 4 and 6 were designed for GalNAc modification.

It is to be understood that, throughout the application, a duplex name without a decimal is equivalent to a duplex name with a decimal which merely references the batch number of the duplex. For example, AD-1560600 is equivalent to AD-1560600.1.

siRNA Synthesis

siRNAs were synthesized and annealed using routine methods known in the art.

Briefly, siRNA sequences were synthesized at 1 μmol scale on a Mermade 192 synthesizer (BioAutomation) using the solid support mediated phosphoramidite chemistry. The solid support was controlled pore glass (500 A) loaded with custom GalNAc ligand or universal solid support (AM biochemical). Ancillary synthesis reagents, 2'-F and 2'-O-Methyl RNA and deoxy phosphoramidites were obtained from Thermo-Fisher (Milwaukee, WI) and Hongene (China). 2'F 2'-O-Methyl, GNA (glycol nucleic acids), 5'phosphate and other modifications were introduced using the corresponding phosphoramidites. Synthesis of 3' GalNAc conjugated single strands was performed on a GalNAc modified CPG support. Custom CPG universal solid support was used for the synthesis of antisense single strands. Coupling time for all phosphoramidites (100 mM in acetonitrile) was 5 minutes employing 5-Ethylthio-1H-tetrazole (ETT) as activator (0.6 M in acetonitrile). Phosphorothioate linkages were generated using a 50 mM solution of 3-((Dimethylamino-methylidene) amino)-3H-1,2,4-dithiazole-3-thione (DDTT, obtained from Chemgenes (Wilmington, MA, USA)) in anhydrous acetonitrile/pyridine (1:1 v/v). Oxidation time was 3 minutes. All sequences were synthesized with final removal of the DMT group ("DMT off").

Upon completion of the solid phase synthesis, oligoribonucleotides were cleaved from the solid support and deprotected in sealed 96 deep well plates using 200 μL Aqueous Methylamine reagents at 60°C for 20 minutes. For sequences containing 2' ribo residues (2'-OH) that are protected with a tert-butyl dimethyl silyl (TBDMS) group, a second step deprotection was performed using TEA.3HF (triethylamine trihydro fluoride) reagent. To the methylamine deprotection solution, 200 μL of dimethyl sulfoxide (DMSO) and 300 μL TEA.3HF reagent was added and the solution was incubated for additional 20 minutes at 60°C. At the end of cleavage and deprotection step, the synthesis plate was allowed to come to room temperature and was precipitated by addition of 1mL of acetontile: ethanol mixture (9:1). The plates were cooled at -80 °C for 2 hours, supernatant decanted carefully with the aid of a multi-channel pipette. The oligonucleotide pellet was re-suspended in 20mM NaOAc buffer and were desalted using a 5 mL HiTrap size exclusion column (GE Healthcare) on an AKTA Purifier System equipped with an A905 autosampler and a Frac 950 fraction collector. Desalted samples were collected in 96-well plates. Samples from each sequence were analyzed by LC-MS to confirm the identity, UV (260 nm) for quantification and a selected set of samples by IEX chromatography to determine purity.

Annealing of single strands was performed on a Tecan liquid handling robot. Equimolar mixture of sense and antisense single strands were combined and annealed in 96 well plates. After combining the complementary single strands, the 96-well plate was sealed tightly and heated in an oven at 100°C for 10 minutes and allowed to come slowly to room temperature over a period 2-3 hours. The concentration of each duplex was normalized to 10 μM in 1X PBS and then submitted for *in vitro* screening assays.

Table 3. Unmodified Sense and Antisense Strand Sequences of CA2 dsRNA Agents for C16 Modification

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000067.3
AD-1560600	AGAUCGGUGCCGAUUCCUGCA	7	32-52	UGCAGGAAUCGGCACCGAUCUGG	142	30-52
AD-1560617	CGCGACCAUGUCCCAUCACUA	8	69-89	UAGUGAUGGGACAUGGUCGCGCU	143	67-89
AD-1560622	GUACGGCAAACACAACGGACA	9	93-113	UGUCCGUUGUGUUUGCCGUACCC	144	91-113
AD-1560628	CAAACACAACGGACCUGAGCA	10	99-119	UGCUCAGGUCCGUUGUGUUUGCC	145	97-119
AD-1560638	GGACCUGAGCACUGGCAUAAA	11	109-129	UUUAUGCCAGUGCUCAGGUCCGU	146	107-129
AD-1560644	GAGCACUGGCAUAAGGACUUA	12	115-135	UAAGUCCUUAUGCCAGUGCUCAG	147	113-135
AD-1560655	GUUGACAUCGACACUCAUACA	13	166-186	UGUAUGAGUGUCGAUGUCAACAG	148	164-186
AD-1560665	ACACUCAUACAGCCAAGUAUA	14	176-196	UAUACUUGGCUGUAUGAGUGUCG	149	174-196
AD-1560672	UACAGCCAAGUAUGACCCUUA	15	183-203	UAAGGGUCAUACUUGGCUGUAUG	150	181-203
AD-1560678	CAAGUAUGACCCUUCCCUGAA	16	189-209	UUCAGGGAAGGGUCAUACUUGGC	151	187-209
AD-1560684	UGUCUGUUUCCUAUGAUCAAA	17	215-235	UUUGAUCAUAGGAAACAGACAGG	152	213-235
AD-1560693	CCUAUGAUCAAGCAACUUCCA	18	224-244	UGGAAGUUGCUUGAUCAUAGGAA	153	222-244
AD-1560701	CAAGCAACUUCCCUGAGGAUA	19	232-252	UAUCCUCAGGGAAGUUGCUUGAU	154	230-252
AD-1560711	CCCUGAGGAUCCUCAACAAUA	20	242-262	UAUUGUUGAGGAUCCUCAGGGAA	155	240-262
AD-1560720	UCCUCAACAAUGGUCAUGCUA	21	251-271	UAGCAUGACCAUUGUUGAGGAUC	156	249-271

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000067.3
AD-1560726	ACAAUGGUCAUGCUUUCAACA	22	257-277	UGUUGAAAGCAUGACCAUUGUUG	157	255-277
AD-1560735	AUGCUUUCAACGUGGAGUUUA	23	266-286	UAAACUCCACGUUGAAAGCAUGA	158	264-286
AD-1560745	AACGUGGAGUUUGAUGACUCA	24	274-294	UGAGUCAUCAAACUCCACGUUGA	159	272-294
AD-1560752	UGAUGACUCUCAGGACAAAGA	25	285-305	UCUUUGUCCUGAGAGUCAUCAAA	160	283-305
AD-1560759	UCUCAGGACAAAGCAGUGCUA	26	292-312	UAGCACUGCUUUGUCCUGAGAGU	161	290-312
AD-1560765	GACAAAGCAGUGCUCAAGGGA	27	298-318	UCCCUUGAGCACUGCUUUGUCCU	162	296-318
AD-1560777	UGGCACUUACAGAUUGAUUCA	28	330-350	UGAAUCAAUCUGUAAGUGCCAUC	163	328-350
AD-1560783	UUACAGAUUGAUUCAGUUUCA	29	336-356	UGAAACUGAAUCAAUCUGUAAGU	164	334-356
AD-1560792	AUUCAGUUUCACUUUCACUGA	30	346-366	UCAGUGAAAGUGAAACUGAAUCA	165	344-366
AD-1560798	UCACUUGAUGGACAAGGUUCA	31	370-390	UGAACCUUGUCCAUCAAGUGAAC	166	368-390
AD-1560804	GAUGGACAAGGUUCAGAGCAA	32	376-396	UUGCUCUGAACCUUGUCCAUCAA	167	374-396
AD-1560810	CAAGGUUCAGAGCAUACUGUA	33	382-402	UACAGUAUGCUCUGAACCUUGUC	168	380-402
AD-1560816	UCAGAGCAUACUGUGGAUAAA	34	388-408	UUUAUCCACAGUAUGCUCUGAAC	169	386-408
AD-1560837	AAGAAAUAUGCUGCAGAACUA	35	409-429	UAGUUCUGCAGCAUAUUUCUUUU	170	407-429
AD-1560845	UAUGCUGCAGAACUUCACUUA	36	415-435	UAAGUGAAGUUCUGCAGCAUAUU	171	413-435
AD-1560851	GCAGAACUUCACUUGGUUCAA	37	421-441	UUGAACCAAGUGAAGUUCUGCAG	172	419-441
AD-1560843	CUUCACUUGGUUCACUGGAAA	38	817-837	UUUCCAGUGAACCAAGUGAAGUU	173	
AD-1560862	UUUGGGAAAGCUGUGCAGCAA	39	463-483	UUGCUGCACAGCUUUCCCAAAAU	174	461-483
AD-1560874	GUGCAGCAACCUGAUGGACUA	40	475-495	UAGUCCAUCAGGUUGCUGCACAG	175	473-495
AD-1560880	CAACCUGAUGGACUGGCCGUA	41	481-501	UACGGCCAGUCCAUCAGGUUGCU	176	479-501
AD-1560892	CUGGCCGUUCUAGGUAUUUUA	42	493-513	UAAAAUACCUAGAACGGCCAGUC	177	491-513
AD-1560895	UGAAGGUUGGCAGCGCUAAAA	43	515-535	UUUUAGCGCUGCCAACCUUCAAA	178	513-535
AD-1560904	GCAGCGCUAAACCGGGCCUUA	44	524-544	UAAGGCCCGGUUUAGCGCUGCCA	179	522-544

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000067.3
AD-1560915	CCGGGCCUUCAGAAAGUUGUA	45	535-555	UACAACUUUCUGAAGGCCCGGUU	180	533-555
AD-1560921	CUUCAGAAAGUUGUUGAUGUA	46	541-561	UACAUCAACAACUUUCUGAAGGC	181	539-561
AD-1560930	GUUGUUGAUGUGCUGGAUUCA	47	550-570	UGAAUCCAGCACAUCAACAACUU	182	548-570
AD-1560941	GCUGGAUUCCAUUAAAACAAA	48	561-581	UUUGUUUUAAUGGAAUCCAGCAC	183	559-581
AD-1560948	UCCAUUAAAACAAAGGGCAAA	49	568-588	UUUGCCCUUUGUUUUAAUGGAAU	184	566-588
AD-1560954	AAAACAAAGGGCAAGAGUGCA	50	574-594	UGCACUCUUGCCCUUUGUUUUAA	185	572-594
AD-1560963	GGCAAGAGUGCUGACUUCACA	51	583-603	UGUGAAGUCAGCACUCUUGCCCU	186	581-603
AD-1560970	GUGCUGACUUCACUAACUUCA	52	590-610	UGAAGUUAGUGAAGUCAGCACUC	187	588-610
AD-1560976	ACUUCACUAACUUCGAUCCUA	53	596-616	UAGGAUCGAAGUUAGUGAAGUCA	188	594-616
AD-1560989	CGAUCCUCGUGGCCUCCUUCA	54	609-629	UGAAGGAGGCCACGAGGAUCGAA	189	607-629
AD-1560996	UCGUGGCCUCCUUCCUGAAUA	55	615-635	UAUUCAGGAAGGAGGCCACGAGG	190	613-635
AD-1561002	CCUCCUUCCUGAAUCCUUGGA	56	621-641	UCCAAGGAUUCAGGAAGGAGGCC	191	619-641
AD-1561009	CCUGAAUCCUUGGAUUACUGA	57	628-648	UCAGUAAUCCAAGGAUUCAGGAA	192	626-648
AD-1561015	UCCUUGGAUUACUGGACCUAA	58	634-654	UUAGGUCCAGUAAUCCAAGGAUU	193	632-654
AD-1561031	CCUACCCAGGCUCACUGACCA	59	650-670	UGGUCAGUGAGCCUGGGUAGGUC	194	648-670
AD-1561037	CCUCUUCUGGAAUGUGUGACA	60	676-696	UGUCACACAUUCCAGAAGAGGAG	195	674-696
AD-1561043	UGGAAUGUGUGACCUGGAUUA	61	683-703	UAAUCCAGGUCACACAUUCCAGA	196	681-703
AD-1561050	UGUGACCUGGAUUGUGCUCAA	62	690-710	UUGAGCACAAUCCAGGUCACACA	197	688-710
AD-1561056	CUGGAUUGUGCUCAAGGAACA	63	696-716	UGUUCCUUGAGCACAAUCCAGGU	198	694-716
AD-1561066	CUCAAGGAACCCAUCAGCGUA	64	706-726	UACGCUGAUGGGUUCCUUGAGCA	199	704-726
AD-1561072	GAACCCAUCAGCGUCAGCAGA	65	712-732	UCUGCUGACGCUGAUGGGUUCCU	200	710-732
AD-1475424	AGAACUGAUGGUGGACAACUA	66	719-739	UAGUUGUCCACCAUCAGUUCUUC	201	717-739
AD-1561092	CGAGCAGGUGUUGAAAUUCCA	67	732-752	UGGAAUUUCAACACCUGCUCGCU	202	730-752

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_0000 67.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3
AD-1561100	GGUGUUGAAAU UCCGUAAACA	68	738-758	UGUUUACGGAAU UUCAACACCUG	203	736-758
AD-1561106	GAAAUUCCGUA AACUUAACUA	69	744-764	UAGUUAAGUUUA CGGAAUUUCAA	204	742-764
AD-1561112	CCGUAAACUUA ACUUCAAUGA	70	750-770	UCAUUGAAGUUA AGUUUACGGAA	205	748-770
AD-1561116	GAGGGUGAACC CGAAGAACUA	71	772-792	UAGUUCUUCGGG UUCACCCUCCC	206	770-792
AD-1561122	GAACCCGAAGA ACUGAUGGUA	72	778-798	UACCAUCAGUUC UUCGGGUUCAC	207	776-798
AD-1561130	AUGGUGGACAA CUGGCGCCCA	73	793-813	UGGGCGCCAGUU GUCCACCAUCA	208	791-813
AD-1561146	CCAGCUCAGCC ACUGAAGAAA	74	811-831	UUUCUUCAGUGG CUGAGCUGGGC	209	809-831
AD-1561152	CAGCCACUGAA GAACAGGCAA	75	817-837	UUGCCUGUUCUU CAGUGGCUGAG	210	815-837
AD-1561158	CUGAAGAACAG GCAAAUCAAA	76	823-843	UUUGAUUUGCCU GUUCUUCAGUG	211	821-843
AD-1446763	UCACUGGAACA CCAAAUAUGA	77	828-848	UCAUAUUUGGUG UUCCAGUGAAC	212	826-848
AD-1561168	GGCAAAUCAAA GCUUCCUUCA	78	833-853	UGAAGGAAGCUU UGAUUUGCCUG	213	831-853
AD-1561175	CAAAGCUUCCU UCAAAUAAGA	79	840-860	UCUUAUUUGAAG GAAGCUUUGAU	214	838-860
AD-1561181	UUCCUUCAAAU AAGAUGGUCA	80	846-866	UGACCAUCUUAU UUGAAGGAAGC	215	844-866
AD-1561190	AUAAGAUGGUC CCAUAGUCUA	81	855-875	UAGACUAUGGGA CCAUCUUAUUU	216	853-875
AD-1561196	UGGUCCCAUAG UCUGUAUCCA	82	861-881	UGGAUACAGACU AUGGGACCAUC	217	859-881
AD-1561203	AUAGUCUGUAU CCAAAUAAUA	83	868-888	UAUUAUUUGGAU ACAGACUAUGG	218	866-888
AD-1561210	GUAUCCAAAUA AUGAAUCUUA	84	875-895	UAAGAUUCAUUA UUUGGAUACAG	219	873-895
AD-1561218	AUAAUGAAUCU UCGGGUGUUA	85	883-903	UAACACCCGAAG AUUCAUUAUUU	220	881-903
AD-1561225	AUCUUCGGGUG UUUCCCUUUA	86	890-910	UAAAGGGAAACA CCCGAAGAUUC	221	888-910
AD-1561231	GGGUGUUUCCC UUUAGCUAAA	87	896-916	UUUAGCUAAAGG GAAACACCCGA	222	894-916
AD-1561239	CCCUUUAGCUA AGCACAGAUA	88	904-924	UAUCUGUGCUUA GCUAAAGGGAA	223	902-924
AD-1561245	AGCUAAGCACA GAUCUACCUA	89	910-930	UAGGUAGAUCUG UGCUUAGCUAA	224	908-930
AD-1561254	CAGAUCUACCU UGGUGAUUUA	90	919-939	UAAAUCACCAAG GUAGAUCUGUG	225	917-939

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000067.3
AD-1561261	ACCUUGGUGAUUUGGACCCUA	91	926-946	UAGGGUCCAAAUCACCAAGGUAG	226	924-946
AD-1561272	UUGGACCCUGGUUGCUUUGUA	92	937-957	UACAAAGCAACCAGGGUCCAAAU	227	935-957
AD-1561279	CUGGUUGCUUUGUGUCUAGUA	93	944-964	UACUAGACACAAAGCAACCAGGG	228	942-964
AD-1561285	GCUUUGUGUCUAGUUUUCUAA	94	950-970	UUAGAAAACUAGACACAAAGCAA	229	948-970
AD-1561294	CUAGUUUUCUAGACCCUUCAA	95	959-979	UUGAAGGGUCUAGAAAACUAGAC	230	957-979
AD-1561300	UUCUAGACCCUUCAUCUCUUA	96	965-985	UAAGAGAUGAAGGGUCUAGAAAA	231	963-985
AD-1561306	ACCCUUCAUCUCUUACUUGAA	97	971-991	UUCAAGUAAGAGAUGAAGGGUCU	232	969-991
AD-1561313	AUCUCUUACUUGAUAGACUUA	98	978-998	UAAGUCUAUCAAGUAAGAGAUGA	233	976-998
AD-1561319	UACUUGAUAGACUUACUAAUA	99	984-1004	UAUUAGUAAGUCUAUCAAGUAAG	234	982-1004
AD-1561327	CUUACUAAUAAAAUGUGAAGA	100	995-1015	UCUUCACAUUUUAUUAGUAAGUC	235	993-1015
AD-1561336	AAAAUGUGAAGACUAGACCAA	101	1004-1024	UUGGUCUAGUCUUCACAUUUUAU	236	1002-1024
AD-1561342	UGAAGACUAGACCAAUUGUCA	102	1010-1030	UGACAAUUGGUCUAGUCUUCACA	237	1008-1030
AD-1561349	UAGACCAAUUGUCAUGCUUGA	103	1017-1037	UCAAGCAUGACAAUUGGUCUAGU	238	1015-1037
AD-1561360	UCAUGCUUGACACAACUGCUA	104	1028-1048	UAGCAGUUGUGUCAAGCAUGACA	239	1026-1048
AD-1561366	UUGACACAACUGCUGUGGCUA	105	1034-1054	UAGCCACAGCAGUUGUGUCAAGC	240	1032-1054
AD-1561378	CUGUGGCUGGUUGGUGCUUUA	106	1046-1066	UAAAGCACCAACCAGCCACAGCA	241	1044-1066
AD-1561384	CUGGUUGGUGCUUUGUUUAUA	107	1052-1072	UAUAAACAAAGCACCAACCAGCC	242	1050-1072
AD-1561390	GGUGCUUUGUUUAUGGUAGUA	108	1058-1078	UACUACCAUAAACAAAGCACCAA	243	1056-1078
AD-1561396	UUGUUUAUGGUAGUAGUUUUA	109	1064-1084	UAAAACUACUACCAUAAACAAAG	244	1062-1084
AD-1561402	UGGUAGUAGUUUUUCUGUAAA	110	1071-1091	UUUACAGAAAAACUACUACCAUA	245	1069-1091
AD-1561408	UAGUUUUUCUGUAACACAGAA	111	1077-1097	UUCUGUGUUACAGAAAAACUACU	246	1075-1097
AD-1561414	UUCUGUAACACAGAAUAUAGA	112	1083-1103	UCUAUAUUCUGUGUUACAGAAAA	247	1081-1103
AD-1561422	CACAGAAUAUAGGAUAAGAAA	113	1091-1111	UUUCUUAUCCUAUAUUCUGUGUU	248	1089-1111

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000067.3
AD-1561433	AGAAUAAAGUACCUUGACUUA	114	1114-1134	UAAGUCAAGGUACUUUAUUCUUA	249	1112-1134
AD-1561444	CUUGACUUUGUUCACAGCAUA	115	1126-1146	UAUGCUGUGAACAAAGUCAAGGU	250	1124-1146
AD-1561450	UUUGUUCACAGCAUGUAGGGA	116	1132-1152	UCCCUACAUGCUGUGAACAAAGU	251	1130-1152
AD-1561456	CACAGCAUGUAGGGUGAUGAA	117	1138-1158	UUCAUCACCCUACAUGCUGUGAA	252	1136-1158
AD-1561465	UAGGGUGAUGAGCACUCACAA	118	1147-1167	UUGUGAGUGCUCAUCACCCUACA	253	1145-1167
AD-1561471	GAUGAGCACUCACAAUUGUUA	119	1153-1173	UAACAAUUGUGAGUGCUCAUCAC	254	1151-1173
AD-1561478	ACUCACAAUUGUUGACUAAAA	120	1160-1180	UUUUAGUCAACAAUUGUGAGUGC	255	1158-1180
AD-1561489	UUGACUAAAAUGCUGCUUUUA	121	1171-1191	UAAAAGCAGCAUUUUAGUCAACA	256	1169-1191
AD-1561498	AUGCUGCUUUUAAAACAUAGA	122	1180-1200	UCUAUGUUUUAAAAGCAGCAUUU	257	1178-1200
AD-1561504	CUUUUAAAACAUAGGAAAGUA	123	1186-1206	UACUUUCCUAUGUUUUAAAAGCA	258	1184-1206
AD-1561513	CAUAGGAAAGUAGAAUGGUUA	124	1195-1215	UAACCAUUCUACUUUCCUAUGUU	259	1193-1215
AD-1561521	AGUAGAAUGGUUGAGUGCAAA	125	1203-1223	UUUGCACUCAACCAUUCUACUUU	260	1201-1223
AD-1561527	AUGGUUGAGUGCAAAUCCAUA	126	1209-1229	UAUGGAUUUGCACUCAACCAUUC	261	1207-1229
AD-1561534	AGUGCAAAUCCAUAGCACAAA	127	1216-1236	UUUGUGCUAUGGAUUUGCACUCA	262	1214-1236
AD-1561542	UCCAUAGCACAAGAUAAAUUA	128	1224-1244	UAAUUUAUCUUGUGCUAUGGAUU	263	1222-1244
AD-1561551	CAAGAUAAAUUGAGCUAGUUA	129	1233-1253	UAACUAGCUCAAUUUAUCUUGUG	264	1231-1253
AD-1561562	GAGCUAGUUAAGGCAAAUCAA	130	1244-1264	UUGAUUUGCCUUAACUAGCUCAA	265	1242-1264
AD-1561570	UAAGGCAAAUCAGGUAAAAUA	131	1252-1272	UAUUUUACCUGAUUUGCCUUAAC	266	1250-1272
AD-1561581	AGGUAAAAUAGUCAUGAUUCA	132	1263-1283	UGAAUCAUGACUAUUUUACCUGA	267	1261-1283
AD-1561591	GUCAUGAUUCUAUGUAAUGUA	133	1273-1293	UACAUUACAUAGAAUCAUGACUA	268	1271-1293
AD-1561601	UAUGUAAUGUAAACCAGAAAA	134	1283-1303	UUUUCUGGUUUACAUUACAUAGA	269	1281-1303
AD-1561613	UCAUGAUUUCAAGAUGUUAUA	135	1313-1333	UAUAACAUCUUGAAAUCAUGAAC	270	1311-1333
AD-1561651	CUUUUGAAUUACAGAGAUAUA	136	1411-1431	UAUAUCUCUGUAAUUCAAAAGUC	271	1409-1431

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_0000 67.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3
AD-1561679	UUAGAGUUGUG AUACAGAGUA	137	1463-1483	UACUCUGUAUCA CAACUCUAAUU	272	1461-1483
AD-1561686	UACAGAGUAUA UUUCCAUUCA	138	1475-1495	UGAAUGGAAAUA UACUCUGUAUC	273	1473-1495
AD-1561694	AUAUUUCCAUU CAGACAAUAA	139	1483-1503	UUAUUGUCUGAA UGGAAAUAUAC	274	1481-1503
AD-1561703	UUCAGACAAUA UAUCAUAACA	140	1492-1512	UGUUAUGAUAUA UUGUCUGAAUG	275	1490-1512
AD-1447598	UUGUGAUACAG AGUAUAUUUA	141	1835-1855	UAAAUAUACUCU GUAUCACAACU	276	1833-1855

Table 4. Unmodified Sense and Antisense Strand Sequences of CA2 dsRNA Agents for GalNAc Modification

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3
AD-1559459	AGAUCGGUGCC GAUUCCUGCU	277	32-52	AGCAGGAAUCGG CACCGAUCUGG	412	30-52
AD-1559476	CGCGACCAUGU CCCAUCACUU	278	69-89	AAGUGAUGGGAC AUGGUCGCGCU	413	67-89
AD-1559481	GUACGGCAAAC ACAACGGACU	279	93-113	AGUCCGUUGUGU UUGCCGUACCC	414	91-113
AD-1559487	CAAACACAACG GACCUGAGCU	280	99-119	AGCUCAGGUCCG UUGUGUUUGCC	415	97-119
AD-1559497	GGACCUGAGCA CUGGCAUAAU	281	109-129	AUUAUGCCAGUG CUCAGGUCCGU	416	107-129
AD-1559503	GAGCACUGGCA UAAGGACUUU	282	115-135	AAAGUCCUUAUG CCAGUGCUCAG	417	113-135
AD-1559514	GUUGACAUCGA CACUCAUACU	283	166-186	AGUAUGAGUGUC GAUGUCAACAG	418	164-186
AD-1559524	ACACUCAUACA GCCAAGUAUU	284	176-196	AAUACUUGGCUG UAUGAGUGUCG	419	174-196
AD-1559531	UACAGCCAAGU AUGACCCUUU	285	183-203	AAAGGGUCAUAC UUGGCUGUAUG	420	181-203
AD-1559537	CAAGUAUGACC CUUCCCUGAU	286	189-209	AUCAGGGAAGGG UCAUACUUGGC	421	187-209
AD-1559543	UGUCUGUUUCC UAUGAUCAAU	287	215-235	AUUGAUCAUAGG AAACAGACAGG	422	213-235
AD-1559552	CCUAUGAUCAA GCAACUUCCU	288	224-244	AGGAAGUUGCUU GAUCAUAGGAA	423	222-244
AD-1559560	CAAGCAACUUC CCUGAGGAUU	289	232-252	AAUCCUCAGGGA AGUUGCUUGAU	424	230-252
AD-1559570	CCCUGAGGAUC CUCAACAAUU	290	242-262	AAUUGUUGAGGA UCCUCAGGGAA	425	240-262

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3
AD-1559579	UCCUCAACAAU GGUCAUGCUU	291	251-271	AAGCAUGACCAU UGUUGAGGAUC	426	249-271
AD-1559585	ACAAUGGUCAU GCUUUCAACU	292	257-277	AGUUGAAAGCAU GACCAUUGUUG	427	255-277
AD-1559594	AUGCUUUCAAC GUGGAGUUUU	293	266-286	AAAACUCCACGU UGAAAGCAUGA	428	264-286
AD-1559602	AACGUGGAGUU UGAUGACUCU	294	274-294	AGAGUCAUCAAA CUCCACGUUGA	429	272-294
AD-1559613	UGAUGACUCUC AGGACAAAGU	295	285-305	ACUUUGUCCUGA GAGUCAUCAAA	430	283-305
AD-1559620	UCUCAGGACAA AGCAGUGCUU	296	292-312	AAGCACUGCUUU GUCCUGAGAGU	431	290-312
AD-1559626	GACAAAGCAGU GCUCAAGGGU	297	298-318	ACCCUUGAGCAC UGCUUUGUCCU	432	296-318
AD-1559638	UGGCACUUACA GAUUGAUUCU	298	330-350	AGAAUCAAUCUG UAAGUGCCAUC	433	328-350
AD-1559644	UUACAGAUUGA UUCAGUUUCU	299	336-356	AGAAACUGAAUC AAUCUGUAAGU	434	334-356
AD-1559654	AUUCAGUUUCA CUUUCACUGU	300	346-366	ACAGUGAAAGUG AAACUGAAUCA	435	344-366
AD-1559660	UCACUUGAUGG ACAAGGUUCU	301	370-390	AGAACCUUGUCC AUCAAGUGAAC	436	368-390
AD-1559666	GAUGGACAAGG UUCAGAGCAU	302	376-396	AUGCUCUGAACC UUGUCCAUCAA	437	374-396
AD-1559672	CAAGGUUCAGA GCAUACUGUU	303	382-402	AACAGUAUGCUC UGAACCUUGUC	438	380-402
AD-1559678	UCAGAGCAUAC UGUGGAUAAU	304	388-408	AUUAUCCACAGU AUGCUCUGAAC	439	386-408
AD-1559699	AAGAAAUAUGC UGCAGAACUU	305	409-429	AAGUUCUGCAGC AUAUUUCUUUU	440	407-429
AD-1559705	UAUGCUGCAGA ACUUCACUUU	306	415-435	AAAGUGAAGUUC UGCAGCAUAUU	441	413-435
AD-1559711	GCAGAACUUCA CUUGGUUCAU	307	421-441	AUGAACCAAGUG AAGUUCUGCAG	442	419-441
AD-1559717	CUUCACUUGGU UCACUGGAAU	308	427-447	AUUCCAGUGAAC CAAGUGAAGUU	443	425-447
AD-1559728	UCACUGGAACA CCAAAUAUGU	309	438-458	ACAUAUUUGGUG UUCCAGUGAAC	444	436-458
AD-1559735	UUUGGGAAAGC UGUGCAGCAU	310	463-483	AUGCUGCACAGC UUUCCCAAAAU	445	461-483
AD-1559747	GUGCAGCAACC UGAUGGACUU	311	475-495	AAGUCCAUCAGG UUGCUGCACAG	446	473-495
AD-1559753	CAACCUGAUGG ACUGGCCGUU	312	481-501	AACGGCCAGUCC AUCAGGUUGCU	447	479-501
AD-1559765	CUGGCCGUUCU AGGUAUUUUU	313	493-513	AAAAAUACCUAG AACGGCCAGUC	448	491-513

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3
AD-1559768	UGAAGGUUGGC AGCGCUAAAU	314	515-535	AUUUAGCGCUGC CAACCUUCAAA	449	513-535
AD-1559777	GCAGCGCUAAA CCGGGCCUUU	315	524-544	AAAGGCCCGGUU UAGCGCUGCCA	450	522-544
AD-1559788	CCGGGCCUUCA GAAAGUUGUU	316	535-555	AACAACUUUCUG AAGGCCCGGUU	451	533-555
AD-1559794	CUUCAGAAAGU UGUUGAUGUU	317	541-561	AACAUCAACAAC UUUCUGAAGGC	452	539-561
AD-1559803	GUUGUUGAUGU GCUGGAUUCU	318	550-570	AGAAUCCAGCAC AUCAACAACUU	453	548-570
AD-1559814	GCUGGAUUCCA UUAAAACAAU	319	561-581	AUUGUUUUAAUG GAAUCCAGCAC	454	559-581
AD-1559821	UCCAUUAAAAC AAAGGGCAAU	320	568-588	AUUGCCCUUUGU UUUAAUGGAAU	455	566-588
AD-1559827	AAAACAAAGGG CAAGAGUGCU	321	574-594	AGCACUCUUGCC CUUUGUUUUAA	456	572-594
AD-1559836	GGCAAGAGUGC UGACUUCACU	322	583-603	AGUGAAGUCAGC ACUCUUGCCCU	457	581-603
AD-1559843	GUGCUGACUUC ACUAACUUCU	323	590-610	AGAAGUUAGUGA AGUCAGCACUC	458	588-610
AD-1559849	ACUUCACUAAC UUCGAUCCUU	324	596-616	AAGGAUCGAAGU UAGUGAAGUCA	459	594-616
AD-1559862	CGAUCCUCGUG GCCUCCUUCU	325	609-629	AGAAGGAGGCCA CGAGGAUCGAA	460	607-629
AD-1559868	UCGUGGCCUCC UUCCUGAAUU	326	615-635	AAUUCAGGAAGG AGGCCACGAGG	461	613-635
AD-1559874	CCUCCUUCCUG AAUCCUUGGU	327	621-641	ACCAAGGAUUCA GGAAGGAGGCC	462	619-641
AD-1559881	CCUGAAUCCUU GGAUUACUGU	328	628-648	ACAGUAAUCCAA GGAUUCAGGAA	463	626-648
AD-1559887	UCCUUGGAUUA CUGGACCUAU	329	634-654	AUAGGUCCAGUA AUCCAAGGAUU	464	632-654
AD-1559903	CCUACCCAGGC UCACUGACCU	330	650-670	AGGUCAGUGAGC CUGGGUAGGUC	465	648-670
AD-1559909	CCUCUUCUGGA AUGUGUGACU	331	676-696	AGUCACACAUUC CAGAAGAGGAG	466	674-696
AD-1559916	UGGAAUGUGUG ACCUGGAUUU	332	683-703	AAAUCCAGGUCA CACAUUCCAGA	467	681-703
AD-1559923	UGUGACCUGGA UUGUGCUCAU	333	690-710	AUGAGCACAAUC CAGGUCACACA	468	688-710
AD-1559929	CUGGAUUGUGC UCAAGGAACU	334	696-716	AGUUCCUUGAGC ACAAUCCAGGU	469	694-716
AD-1559939	CUCAAGGAACC CAUCAGCGUU	335	706-726	AACGCUGAUGGG UUCCUUGAGCA	470	704-726
AD-1559945	GAACCCAUCAG CGUCAGCAGU	336	712-732	ACUGCUGACGCU GAUGGGUUCCU	471	710-732

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3
AD-1559965	CGAGCAGGUGU UGAAAUUCCU	337	732-752	AGGAAUUUCAAC ACCUGCUCGCU	472	730-752
AD-1559971	GGUGUUGAAAU UCCGUAAACU	338	738-758	AGUUUACGGAAU UUCAACACCUG	473	736-758
AD-1559977	GAAAUUCCGUA AACUUAACUU	339	744-764	AAGUUAAGUUUA CGGAAUUUCAA	474	742-764
AD-1559983	CCGUAAACUUA ACUUCAAUGU	340	750-770	ACAUUGAAGUUA AGUUUACGGAA	475	748-770
AD-1559987	GAGGGUGAACC CGAAGAACUU	341	772-792	AAGUUCUUCGGG UUCACCCUCCC	476	770-792
AD-1559993	GAACCCGAAGA ACUGAUGGUU	342	778-798	AACCAUCAGUUC UUCGGGUUCAC	477	776-798
AD-1560001	AGAACUGAUGG UGGACAACUU	343	786-806	AAGUUGUCCACC AUCAGUUCUUC	478	784-806
AD-1560008	AUGGUGGACAA CUGGCGCCCU	344	793-813	AGGGCGCCAGUU GUCCACCAUCA	479	791-813
AD-1560024	CCAGCUCAGCC ACUGAAGAAU	345	811-831	AUUCUUCAGUGG CUGAGCUGGGC	480	809-831
AD-1560030	CAGCCACUGAA GAACAGGCAU	346	817-837	AUGCCUGUUCUU CAGUGGCUGAG	481	815-837
AD-1560036	CUGAAGAACAG GCAAAUCAAU	347	823-843	AUUGAUUUGCCU GUUCUUCAGUG	482	821-843
AD-1560046	GGCAAAUCAAA GCUUCCUUCU	348	833-853	AGAAGGAAGCUU UGAUUUGCCUG	483	831-853
AD-1560053	CAAAGCUUCCU UCAAAUAAGU	349	840-860	ACUUAUUUGAAG GAAGCUUUGAU	484	838-860
AD-1560059	UUCCUUCAAAU AAGAUGGUCU	350	846-866	AGACCAUCUUAU UUGAAGGAAGC	485	844-866
AD-1560068	AUAAGAUGGUC CCAUAGUCUU	351	855-875	AAGACUAUGGGA CCAUCUUAUUU	486	853-875
AD-1560074	UGGUCCCAUAG UCUGUAUCCU	352	861-881	AGGAUACAGACU AUGGGACCAUC	487	859-881
AD-1560081	AUAGUCUGUAU CCAAAUAAUU	353	868-888	AAUUAUUUGGAU ACAGACUAUGG	488	866-888
AD-1560088	GUAUCCAAAUA AUGAAUCUUU	354	875-895	AAAGAUUCAUUA UUUGGAUACAG	489	873-895
AD-1560096	AUAAUGAAUCU UCGGGUGUUU	355	883-903	AAACACCCGAAG AUUCAUUAUUU	490	881-903
AD-1560103	AUCUUCGGGUG UUUCCCUUUU	356	890-910	AAAAGGGAAACA CCCGAAGAUUC	491	888-910
AD-1560109	GGGUGUUUCCC UUUAGCUAAU	357	896-916	AUUAGCUAAAGG GAAACACCCGA	492	894-916
AD-1560117	CCCUUUAGCUA AGCACAGAUU	358	904-924	AAUCUGUGCUUA GCUAAAGGGAA	493	902-924
AD-1560123	AGCUAAGCACA GAUCUACCUU	359	910-930	AAGGUAGAUCUG UGCUUAGCUAA	494	908-930

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3
AD-1560132	CAGAUCUACCU UGGUGAUUUU	360	919-939	AAAAUCACCAAG GUAGAUCUGUG	495	917-939
AD-1560139	ACCUUGGUGAU UUGGACCCUU	361	926-946	AAGGGUCCAAAU CACCAAGGUAG	496	924-946
AD-1560150	UUGGACCCUGG UUGCUUUGUU	362	937-957	AACAAAGCAACC AGGGUCCAAAU	497	935-957
AD-1560157	CUGGUUGCUUU GUGUCUAGUU	363	944-964	AACUAGACACAA AGCAACCAGGG	498	942-964
AD-1560163	GCUUUGUGUCU AGUUUUCUAU	364	950-970	AUAGAAAACUAG ACACAAAGCAA	499	948-970
AD-1560172	CUAGUUUUCUA GACCCUUCAU	365	959-979	AUGAAGGGUCUA GAAAACUAGAC	500	957-979
AD-1560178	UUCUAGACCCU UCAUCUCUUU	366	965-985	AAAGAGAUGAAG GGUCUAGAAAA	501	963-985
AD-1560184	ACCCUUCAUCU CUUACUUGAU	367	971-991	AUCAAGUAAGAG AUGAAGGGUCU	502	969-991
AD-1560191	AUCUCUUACUU GAUAGACUUU	368	978-998	AAAGUCUAUCAA GUAAGAGAUGA	503	976-998
AD-1560197	UACUUGAUAGA CUUACUAAUU	369	984-1004	AAUUAGUAAGUC UAUCAAGUAAG	504	982-1004
AD-1560205	CUUACUAAUAA AAUGUGAAGU	370	995-1015	ACUUCACAUUUU AUUAGUAAGUC	505	993-1015
AD-1560214	AAAAUGUGAAG ACUAGACCAU	371	1004-1024	AUGGUCUAGUCU UCACAUUUUAU	506	1002-1024
AD-1560220	UGAAGACUAGA CCAAUUGUCU	372	1010-1030	AGACAAUUGGUC UAGUCUUCACA	507	1008-1030
AD-1560227	UAGACCAAUUG UCAUGCUUGU	373	1017-1037	ACAAGCAUGACA AUUGGUCUAGU	508	1015-1037
AD-1560238	UCAUGCUUGAC ACAACUGCUU	374	1028-1048	AAGCAGUUGUGU CAAGCAUGACA	509	1026-1048
AD-1560244	UUGACACAACU GCUGUGGCUU	375	1034-1054	AAGCCACAGCAG UUGUGUCAAGC	510	1032-1054
AD-1560256	CUGUGGCUGGU UGGUGCUUUU	376	1046-1066	AAAAGCACCAAC CAGCCACAGCA	511	1044-1066
AD-1560262	CUGGUUGGUGC UUUGUUUAUU	377	1052-1072	AAUAAACAAAGC ACCAACCAGCC	512	1050-1072
AD-1560268	GGUGCUUUGUU UAUGGUAGUU	378	1058-1078	AACUACCAUAAA CAAAGCACCAA	513	1056-1078
AD-1560274	UUGUUUAUGGU AGUAGUUUUU	379	1064-1084	AAAAACUACUAC CAUAAACAAAG	514	1062-1084
AD-1560280	UGGUAGUAGUU UUUCUGUAAU	380	1071-1091	AUUACAGAAAAA CUACUACCAUA	515	1069-1091
AD-1560286	UAGUUUUUCUG UAACACAGAU	381	1077-1097	AUCUGUGUUACA GAAAAACUACU	516	1075-1097
AD-1560292	UUCUGUAACAC AGAAUAUAGU	382	1083-1103	ACUAUAUUCUGU GUUACAGAAAA	517	1081-1103

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3
AD-1560300	CACAGAAUAUAGGAUAAGAAU	383	1091-1111	AUUCUUAUCCUAUAUUCUGUGUU	518	1089-1111
AD-1560311	AGAAUAAAGUACCUUGACUUU	384	1114-1134	AAAGUCAAGGUACUUUAUUCUUA	519	1112-1134
AD-1560323	CUUGACUUUGUUCACAGCAUU	385	1126-1146	AAUGCUGUGAACAAAGUCAAGGU	520	1124-1146
AD-1560329	UUUGUUCACAGCAUGUAGGGU	386	1132-1152	ACCCUACAUGCUGUGAACAAAGU	521	1130-1152
AD-1560335	CACAGCAUGUAGGGUGAUGAU	387	1138-1158	AUCAUCACCCUACAUGCUGUGAA	522	1136-1158
AD-1560344	UAGGGUGAUGAGCACUCACAU	388	1147-1167	AUGUGAGUGCUCAUCACCCUACA	523	1145-1167
AD-1560350	GAUGAGCACUCACAAUUGUUU	389	1153-1173	AAACAAUUGUGAGUGCUCAUCAC	524	1151-1173
AD-1560357	ACUCACAAUUGUUGACUAAAU	390	1160-1180	AUUUAGUCAACAAUUGUGAGUGC	525	1158-1180
AD-1560368	UUGACUAAAAUGCUGCUUUUU	391	1171-1191	AAAAAGCAGCAUUUUAGUCAACA	526	1169-1191
AD-1560377	AUGCUGCUUUUAAAACAUAGU	392	1180-1200	ACUAUGUUUUAAAAGCAGCAUUU	527	1178-1200
AD-1560383	CUUUUAAAACAUAGGAAAGUU	393	1186-1206	AACUUUCCUAUGUUUUAAAAGCA	528	1184-1206
AD-1560392	CAUAGGAAAGUAGAAUGGUUU	394	1195-1215	AAACCAUUCUACUUUCCUAUGUU	529	1193-1215
AD-1560400	AGUAGAAUGGUUGAGUGCAAU	395	1203-1223	AUUGCACUCAACCAUUCUACUUU	530	1201-1223
AD-1560406	AUGGUUGAGUGCAAAUCCAUU	396	1209-1229	AAUGGAUUUGCACUCAACCAUUC	531	1207-1229
AD-1560413	AGUGCAAAUCCAUAGCACAAU	397	1216-1236	AUUGUGCUAUGGAUUUGCACUCA	532	1214-1236
AD-1560421	UCCAUAGCACAAGAUAAAUUU	398	1224-1244	AAAUUUAUCUUGUGCUAUGGAUU	533	1222-1244
AD-1560430	CAAGAUAAAUUGAGCUAGUUU	399	1233-1253	AAACUAGCUCAAUUUAUCUUGUG	534	1231-1253
AD-1560441	GAGCUAGUUAAGGCAAAUCAU	400	1244-1264	AUGAUUUGCCUUAACUAGCUCAA	535	1242-1264
AD-1560449	UAAGGCAAAUCAGGUAAAAUU	401	1252-1272	AAUUUUACCUGAUUUGCCUUAAC	536	1250-1272
AD-1560460	AGGUAAAAUAGUCAUGAUUCU	402	1263-1283	AGAAUCAUGACUAUUUUACCUGA	537	1261-1283
AD-1560470	GUCAUGAUUCUAUGUAAUGUU	403	1273-1293	AACAUUACAUAGAAUCAUGACUA	538	1271-1293
AD-1560480	UAUGUAAUGUAAACCAGAAAU	404	1283-1303	AUUUCUGGUUUACAUUACAUAGA	539	1281-1303
AD-1560492	UCAUGAUUUCAAGAUGUUAUU	405	1313-1333	AAUAACAUCUUGAAAUCAUGAAC	540	1311-1333

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3
AD-1560528	CUUUUGAAUUA CAGAGAUAUU	406	1411-1431	AAUAUCUCUGUA AUUCAAAAGUC	541	1409-1431
AD-1560556	UUAGAGUUGUG AUACAGAGUU	407	1463-1483	AACUCUGUAUCA CAACUCUAAUU	542	1461-1483
AD-1560562	UUGUGAUACAG AGUAUAUUUU	408	1469-1489	AAAAUAUACUCU GUAUCACAACU	543	1467-1489
AD-1560568	UACAGAGUAUA UUUCCAUUCU	409	1475-1495	AGAAUGGAAAUA UACUCUGUAUC	544	1473-1495
AD-1560576	AUAUUUCCAUU CAGACAAUAU	410	1483-1503	AUAUUGUCUGAA UGGAAAUAUAC	545	1481-1503
AD-1560585	UUCAGACAAUA UAUCAUAACU	411	1492-1512	AGUUAUGAUAUA UUGUCUGAAUG	546	1490-1512

Table 5. Modified Sense and Antisense Strand Sequences of CA2 dsRNA Agents with C16 Modification

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1560600	asgsauc(Ghd)GfuGf CfCfgauuccugscsa	547	VPusGfscagGfaAfUfc ggcAfcCfgaucusgsg	682	CCAGAUCGGUGC CGAUUCCUGCC	817
AD-1560617	csgscga(Chd)CfaUf GfUfcccaucacsusa	548	VPusAfsgugAfuGfGf gacaUfgGfucgcgscsu	683	AGCGCGACCAUG UCCCAUCACUG	818
AD-1560622	gsusacg(Ghd)CfaAf AfCfacaacggascsa	549	VPusGfsuccGfuUfGfu guuUfgCfcguacscsc	684	GGGUACGGCAAA CACAACGGACC	819
AD-1560628	csasaac(Ahd)CfaAf CfGfgaccugagscsa	550	VPusGfscucAfgGfUfc cguUfgUfguuugscsc	685	GGCAAACACAAC GGACCUGAGCA	820
AD-1560638	gsgsacc(Uhd)GfaGf CfAfcuggcauasasa	551	VPusUfsuauGfcCfAfg ugcUfcAfgguccsgsu	686	ACGGACCUGAGC ACUGGCAUAAG	821
AD-1560644	gsasgca(Chd)UfgGf CfAfuaaggacususa	552	VPusAfsaguCfcUfUfa ugcCfaGfugcucsasg	687	CUGAGCACUGGC AUAAGGACUUC	822
AD-1560655	gsusuga(Chd)AfuCf GfAfcacucauascsa	553	VPusGfsuauGfaGfUfg ucgAfuGfucaacsasg	688	CUGUUGACAUCG ACACUCAUACA	823
AD-1560665	ascsacu(Chd)AfuAf CfAfgccaaguasusa	554	VPusAfsuacUfuGfGfc uguAfuGfaguguscsg	689	CGACACUCAUAC AGCCAAGUAUG	824
AD-1560672	usascag(Chd)CfaAf GfUfaugacccususa	555	VPusAfsaggGfuCfAfu acuUfgGfcuguasusg	690	CAUACAGCCAAG UAUGACCCUUC	825
AD-1560678	csasagu(Ahd)UfgAf CfCfcuucccugsasa	556	VPusUfscagGfgAfAfg gguCfaUfacuugsgsc	691	GCCAAGUAUGAC CCUUCCCUGAA	826
AD-1560684	usgsucu(Ghd)UfuUf CfCfuaugaucasasa	557	VPusUfsugaUfcAfUfa ggaAfaCfagacasgsg	692	CCUGUCUGUUUC CUAUGAUCAAG	827
AD-1560693	cscsuau(Ghd)AfuCf AfAfgcaacuucscsa	558	VPusGfsgaaGfuUfGfc uugAfuCfauaggsasa	693	UUCCUAUGAUCA AGCAACUUCCC	828
AD-1560701	csasagc(Ahd)AfcUf UfCfccugaggasusa	559	VPusAfsuccUfcAfGfg gaaGfuUfgcuugsasu	694	AUCAAGCAACUU CCCUGAGGAUC	829

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1560711	cscscug(Ahd)GfgAfUfCfcucaacaasusa	560	VPusAfsuugUfuGfAfggauCfcUfcagggsasa	695	UUCCCUGAGGAUCCUCAACAAUG	830
AD-1560720	uscscuc(Ahd)AfcAfAfUfggucaugcsusa	561	VPusAfsgcaUfgAfCfcauuGfuUfgaggasusc	696	GAUCCUCAACAAUGGUCAUGCUU	831
AD-1560726	ascsaau(Ghd)GfuCfAfUfgcuuucaascsa	562	VPusGfsuugAfaAfGfcaugAfcCfauugususg	697	CAACAAUGGUCAUGCUUUCAACG	832
AD-1560735	asusgcu(Uhd)UfcAfAfCfguggaguususa	563	VPusAfsaacUfcCfAfcguuGfaAfagcausgsa	698	UCAUGCUUUCAACGUGGAGUUUG	833
AD-1560745	asascgu(Ghd)GfaGfUfUfugaugacuscsa	564	VPusGfsaguCfaUfCfaaacUfcCfacguusgsa	699	UCAACGUGGAGUUUGAUGACUCU	834
AD-1560752	usgsaug(Ahd)CfuCfUfCfaggacaaasgsa	565	VPusCfsuuuGfuCfCfugagAfgUfcaucasasa	700	UUUGAUGACUCUCAGGACAAAGC	835
AD-1560759	uscsuca(Ghd)GfaCfAfAfagcagugcsusa	566	VPusAfsgcaCfuGfCfuuugUfcCfugagasgsu	701	ACUCUCAGGACAAAGCAGUGCUC	836
AD-1560765	gsascaa(Ahd)GfcAfGfUfgcucaaggsgsa	567	VPusCfsccuUfgAfGfcacuGfcUfuugucscsu	702	AGGACAAAGCAGUGCUCAAGGGA	837
AD-1560777	usgsgca(Chd)UfuAfCfAfgauugauuscsa	568	VPusGfsaauCfaAfUfcuguAfaGfugccasusc	703	GAUGGCACUUACAGAUUGAUUCA	838
AD-1560783	ususaca(Ghd)AfuUfGfAfuucaguuuscsa	569	VPusGfsaaaCfuGfAfaucaAfuCfuguaasgsu	704	ACUUACAGAUUGAUUCAGUUUCA	839
AD-1560792	asususca(Ghd)UfuUfCfAfcuuucacusgsa	570	VPusCfsaguGfaAfAfgugaAfaCfugaauscsa	705	UGAUUCAGUUUCACUUUCACUGG	840
AD-1560798	uscsacu(Uhd)GfaUfGfGfacaagguuscsa	571	VPusGfsaacCfuUfGfuccaUfcAfagugasasc	706	GUUCACUUGAUGGACAAGGUUCA	841
AD-1560804	gsasugg(Ahd)CfaAfGfGfuucagagcsasa	572	VPusUfsgcuCfuGfAfaccuUfgUfccaucsasa	707	UUGAUGGACAAGGUUCAGAGCAU	842
AD-1560810	csasagg(Uhd)UfcAfGfAfgcauacugsusa	573	VPusAfscagUfaUfGfcucuGfaAfccuugsusc	708	GACAAGGUUCAGAGCAUACUGUG	843
AD-1560816	uscsaga(Ghd)CfaUfAfCfuguggauasasa	574	VPusUfsuauCfcAfCfaguaUfgCfucugasasc	709	GUUCAGAGCAUACUGUGGAUAAA	844
AD-1560837	asasgaa(Ahd)UfaUfGfCfugcagaacsusa	575	VPusAfsguuCfuGfCfagcaUfaUfuucuususu	710	AAAAGAAAUAUGCUGCAGAACUU	845
AD-1560845	usasugc(Uhd)GfcAfGfAfacuucacususa	576	VPusAfsaguGfaAfGfuucuGfcAfgcauasusu	711	AAUAUGCUGCAGAACUUCACUUG	846
AD-1560851	gscsaga(Ahd)CfuUfCfAfcuugguucsasa	577	VPusUfsgaaCfcAfAfgugaAfgUfucugcsasg	712	CUGCAGAACUUCACUUGGUUCAC	847
AD-1560843	csusuca(Chd)UfuGfGfUfucacuggasasa	578	VPusUfsuccAfgUfGfaaccAfaGfugaagsusu	713	AACUUCACUUGGUUCACUGGAAC	848
AD-1560862	ususugg(Ghd)AfaAfGfCfugugcagcsasa	579	VPusUfsgcuGfcAfCfagcuUfuCfccaaasasu	714	AUUUUGGGAAAGCUGUGCAGCAA	849
AD-1560874	gsusgca(Ghd)CfaAfCfCfugauggacsusa	580	VPusAfsgucCfaUfCfaggguUfgCfugcacsasg	715	CUGUGCAGCAACCUGAUGGACUG	850
AD-1560880	csasacc(Uhd)GfaUfGfGfacuggccgsusa	581	VPusAfscggCfcAfGfuccaUfcAfgguugscsu	716	AGCAACCUGAUGGACUGGCCGUU	851
AD-1560892	csusggc(Chd)GfuUfCfUfagguauuususa	582	VPusAfsaaaUfaCfCfuagaAfcGfgccagsusc	717	GACUGGCCGUUCUAGGUAUUUUU	852

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1560895	usgsaag(Ghd)UfuGfGfCfagcgcuaasasa	583	VPusUfsuuaGfcGfCfugccAfaCfcuucasasa	718	UUUGAAGGUUGGCAGCGCUAAAC	853
AD-1560904	gscsagc(Ghd)CfuAfAfAfccgggccususa	584	VPusAfsaggCfcCfGfguuuAfgCfgcugcscsa	719	UGGCAGCGCUAAACCGGGCCUUC	854
AD-1560915	cscsggg(Chd)CfuUfCfAfgaaaguugsusa	585	VPusAfscaaCfuUfUfcugaAfgGfcccggsusu	720	AACCGGGCCUUCAGAAAGUUGUU	855
AD-1560921	csusuca(Ghd)AfaAfGfUfuguugaugsusa	586	VPusAfscauCfaAfCfaacuUfuCfugaagsgsc	721	GCCUUCAGAAAGUUGUUGAUGUG	856
AD-1560930	gsusugu(Uhd)GfaUfGfUfgcuggauuscsa	587	VPusGfsaauCfcAfGfcacaUfcAfacaacsusu	722	AAGUUGUUGAUGUGCUGGAUUCC	857
AD-1560941	gscsugg(Ahd)UfuCfCfAfuuaaaacasasa	588	VPusUfsuguUfuUfAfauggAfaUfccagcsasc	723	GUGCUGGAUUCCAUUAAAACAAA	858
AD-1560948	uscscau(Uhd)AfaAfAfCfaaagggcasasa	589	VPusUfsugcCfcUfUfuguuUfuAfauggasasu	724	AUUCCAUUAAAACAAAGGGCAAG	859
AD-1560954	asasaac(Ahd)AfaGfGfGfcaagagugscsa	590	VPusGfscacUfcUfUfgcccUfuUfguuuusasa	725	UUAAAACAAAGGGCAAGAGUGCU	860
AD-1560963	gsgscaa(Ghd)AfgUfGfCfugacuucascsa	591	VPusGfsugaAfgUfCfagcaCfuCfuugccscsu	726	AGGGCAAGAGUGCUGACUUCACU	861
AD-1560970	gsusgcu(Ghd)AfcUfUfCfacuaacuuscsa	592	VPusGfsaagUfuAfGfugaaGfuCfagcacsusc	727	GAGUGCUGACUUCACUAACUUCG	862
AD-1560976	ascsuuc(Ahd)CfuAfAfCfuucgauccsusa	593	VPusAfsggaUfcGfAfaguuAfgUfgaaguscsa	728	UGACUUCACUAACUUCGAUCCUC	863
AD-1560989	csgsauc(Chd)UfcGfUfGfgccuccuuscsa	594	VPusGfsaagGfaGfGfccacGfaGfgaucgsasa	729	UUCGAUCCUCGUGGCCUCCUUCC	864
AD-1560996	uscsgug(Ghd)CfcUfCfCfuuccugaasusa	595	VPusAfsuucAfgGfAfaggaGfgCfcacgasgsg	730	CCUCGUGGCCUCCUUCCUGAAUC	865
AD-1561002	cscsucc(Uhd)UfcCfUfGfaauccuugsgsa	596	VPusCfscaaGfgAfUfucagGfaAfggaggscsc	731	GGCCUCCUUCCUGAAUCCUUGGA	866
AD-1561009	cscsuga(Ahd)UfcCfUfUfgguauacusgsa	597	VPusCfsaguAfaUfCfcaagGfaUfucaggsasa	732	UUCCUGAAUCCUUGGAUUACUGG	867
AD-1561015	uscscuu(Ghd)GfaUfUfAfcuggaccusasa	598	VPusUfsaggUfcCfAfguaaUfcCfaaggasusu	733	AAUCCUUGGAUUACUGGACCUAC	868
AD-1561031	cscsuac(Chd)CfaGfGfCfucacugacscsa	599	VPusGfsgucAfgUfGfaggccUfgGfguaggsusc	734	GACCUACCCAGGCUCACUGACCA	869
AD-1561037	cscsucu(Uhd)CfuGfGfAfaugugugascsa	600	VPusGfsucaCfaCfAfuuccAfgAfagaggsasg	735	CUCCUCUUCUGGAAUGUGUGACC	870
AD-1561043	usgsgaa(Uhd)GfuGfUfGfaccuggaususa	601	VPusAfsaucCfaGfGfucacAfcAfuuccasgsa	736	UCUGGAAUGUGUGACCUGGAUUG	871
AD-1561050	usgsuga(Chd)CfuGfGfAfuugugcucsasa	602	VPusUfsgagCfaCfAfauccAfgGfucacascsa	737	UGUGUGACCUGGAUUGUGCUCAA	872
AD-1561056	csusgga(Uhd)UfgUfGfCfucaaggaascsa	603	VPusGfsuucCfuUfGfagcaCfaAfuccagsgsu	738	ACCUGGAUUGUGCUCAAGGAACC	873
AD-1561066	csuscaa(Ghd)GfaAfCfCfcaucagcgsusa	604	VPusAfscgcUfgAfUfggguUfcCfuugagscsa	739	UGCUCAAGGAACCCAUCAGCGUC	874
AD-1561072	gsasacc(Chd)AfuCfAfGfcgucagcasgsa	605	VPusCfsugcUfgAfCfgcugAfuGfgguucscsu	740	AGGAACCCAUCAGCGUCAGCAGC	875

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1475424	asgsaac(Uhd)GfaUfGfGfuggacaacsusa	606	VPusAfsguuGfuCfCfaccaUfcAfguucususc	741	GAAGAACUGAUGGUGGACAACUG	876
AD-1561092	csgsagc(Ahd)GfgUfGfUfugaaauucscsa	607	VPusGfsgaaUfuUfCfaacaCfcUfgcucgscsu	742	AGCGAGCAGGUGUUGAAAUUCCG	877
AD-1561100	gsgsugu(Uhd)GfaAfAfUfuccguaaascsa	608	VPusGfsuuuAfcGfGfaauuUfcAfacaccsusg	743	CAGGUGUUGAAAUUCCGUAAACU	878
AD-1561106	gsasaau(Uhd)CfcGfUfAfaacuuaacsusa	609	VPusAfsguuAfaGfUfuuacGfgAfauuucsasa	744	UUGAAAUUCCGUAAACUUAACUU	879
AD-1561112	cscsgua(Ahd)AfcUfUfAfacuucaausgsa	610	VPusCfsauuGfaAfGfuuaaGfuUfuacggsasa	745	UUCCGUAAACUUAACUUCAAUGG	880
AD-1561116	gsasggg(Uhd)GfaAfCfCfcgaagaacsusa	611	VPusAfsguuCfuUfCfggguUfcAfcccucscsc	746	GGGAGGGUGAACCCGAAGAACUG	881
AD-1561122	gsasacc(Chd)GfaAfGfAfacugauggsusa	612	VPusAfsccaUfcAfGfuucuUfcGfgguucsasc	747	GUGAACCCGAAGAACUGAUGGUG	882
AD-1561130	asusggu(Ghd)GfaCfAfAfcuggcgcccsca	613	VPusGfsggcGfcCfAfguugUfcCfaccausesa	748	UGAUGGUGGACAACUGGCGCCCA	883
AD-1561146	cscsagc(Uhd)CfaGfCfCfacugaagagasa	614	VPusUfsucuUfcAfGfuggcUfgAfgcuggsgsc	749	GCCCAGCUCAGCCACUGAAGAAC	884
AD-1561152	csasgcc(Ahd)CfuGfAfAfgaacaggcsasa	615	VPusUfsgccUfgUfUfcuucAfgUfggcugsasg	750	CUCAGCCACUGAAGAACAGGCAA	885
AD-1561158	csusgaa(Ghd)AfaCfAfGfgcaaaucasasa	616	VPusUfsugaUfuUfGfccugUfuCfuucagsusg	751	CACUGAAGAACAGGCAAAUCAAA	886
AD-1446763	uscsacu(Ghd)GfaAfCfAfccaaauausgsa	617	VPusCfsauaUfuUfGfguguUfcCfagugasasc	752	GUUCACUGGAACACCAAAUAUGG	887
AD-1561168	gsgscaa(Ahd)UfcAfAfAfgcuuccuuscsa	618	VPusGfsaagGfaAfGfcuuuGfaUfuugccsusg	753	CAGGCAAAUCAAAGCUUCCUUCA	888
AD-1561175	csasaag(Chd)UfuCfCfUfucaaauaasgsa	619	VPusCfsuuaUfuUfGfaaggAfaGfcuuugsasu	754	AUCAAAGCUUCCUUCAAAUAAGA	889
AD-1561181	ususccu(Uhd)CfaAfAfUfaagauggcscsa	620	VPusGfsaccAfuCfUfuauuUfgAfaggaasgsc	755	GCUUCCUUCAAAUAAGAUGGUCC	890
AD-1561190	asusaag(Ahd)UfgGfUfCfccauagucsusa	621	VPusAfsgacUfaUfGfggacCfaUfcuuaususu	756	AAAUAAGAUGGUCCCAUAGUCUG	891
AD-1561196	usgsguc(Chd)CfaUfAfGfucuguaucscsa	622	VPusGfsgauAfcAfGfacuaUfgGfgaccasusc	757	GAUGGUCCCAUAGUCUGUAUCCA	892
AD-1561203	asusagu(Chd)UfgUfAfUfccaaauaasusa	623	VPusAfsuuaUfuUfGfgauaCfaGfacuausgsg	758	CCAUAGUCUGUAUCCAAAUAAUG	893
AD-1561210	gsusauc(Chd)AfaAfUfAfaugaaucususa	624	VPusAfsagaUfuCfAfuuauUfuGfgauacsasg	759	CUGUAUCCAAAUAAUGAAUCUUC	894
AD-1561218	asusaau(Ghd)AfaUfCfUfucgggugususa	625	VPusAfsacaCfcCfGfaagaUfuCfauuaususu	760	AAAUAAUGAAUCUUCGGGUGUUU	895
AD-1561225	asuscuu(Chd)GfgGfUfGfuuucccuususa	626	VPusAfsaagGfgAfAfacacCfcGfaagaususc	761	GAAUCUUCGGGUGUUUCCCUUUA	896
AD-1561231	gsgsgug(Uhd)UfuCfCfCfuuuagcuasasa	627	VPusUfsuagCfuAfAfagggAfaAfcaccesgsa	762	UCGGGUGUUUCCCUUUAGCUAAG	897
AD-1561239	csescuu(Uhd)AfgCfUfAfagcacagasusa	628	VPusAfsucuGfuGfCfuuagCfuAfaagggsasa	763	UUCCCUUUAGCUAAGCACAGAUC	898

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1561245	asgscua(Ahd)GfcAfCfAfgaucuaccsusa	629	VPusAfsgguAfgAfUfcuguGfcUfuagcusasa	764	UUAGCUAAGCACAGAUCUACCUU	899
AD-1561254	csasgau(Chd)UfaCfCfUfuggugauususa	630	VPusAfsaauCfaCfCfaaggUfaGfaucugsusg	765	CACAGAUCUACCUUGGUGAUUUG	900
AD-1561261	ascscuu(Ghd)GfuGfAfUfuuggacccsusa	631	VPusAfsgggUfcCfAfaaucAfcCfaaggusasg	766	CUACCUUGGUGAUUUGGACCCUG	901
AD-1561272	ususgga(Chd)CfcUfGfGfuugcuuugsusa	632	VPusAfscaaAfgCfAfaccaGfgGfuccaasasu	767	AUUUGGACCCUGGUUGCUUUGUG	902
AD-1561279	csusggu(Uhd)GfcUfUfUfgugucuagsusa	633	VPusAfscuaGfaCfAfcaaaGfcAfaccagsgsg	768	CCCUGGUUGCUUUGUGUCUAGUU	903
AD-1561285	gscsuuu(Ghd)UfgUfCfUfaguuuucusasa	634	VPusUfsagaAfaAfCfuagaCfaCfaaagcsasa	769	UUGCUUUGUGUCUAGUUUUCUAG	904
AD-1561294	csusagu(Uhd)UfuCfUfAfgacccuucsasa	635	VPusUfsgaaGfgGfUfcuagAfaAfacuagsasc	770	GUCUAGUUUUCUAGACCCUUCAU	905
AD-1561300	ususcua(Ghd)AfcCfCfUfucaucucususa	636	VPusAfsagaGfaUfGfaaggGfuCfuagaasasa	771	UUUUCUAGACCCUUCAUCUCUUA	906
AD-1561306	ascsccu(Uhd)CfaUfCfUfcuuacuugsasa	637	VPusUfscaaGfuAfAfgagaUfgAfagggcscsu	772	AGACCCUUCAUCUCUUACUUGAU	907
AD-1561313	asuscuc(Uhd)UfaCfUfUfgauagacususa	638	VPusAfsaguCfuAfUfcaagUfaAfgagausgsa	773	UCAUCUCUUACUUGAUAGACUUA	908
AD-1561319	usascuu(Ghd)AfuAfGfAfcuuacuaasusa	639	VPusAfsuuaGfuAfAfgucuAfuCfaaguasasg	774	CUUACUUGAUAGACUUACUAAUA	909
AD-1561327	csusuac(Uhd)AfaUfAfAfaaugugaasgsa	640	VPusCfsuucAfcAfUfuuuaUfuAfguaagsusc	775	GACUUACUAAUAAAAUGUGAAGA	910
AD-1561336	asasaau(Ghd)UfgAfAfGfacuagaccsasa	641	VPusUfsgguCfuAfGfucuuCfaCfauuuusasu	776	AUAAAAUGUGAAGACUAGACCAA	911
AD-1561342	usgsaag(Ahd)CfuAfGfAfccaauugucsa	642	VPusGfsacaAfuUfGfgucuAfgUfcuucascsa	777	UGUGAAGACUAGACCAAUUGUCA	912
AD-1561349	usasgac(Chd)AfaUfUfGfucaugcuusgsa	643	VPusCfsaagCfaUfGfacaaUfuGfgucuasgsu	778	ACUAGACCAAUUGUCAUGCUUGA	913
AD-1561360	uscsaug(Chd)UfuGfAfCfacaacugcsusa	644	VPusAfsgcaGfuUfGfugucAfaGfcaugascsa	779	UGUCAUGCUUGACACAACUGCUG	914
AD-1561366	ususgac(Ahd)CfaAfCfUfgcuguggcsusa	645	VPusAfsgccAfcAfGfcaguUfgUfgucaasgsc	780	GCUUGACACAACUGCUGUGGCUG	915
AD-1561378	csusgug(Ghd)CfuGfGfUfuggugcuususa	646	VPusAfsaagCfaCfCfaaccAfgCfcacagscsa	781	UGCUGUGGCUGGUUGGUGCUUUG	916
AD-1561384	csusggu(Uhd)GfgUfGfCfuuuguuuasusa	647	VPusAfsuaaAfcAfAfagcaCfcAfaccagscsc	782	GGCUGGUUGGUGCUUUGUUUAUG	917
AD-1561390	gsgsugc(Uhd)UfuGfUfUfuaugguagsusa	648	VPusAfscuaCfcAfUfaaacAfaAfgcaccsasa	783	UUGGUGCUUUGUUUAUGGUAGUA	918
AD-1561396	ususguu(Uhd)AfuGfGfUfaguaguuususa	649	VPusAfsaaaCfuAfCfuaccAfuAfaacaasasg	784	CUUUGUUUAUGGUAGUAGUUUUU	919
AD-1561402	usgsgua(Ghd)UfaGfUfUfuuucuguasasa	650	VPusUfsuacAfgAfAfaaacUfaCfuaccasusa	785	UAUGGUAGUAGUUUUUCUGUAAC	920
AD-1561408	usasguu(Uhd)UfuCfUfGfuaacacagsasa	651	VPusUfscugUfgUfUfacagAfaAfaacuascsu	786	AGUAGUUUUUCUGUAACACAGAA	921

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1561414	ususcug(Uhd)AfaCfAfCfagaauauasgsa	652	VPusCfsuauAfuUfCfugugUfuAfcagaasasa	787	UUUUCUGUAACACAGAAUAUAGG	922
AD-1561422	csascag(Ahd)AfuAfUfAfggauaagasasa	653	VPusUfsucuUfaUfCfcuauAfuUfcugugsusu	788	AACACAGAAUAUAGGAUAAGAAA	923
AD-1561433	asgsaau(Ahd)AfaGfUfAfccuugacususa	654	VPusAfsaguCfaAfGfguacUfuUfauucususa	789	UAAGAAUAAAGUACCUUGACUUU	924
AD-1561444	csusuga(Chd)UfuUfGfUfucacagcasusa	655	VPusAfsugcUfgUfGfaacaAfaGfucaagsgsu	790	ACCUUGACUUUGUUCACAGCAUG	925
AD-1561450	ususugu(Uhd)CfaCfAfGfcauguaggsgsa	656	VPusCfsccuAfcAfUfgcugUfgAfacaaasgsu	791	ACUUUGUUCACAGCAUGUAGGGU	926
AD-1561456	csascag(Chd)AfuGfUfAfgggugaugsasa	657	VPusUfscauCfaCfCfcuacAfuGfcugugsasa	792	UUCACAGCAUGUAGGGUGAUGAG	927
AD-1561465	usasggg(Uhd)GfaUfGfAfgcacucacsasa	658	VPusUfsgugAfgUfGfcucaUfcAfcccuascsa	793	UGUAGGGUGAUGAGCACUCACAA	928
AD-1561471	gsasuga(Ghd)CfaCfUfCfacaauugususa	659	VPusAfsacaAfuUfGfugagUfgCfucaucsasc	794	GUGAUGAGCACUCACAAUUGUUG	929
AD-1561478	ascsuca(Chd)AfaUfUfGfuugacuaasasa	660	VPusUfsuuaGfuCfAfacaaUfuGfugagusgsc	795	GCACUCACAAUUGUUGACUAAAA	930
AD-1561489	ususgac(Uhd)AfaAfAfUfgcugcuuususa	661	VPusAfsaaaGfcAfGfcauuUfuAfgucaasasa	796	UGUUGACUAAAAUGCUGCUUUUA	931
AD-1561498	asusgcu(Ghd)CfuUfUfUfaaaacauasgsa	662	VPusCfsuauGfuUfUfuaaaAfgCfagcaususu	797	AAAUGCUGCUUUUAAAACAUAGG	932
AD-1561504	csususuu(Ahd)AfaAfCfAfuaggaaagsusa	663	VPusAfscuuUfcCfUfauguUfuUfaaaagscsa	798	UGCUUUUAAAACAUAGGAAAGUA	933
AD-1561513	csasuag(Ghd)AfaAfGfUfagaauggususa	664	VPusAfsaccAfuUfCfuacuUfuCfcuaugsusu	799	AACAUAGGAAAGUAGAAUGGUUG	934
AD-1561521	asgsuag(Ahd)AfuGfGfUfugagugcasasa	665	VPusUfsugcAfcUfCfaaccAfuUfcuacususu	800	AAAGUAGAAUGGUUGAGUGCAAA	935
AD-1561527	asusggu(Uhd)GfaGfUfGfcaaauccasusa	666	VPusAfsuggAfuUfUfgcacUfcAfaccaususc	801	GAAUGGUUGAGUGCAAAUCCAUA	936
AD-1561534	asgsugc(Ahd)AfaUfCfCfauagcacasasa	667	VPusUfsuguGfcUfAfuggaUfuUfgcacuscsa	802	UGAGUGCAAAUCCAUAGCACAAG	937
AD-1561542	uscscau(Ahd)GfcAfCfAfagauaaaususa	668	VPusAfsauuUfaUfCfuguGfcUfauggasusu	803	AAUCCAUAGCACAAGAUAAAUUG	938
AD-1561551	csasaga(Uhd)AfaAfUfUfgagcuagususa	669	VPusAfsacuAfgCfUfcaauUfuAfucuugsusg	804	CACAAGAUAAAUUGAGCUAGUUA	939
AD-1561562	gsasgcu(Ahd)GfuUfAfAfggcaaaucsasa	670	VPusUfsgauUfuGfCfcuuaAfcUfagcucsasa	805	UUGAGCUAGUUAAGGCAAAUCAG	940
AD-1561570	usasagg(Chd)AfaAfUfCfagguaaaasusa	671	VPusAfsuuuUfaCfCfugauUfuGfccuuasasc	806	GUUAAGGCAAAUCAGGUAAAAUA	941
AD-1561581	asgsgua(Ahd)AfaUfAfGfucaugauuscsa	672	VPusGfsaauCfaUfGfacuaUfuUfuaccusgsa	807	UCAGGUAAAAUAGUCAUGAUUCU	942
AD-1561591	gsuscau(Ghd)AfuUfCfUfauguaaaugsusa	673	VPusAfscauUfaCfAfuagaAfuCfaugacsusa	808	UAGUCAUGAUUCUAUGUAAUGUA	943
AD-1561601	usasugu(Ahd)AfuGfUfAfaaccagaasasa	674	VPusUfsuucUfgGfUfuuacAfuUfacauasgsa	809	UCUAUGUAAUGUAAACCAGAAAA	944

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1561613	uscsaug(Ahd)UfuUfCfAfagauguuasusa	675	VPusAfsuaaCfaUfCfuugaAfaUfcaugasasc	810	GUUCAUGAUUUCAAGAUGUUAUA	945
AD-1561651	csusuuu(Ghd)AfaUfUfAfcagagauasusa	676	VPusAfsuauCfuCfUfguaaUfuCfaaaagsusc	811	GACUUUUGAAUUACAGAGAUAUA	946
AD-1561679	ususaga(Ghd)UfuGfUfGfauacagagsusa	677	VPusAfscucUfgUfAfucacAfaCfucuaasusu	812	AAUUAGAGUUGUGAUACAGAGUA	947
AD-1561686	usascag(Ahd)GfuAfUfAfuuuccauuscsa	678	VPusGfsaauGfgAfAfauauAfcUfcuguasusc	813	GAUACAGAGUAUAUUUCCAUUCA	948
AD-1561694	asusauu(Uhd)CfcAfUfUfcagacaausasa	679	VPusUfsauuGfuCfUfgaauGfgAfaauausasc	814	GUAUAUUUCCAUUCAGACAAUAU	949
AD-1561703	ususcag(Ahd)CfaAfUfAfuaucauaascsa	680	VPusGfsuuaUfgAfUfauauUfgUfcugaasusg	815	CAUUCAGACAAUAUAUCAUAACU	950
AD-1447598	ususgug(Ahd)UfaCfAfGfaguauauususa	681	VPusAfsaauAfuAfCfucugUfaUfcacaascsu	816	AGUUGUGAUACAGAGUAUAUUUC	951

Table 6. Modified Sense and Antisense Strand Sequences of CA2 dsRNA Agents with GalNAc Modification

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1559459	asgsaucgGfuGfCfCfgauuccugcuL96	952	asGfscagGfaAfUfcggcAfcCfgaucusgsg	1087	CCAGAUCGGUGCCGAUUCCUGCC	817
AD-1559476	csgscgacCfaUfGfUfcccaucacuuL96	953	asAfsgugAfuGfGfgacaUfgGfucgcgscsu	1088	AGCGCGACCAUGUCCCAUCACUG	818
AD-1559481	gsusacggCfaAfAfCfacaacggacuL96	954	asGfsuccGfuUfGfuguuUfgCfcguacscsc	1089	GGGUACGGCAAACACAACGGACC	819
AD-1559487	csasaacaCfaAfCfGfgaccugagcuL96	955	asGfscucAfgGfUfccguUfgUfguuugscsc	1090	GGCAAACACAACGGACCUGAGCA	820
AD-1559497	gsgsaccuGfaGfCfAfcuggcauaauL96	956	asUfsuauGfcCfAfgugcUfcAfgguccsgsu	1091	ACGGACCUGAGCACUGGCAUAAG	821
AD-1559503	gsasgcacUfgGfCfAfuaaggacuuuL96	957	asAfsaguCfcUfUfaugcCfaGfugcucsasg	1092	CUGAGCACUGGCAUAAGGACUUC	822
AD-1559514	gsusugacAfuCfGfAfcacucauacuL96	958	asGfsuauGfaGfUfgucgAfuGfucaacsasg	1093	CUGUUGACAUCGACACUCAUACA	823
AD-1559524	ascsacucAfuAfCfAfgccaaguauuL96	959	asAfsuacUfuGfGfcuguAfuGfaguguscsg	1094	CGACACUCAUACAGCCAAGUAUG	824
AD-1559531	usascagcCfaAfGfUfaugacccuuuL96	960	asAfsaggGfuCfAfuacuUfgGfcuguasusg	1095	CAUACAGCCAAGUAUGACCCUUC	825
AD-1559537	csasaguaUfgAfCfCfcuuccugauL96	961	asUfscagGfgAfAfggguCfaUfacuugsgsc	1096	GCCAAGUAUGACCCUUCCCUGAA	826
AD-1559543	usgsucugUfuUfCfCfcuaugaucaauL96	962	asUfsugaUfcAfUfaggaAfaCfagacasgsg	1097	CCUGUCUGUUUCCUAUGAUCAAG	827
AD-1559552	cscsuaugAfuCfAfAfgcaacuuccuL96	963	asGfsgaaGfuUfGfcuugAfuCfauaggsasa	1098	UUCCUAUGAUCAAGCAACUUCCC	828

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1559560	csasagcaAfcUfUfCfccugaggauuL96	964	asAfsuccUfcAfGfggaaGfuUfgcuugsasu	1099	AUCAAGCAACUUCCCUGAGGAUC	829
AD-1559570	cscscugaGfgAfUfCfcucaacaauuL96	965	asAfsuugUfuGfAfggauCfcUfcagggsasa	1100	UUCCCUGAGGAUCCUCAACAAUG	830
AD-1559579	uscscucaAfcAfAfUfggucaugcuuL96	966	asAfsgcaUfgAfCfcauuGfuUfgaggasusc	1101	GAUCCUCAACAAUGGUCAUGCUU	831
AD-1559585	ascsaaugGfuCfAfUfgcuuucaacuL96	967	asGfsuugAfaAfGfcaugAfcCfauugususg	1102	CAACAAUGGUCAUGCUUUCAACG	832
AD-1559594	asusgcuuUfcAfAfCfguggaguuuuL96	968	asAfsaacUfcCfAfcguuGfaAfagcausgsa	1103	UCAUGCUUUCAACGUGGAGUUUG	833
AD-1559602	asascgugGfaGfUfUfugaugacucuL96	969	asGfsaguCfaUfCfaaacUfcCfacguusgsa	1104	UCAACGUGGAGUUUGAUGACUCU	834
AD-1559613	usgsaugaCfuCfUfCfaggacaaaguL96	970	asCfsuuuGfuCfCfugagAfgUfcaucasasa	1105	UUUGAUGACUCUCAGGACAAAGC	835
AD-1559620	uscsucagGfaCfAfAfagcagugcuuL96	971	asAfsgcaCfuGfCfuuugUfcCfugagasgsu	1106	ACUCUCAGGACAAAGCAGUGCUC	836
AD-1559626	gsascaaaGfcAfGfUfgcucaaggguL96	972	asCfsccuUfgAfGfcacuGfcUfuugucscsu	1107	AGGACAAAGCAGUGCUCAAGGGA	837
AD-1559638	usgsgcacUfuAfCfAfgauugauucuL96	973	asGfsaauCfaAfUfcuguAfaGfugccasusc	1108	GAUGGCACUUACAGAUUGAUUCA	838
AD-1559644	ususacagAfuUfGfAfuucaguuucuL96	974	asGfsaaaCfuGfAfaucaAfuCfuguaasgsu	1109	ACUUACAGAUUGAUUCAGUUUCA	839
AD-1559654	asusucagUfuUfCfAfcuuucacuguL96	975	asCfsaguGfaAfAfgugaAfaCfugaauscsa	1110	UGAUUCAGUUUCACUUUCACUGG	840
AD-1559660	uscsacuuGfaUfGfGfgfacaagguucuL96	976	asGfsaacCfuUfGfuccaUfcAfagugasasc	1111	GUUCACUUGAUGGACAAGGUUCA	841
AD-1559666	gsasuggaCfaAfGfGfGfuucagagcauL96	977	asUfsgcuCfuGfAfaccuUfgUfccaucsasa	1112	UUGAUGGACAAGGUUCAGAGCAU	842
AD-1559672	csasagguUfcAfGfAfAfgcauacuguuL96	978	asAfscagUfaUfGfcucuGfaAfccuugsusc	1113	GACAAGGUUCAGAGCAUACUGUG	843
AD-1559678	uscsagagCfaUfAfCfCfuguggauaauL96	979	asUfsuauCfcAfCfaguaUfgCfucugasasc	1114	GUUCAGAGCAUACUGUGGAUAAA	844
AD-1559699	asasgaaaUfaUfGfCfCfugcagaacuuL96	980	asAfsguuCfuGfCfagcaUfaUfuucuususu	1115	AAAAGAAAUAUGCUGCAGAACUU	845
AD-1559705	usasugcuGfcAfGfAfAfacuucacuuuL96	981	asAfsaguGfaAfGfuucuGfcAfgcauasusu	1116	AAUAUGCUGCAGAACUUCACUUG	846
AD-1559711	gscsagaaCfuUfCfAffcuugguucauL96	982	asUfsgaaCfcAfAfgugaAfgUfucugcsasg	1117	CUGCAGAACUUCACUUGGUUCAC	847
AD-1559717	csusucacUfuGfGfUfUfucacuggaauL96	983	asUfsuccAfgUfGfaaccAfaGfugaagsusu	1118	AACUUCACUUGGUUCACUGGAAC	848
AD-1559728	uscsacugGfaAfCfAfAfccaaauauguL96	984	asCfsauaUfuUfGfgugaUfcCfagugasasc	1119	GUUCACUGGAACACCAAAUAUGG	849
AD-1559735	ususugggAfaAfGfCfCfugugcagcauL96	985	asUfsgcuGfcAfCfagcaUfuCfccaaasasu	1120	AUUUUGGGAAAGCUGUGCAGCAA	850
AD-1559747	gsusgcagCfaAfCfCfCfugauggacuuL96	986	asAfsgucCfaUfCfaggaUfgCfugcacsasg	1121	CUGUGCAGCAACCUGAUGGACUG	851

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1559753	csasaccuGfaUfGfG facuggccguuL96	987	asAfscggCfcAfGfucca UfcAfgguugscsu	1122	AGCAACCUGAUG GACUGGCCGUU	852
AD-1559765	csusggccGfuUfCfU fagguauuuuuL96	988	asAfsaaaUfaCfCfuaga AfcGfgccagsusc	1123	GACUGGCCGUUC UAGGUAUUUUU	853
AD-1559768	usgsaaggUfuGfGf Cfagcgcuaaaul96	989	asUfsuuaGfcGfCfugcc AfaCfcuucasasa	1124	UUUGAAGGUUGG CAGCGCUAAAC	854
AD-1559777	gscsagcgCfuAfAfA fccgggccuuuL96	990	asAfsaggCfcCfGfguuu AfgCfgcugcscsa	1125	UGGCAGCGCUAA ACCGGGCCUUC	855
AD-1559788	cscsggggCfuUfCfA fgaaaguuguuL96	991	asAfscaaCfuUfUfcuga AfgGfcccggsusu	1126	AACCGGGCCUUC AGAAAGUUGUU	856
AD-1559794	csusucagAfaAfGfU fuguugauguuL96	992	asAfscauCfaAfCfaacu UfuCfugaagsgsc	1127	GCCUUCAGAAAG UUGUUGAUGUG	857
AD-1559803	gsusuguuGfaUfGf Ufgcuggauucul96	993	asGfsaauCfcAfGfcaca UfcAfacaacsusu	1128	AAGUUGUUGAUG UGCUGGAUUCC	858
AD-1559814	gscsuggaUfuCfCfA fuuaaaacaauL96	994	asUfsuguUfuUfAfaugg AfaUfccagcsasc	1129	GUGCUGGAUUCC AUUAAAACAAA	859
AD-1559821	uscscauuAfaAfAfC faaagggcaauL96	995	asUfsugcCfcUfUfuguu UfuAfauggasasu	1130	AUUCCAUUAAAA CAAAGGGCAAG	860
AD-1559827	asasaacaAfaGfGfG fcaagagugcuL96	996	asGfscacUfcUfUfgccc UfuUfguuuusasa	1131	UUAAAACAAAGG GCAAGAGUGCU	861
AD-1559836	gsgscaagAfgUfGfC fugacuucacuL96	997	asGfsugaAfgUfCfagca CfuCfuugccscsu	1132	AGGGCAAGAGUG CUGACUUCACU	862
AD-1559843	gsusgcugAfcUfUf Cfacuaacuucul96	998	asGfsaagUfuAfGfugaa GfuCfagcacsusc	1133	GAGUGCUGACUU CACUAACUUCG	863
AD-1559849	ascsuucaCfuAfAfC fuucgauccuuL96	999	asAfsggaUfcGfAfaguu AfgUfgaagusesa	1134	UGACUUCACUAA CUUCGAUCCUC	864
AD-1559862	csgsauccUfcGfUfG fgccuccuucuL96	1000	asGfsaagGfaGfGfccac GfaGfgaucgsasa	1135	UUCGAUCCUCGU GGCCUCCUUCC	865
AD-1559868	uscsguggCfcUfCfC fuuccugaauuL96	1001	asAfsuucAfgGfAfagga GfgCfcacgasgsg	1136	CCUCGUGGCCUC CUUCCUGAAUC	866
AD-1559874	cscsuccuUfcCfUfG faauccuugguL96	1002	asCfscaaGfgAfUfucag GfaAfggaggcsesc	1137	GGCCUCCUUCCU GAAUCCUUGGA	867
AD-1559881	cscsugaaUfcCfUfU fggauuacuguL96	1003	asCfsaguAfaUfCfcaag GfaUfucaggsasa	1138	UUCCUGAAUCCU UGGAUUACUGG	868
AD-1559887	uscscuugGfaUfUf Afcuggaccuaul96	1004	asUfsaggUfcCfAfguaa UfcCfaaggasusu	1139	AAUCCUUGGAUU ACUGGACCUAC	869
AD-1559903	cscsuaccCfaGfGfC fucacugaccuL96	1005	asGfsgucAfgUfGfagcc UfgGfguaggsusc	1140	GACCUACCCAGG CUCACUGACCA	870
AD-1559909	cscsucuuCfuGfGfA faugugugacuL96	1006	asGfsucaCfaCfAfuucc AfgAfagaggsasg	1141	CUCCUCUUCUGG AAUGUGUGACC	871
AD-1559916	usgsgaauGfuGfUf Gfaccuggauuul96	1007	asAfsaucCfaGfGfucac AfcAfuuccasgsa	1142	UCUGGAAUGUGU GACCUGGAUUG	872
AD-1559923	usgsugacCfuGfGf Afuugugcucaul96	1008	asUfsgagCfaCfAfaucc AfgGfucacascsa	1143	UGUGUGACCUGG AUUGUGCUCAA	873
AD-1559929	csusggauUfgUfGf Cfucaaggaacul96	1009	asGfsuucCfuUfGfagca CfaAfuccagsgsu	1144	ACCUGGAUUGUG CUCAAGGAACC	874

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1559939	csuscaagGfaAfCfCfcaucagcguuL96	1010	asAfscgcUfgAfUfgggcUfcCfuugagscsa	1145	UGCUCAAGGAACCCAUCAGCGUC	875
AD-1559945	gsasacccAfuCfAfGfcgucagcaguL96	1011	asCfsugcUfgAfCfgcugAfuGfgguucscsu	1146	AGGAACCCAUCAGCGUCAGCAGC	876
AD-1559965	csgsagcaGfgUfGfUfugaaauuccuL96	1012	asGfsgaaUfuUfCfaacaCfcUfgcucgscsu	1147	AGCGAGCAGGUGUUGAAAUUCCG	877
AD-1559971	gsgsuguuGfaAfAfUfuccguaaacuL96	1013	asGfsuuuAfcGfGfaauuUfcAfacaccsusg	1148	CAGGUGUUGAAAUUCCGUAAACU	878
AD-1559977	gsasaauuCfcGfUfAfaacuuaacuuL96	1014	asAfsguuAfaGfUfuuacGfgAfauuucsasa	1149	UUGAAAUUCCGUAAACUUAACUU	879
AD-1559983	cscsguaaAfcUfUfAfacuucaauguL96	1015	asCfsauuGfaAfGfuuaaGfuUfuacggsasa	1150	UUCCGUAAACUUAACUUCAAUGG	880
AD-1559987	gsasggguGfaAfCfCfcgaagaacuuL96	1016	asAfsguuCfuUfCfgggcUfcAfcccucscsc	1151	GGGAGGGUGAACCCGAAGAACUG	881
AD-1559993	gsasacccGfaAfGfAfacugaugguuL96	1017	asAfsccaUfcAfGfuucuUfcGfgguucsasc	1152	GUGAACCCGAAGAACUGAUGGUG	882
AD-1560001	asgsaacuGfaUfGfGfuggacaacuuL96	1018	asAfsguuGfuCfCfaccaUfcAfguucususc	1153	GAAGAACUGAUGGUGGACAACUG	883
AD-1560008	asusggugGfaCfAfAfcuggcgcccuL96	1019	asGfsggcGfcCfAfguugUfcCfaccauscsa	1154	UGAUGGUGGACAACUGGCGCCCA	884
AD-1560024	cscsagcuCfaGfCfCfcfacugaagaauL96	1020	asUfsucuUfcAfGfuggcUfgAfgcuggsgsc	1155	GCCCAGCUCAGCCACUGAAGAAC	885
AD-1560030	csasgccaCfuGfAfAfafgaacaggcauL96	1021	asUfsgccUfgUfUfcuucAfgUfggcugsasg	1156	CUCAGCCACUGAAGAACAGGCAA	886
AD-1560036	csusgaagAfaCfAfGfgcaaaucaauL96	1022	asUfsugaUfuUfGfccugUfuCfuucagsusg	1157	CACUGAAGAACAGGCAAAUCAAA	887
AD-1560046	gsgscaaaUfcAfAfAfafgcuuccuucuL96	1023	asGfsaagGfaAfGfcuuuGfaUfuugccsusg	1158	CAGGCAAAUCAAAGCUUCCUUCA	888
AD-1560053	csasaagcUfuCfCfUfufucaaauaaguL96	1024	asCfsuuaUfuUfGfaaggAfaGfcuuugsasu	1159	AUCAAAGCUUCCUUCAAAUAAGA	889
AD-1560059	ususccuuCfaAfAfUfufaagauggucuL96	1025	asGfsaccAfuCfUfuauuUfgAfaggaasgsc	1160	GCUUCCUUCAAAUAAGAUGGUCC	890
AD-1560068	asusaagaUfgGfUfCfcfccauagucuuL96	1026	asAfsgacUfaUfGfggacCfaUfcuuaususu	1161	AAAUAAGAUGGUCCCAUAGUCUG	891
AD-1560074	usgsgucccCfaUfAfGfufucuguauccuL96	1027	asGfsgauAfcAfGfacuaUfgGfgaccasusc	1162	GAUGGUCCCAUAGUCUGUAUCCA	892
AD-1560081	asusagucUfgUfAfUfcfccaaauaauuL96	1028	asAfsuuaUfuUfGfgauaCfaGfacuausgsg	1163	CCAUAGUCUGUAUCCAAAUAAUG	893
AD-1560088	gsusauccAfaAfUfAfafaugaaucuuuL96	1029	asAfsagaUfuCfAfuuauUfuGfgauacsasg	1164	CUGUAUCCAAAUAAUGAAUCUUC	894
AD-1560096	asusaaugAfaUfCfUfufucggguguuuL96	1030	asAfsacaCfcCfGfaagaUfuCfauuaususu	1165	AAAUAAUGAAUCUUCGGGUGUUU	895
AD-1560103	asuscuucGfgGfUfGfufuuuccuuuuL96	1031	asAfsaagGfgAfAfcacaCfcGfaagaususc	1166	GAAUCUUCGGGUGUUUCCCUUUA	896
AD-1560109	gsgsguguUfuCfCfCfcfuuuagcuaauL96	1032	asUfsuagCfuAfAfagggAfaAfcacccsgsa	1167	UCGGGUGUUUCCCUUUAGCUAAG	897

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1560117	cscscuuuAfgCfUfAfagcacagauuL96	1033	asAfsucuGfuGfCfuuagCfuAfaagggsasa	1168	UUCCCUUUAGCUAAGCACAGAUC	898
AD-1560123	asgscuaaGfcAfCfAfgaucuaccuuL96	1034	asAfsgguAfgAfUfcuguGfcUfuagcusasa	1169	UUAGCUAAGCACAGAUCUACCUU	899
AD-1560132	csasgaucUfaCfCfUfuggugauuuuL96	1035	asAfsaauCfaCfCfaaggUfaGfaucugsusg	1170	CACAGAUCUACCUUGGUGAUUUG	900
AD-1560139	ascscuugGfuGfAfUfuuggacccuuL96	1036	asAfsgggUfcCfAfaaucAfcCfaaggusasg	1171	CUACCUUGGUGAUUUGGACCCUG	901
AD-1560150	ususggacCfcUfGfGfuugcuuuguuL96	1037	asAfscaaAfgCfAfaccaGfgGfuccaasasu	1172	AUUUGGACCCUGGUUGCUUUGUG	902
AD-1560157	csusgguuGfcUfUfUfgugucuaguuL96	1038	asAfscuaGfaCfAfcaaaGfcAfaccagsgsg	1173	CCCUGGUUGCUUUGUGUCUAGUU	903
AD-1560163	gscsuuugUfgUfCfUfaguuuucuauL96	1039	asUfsagaAfaAfCfuagaCfaCfaaagcsasa	1174	UUGCUUUGUGUCUAGUUUUCUAG	904
AD-1560172	csusaguuUfuCfUfAfgacccuucauL96	1040	asUfsgaaGfgGfUfcuagAfaAfacuagsasc	1175	GUCUAGUUUUCUAGACCCUUCAU	905
AD-1560178	ususcuagAfcCfCfUfucaucucuuuL96	1041	asAfsagaGfaUfGfaaggGfuCfuagaasasa	1176	UUUUCUAGACCCUUCAUCUCUUA	906
AD-1560184	ascsccuuCfaUfCfUfucuuacuugauL96	1042	asUfscaaGfuAfAfgagaUfgAfaggguscsu	1177	AGACCCUUCAUCUCUUACUUGAU	907
AD-1560191	asuscucuUfaCfUfUfUfgauagacuuuL96	1043	asAfsaguCfuAfUfcaagUfaAfgagausgsa	1178	UCAUCUCUUACUUGAUAGACUUA	908
AD-1560197	usascuugAfuAfGfAfcuuacuaauuL96	1044	asAfsuuaGfuAfAfgucuAfuCfaaguasasg	1179	CUUACUUGAUAGACUUACUAAUA	909
AD-1560205	csusuacuAfaUfAfAfAfaaugugaaguL96	1045	asCfsuucAfcAfUfuuuaUfuAfguaagsusc	1180	GACUUACUAAUAAAAUGUGAAGA	910
AD-1560214	asasaaugUfgAfAfGffacuagaccauL96	1046	asUfsgguCfuAfGfucuuCfaCfauuuusasu	1181	AUAAAAUGUGAAGACUAGACCAA	911
AD-1560220	usgsaagaCfuAfGfAffccaauugucuL96	1047	asGfsacaAfuUfGfgucuAfgUfcuucascsa	1182	UGUGAAGACUAGACCAAUUGUCA	912
AD-1560227	usasgaccAfaUfUfUfGfucaugcuuguL96	1048	asCfsaagCfaUfGfacaaUfuGfgucuasgsu	1183	ACUAGACCAAUUGUCAUGCUUGA	913
AD-1560238	uscsaugcUfuGfAfAfCfacaacugcuuL96	1049	asAfsgcaGfuUfGfugucAfaGfcaugascsa	1184	UGUCAUGCUUGACACAACUGCUG	914
AD-1560244	ususgacaCfaAfCfUfUfgcuguggcuuL96	1050	asAfsgccAfcAfGfcaguUfgUfgucaasgsc	1185	GCUUGACACAACUGCUGUGGCUG	915
AD-1560256	csusguggCfuGfGfUfuggugcuuuuL96	1051	asAfsaagCfaCfCfaaccAfgCfcacagscsa	1186	UGCUGUGGCUGGUUGGUGCUUUG	916
AD-1560262	csusgguuGfgUfGfCfuuuguuuauuL96	1052	asAfsuaaAfcAfAfagcaCfcAfaccagscsc	1187	GGCUGGUUGGUGCUUUGUUUAUG	917
AD-1560268	gsgsugcuUfuGfUfUfUfuaugguaguuL96	1053	asAfscuaCfcAfUfaaacAfaAfgcaccsasa	1188	UUGGUGCUUUGUUUAUGGUAGUA	918
AD-1560274	ususguuuAfuGfGfUfUfaguaguuuuuL96	1054	asAfsaaaCfuAfCfuaccAfuAfaacaasasg	1189	CUUUGUUUAUGGUAGUAGUUUUU	919
AD-1560280	usgsguagUfaGfUfUfUfuuucuguaauL96	1055	asUfsuacAfgAfAfaaacUfaCfuaccasusa	1190	UAUGGUAGUAGUUUUUCUGUAAC	920

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1560286	usasguuuUfuCfUfGfuaacacagauL96	1056	asUfscugUfgUfUfacagAfaAfaacuascsu	1191	AGUAGUUUUUCUGUAACACAGAA	921
AD-1560292	ususcuguAfaCfAfCfagaauauaguL96	1057	asCfsuauAfuUfCfugugUfuAfcagaasasa	1192	UUUUCUGUAACACAGAAUAUAGG	922
AD-1560300	csascagaAfuAfUfAfggauaagaauL96	1058	asUfsucuUfaUfCfcuauAfuUfcugugsusu	1193	AACACAGAAUAUAGGAUAAGAAA	923
AD-1560311	asgsaauaAfaGfUfAfccuugacuuuL96	1059	asAfsaguCfaAfGfguacUfuUfauucususa	1194	UAAGAAUAAAGUACCUUGACUUU	924
AD-1560323	csusugacUfuUfGfUfucacagcauuL96	1060	asAfsugcUfgUfGfaacaAfaGfucaagsgsu	1195	ACCUUGACUUUGUUCACAGCAUG	925
AD-1560329	ususuguuCfaCfAfGfcauguaggguL96	1061	asCfsccuAfcAfUfgcugUfgAfacaaasgsu	1196	ACUUUGUUCACAGCAUGUAGGGU	926
AD-1560335	csascagcAfuGfUfAfgggugaugauL96	1062	asUfscauCfaCfCfcuacAfuGfcugugsasa	1197	UUCACAGCAUGUAGGGUGAUGAG	927
AD-1560344	usasggguGfaUfGfAfgcacucacauL96	1063	asUfsgugAfgUfGfcucaUfcAfcccuascsa	1198	UGUAGGGUGAUGAGCACUCACAA	928
AD-1560350	gsasugagCfaCfUfCfacaauuguuuL96	1064	asAfsacaAfuUfGfugagUfgCfucaucsasc	1199	GUGAUGAGCACUCACAAUUGUUG	929
AD-1560357	ascsucacAfaUfUfGfuugacuaaauL96	1065	asUfsuuaGfuCfAfacaaUfuGfugagusgsc	1200	GCACUCACAAUUGUUGACUAAAA	930
AD-1560368	ususgacuAfaAfAfUfgcugcuuuuuL96	1066	asAfsaaaGfcAfGfcauuUfuAfgucaascsa	1201	UGUUGACUAAAAUGCUGCUUUUA	931
AD-1560377	asusgcugCfuUfUfUfuaaacauaguL96	1067	asCfsuauGfuUfUfuaaaAfgCfagcaususu	1202	AAAUGCUGCUUUUAAAACAUAGG	932
AD-1560383	csusuuuaAfaAfCfAfuaggaaaguuL96	1068	asAfscuuUfcCfUfauguUfuUfaaaagscsa	1203	UGCUUUUAAAACAUAGGAAAGUA	933
AD-1560392	csasuaggAfaAfGfUffagaaugguuuL96	1069	asAfsaccAfuUfCfuacuUfuCfcuaugsusu	1204	AACAUAGGAAAGUAGAAUGGUUG	934
AD-1560400	asgsuagaAfuGfGfUfufugagugcaauL96	1070	asUfsugcAfcUfCfaaccAfuUfcuacususu	1205	AAAGUAGAAUGGUUGAGUGCAAA	935
AD-1560406	asusgguuGfaGfUfGfcaaauccauuL96	1071	asAfsuggAfuUfUfgcacUfcAfaccaususc	1206	GAAUGGUUGAGUGCAAAUCCAUA	936
AD-1560413	asgsugcaAfaUfCfCfauagcacaauL96	1072	asUfsuguGfcUfAfuggaUfuUfgcacuscsa	1207	UGAGUGCAAAUCCAUAGCACAAG	937
AD-1560421	uscscauaGfcAfCfAfagauaaauuuL96	1073	asAfsauuUfaUfCfuuguGfcUfauggasusu	1208	AAUCCAUAGCACAAGAUAAAUUG	938
AD-1560430	csasagauAfaAfUfUfgagcuaguuuL96	1074	asAfsacuAfgCfUfcaauUfuAfucuugsusg	1209	CACAAGAUAAAUUGAGCUAGUUA	939
AD-1560441	gsasgcuaGfuUfAfAfAfggcaaaucauL96	1075	asUfsgauUfuGfCfcuuaAfcUfagcucsasa	1210	UUGAGCUAGUUAAGGCAAAUCAG	940
AD-1560449	usasaggcAfaAfUfCffagguaaaauuL96	1076	asAfsuuuUfaCfCfugauUfuGfccuuasasc	1211	GUUAAGGCAAAUCAGGUAAAAUA	941
AD-1560460	asgsguaaAfaUfAfGffucaugauucuL96	1077	asGfsaauCfaUfGfacuaUfuUfuaccusgsa	1212	UCAGGUAAAAUAGUCAUGAUUCU	942
AD-1560470	gsuscaugAfuUfCfUfufauguaauguuL96	1078	asAfscauUfaCfAfuagaAfuCfaugacsusa	1213	UAGUCAUGAUUCUAUGUAAUGUA	943

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1560480	usasuguaAfuGfUfAfaaccagaaauL96	1079	asUfsuucUfgGfUfuuacAfuUfacauasgsa	1214	UCUAUGUAAUGUAAACCAGAAAA	944
AD-1560492	uscsaugaUfuUfCfAfagauguuauuL96	1080	asAfsuaaCfaUfCfuugaAfaUfcaugasasc	1215	GUUCAUGAUUUCAAGAUGUUAUA	945
AD-1560528	csusuuugAfaUfUfAfcagagauauuL96	1081	asAfsuauCfuCfUfguaaUfuCfaaaagsusc	1216	GACUUUUGAAUUACAGAGAUAUA	946
AD-1560556	ususagagUfuGfUfGfauacagaguuL96	1082	asAfscucUfgUfAfucacAfaCfucuaasusu	1217	AAUUAGAGUUGUGAUACAGAGUA	947
AD-1560562	ususgugaUfaCfAfGfaguauauuuuL96	1083	asAfsaauAfuAfCfucugUfaUfcacaasesu	1218	AGUUGUGAUACAGAGUAUAUUUC	948
AD-1560568	usascagaGfuAfUfAfuuuccauucuL96	1084	asGfsaauGfgAfAfauauAfcUfcuguasusc	1219	GAUACAGAGUAUAUUUCCAUUCA	949
AD-1560576	asusauuuCfcAfUfUfcagacaauauL96	1085	asUfsauuGfuCfUfgaauGfgAfaauausasc	1220	GUAUAUUUCCAUUCAGACAAUAU	950
AD-1560585	ususcagaCfaAfUfAfuaucauaacuL96	1086	asGfsuuaUfgAfUfauauUfgUfcugaasusg	1221	CAUUCAGACAAUAUAUCAUAACU	951

Table 7. Unmodified Sense and Antisense Strand Sequences of CA2 dsRNA Agents

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000067.3
AD-1784188.1	UGUUUCCUAUGAUCAAGCAAA	1222	219-239	UUUGCUTGAUCAUAGGAAACAGA	1533	217-239
AD-1784189.1	UGACUUCACUAACUUCGAUCA	1223	594-614	UGAUCGAAGUUAGUGAAGUCAGC	1534	592-614
AD-1784190.1	CAAAGCUUCCUUCAAAUAAGA	1224	840-860	UCUUAUUUGAAGGAAGCUUUGAU	1535	838-860
AD-1784191.1	UCAAAGCUUCCUUCAAAUAAA	1225	839-859	UUUATUTGAAGGAAGCUUUGAUU	1536	837-859
AD-1784192.1	GUCUGUAUCCAAAUAAUGAAA	1226	871-891	UUUCAUUAUUUGGAUACAGACUA	1537	869-891
AD-1784193.1	GUCUGUAUCCAAAUAAUGAAA	1226	871-891	UUUCAUTAUUUGGAUACAGACUA	1538	869-891
AD-1784194.1	AUUCCGUAAACUUAACUUCAA	1227	747-767	UUGAAGTUAAGUUUACGGAAUUU	1539	745-767
AD-1784195.1	UCCUAUGAUCAAGCAACUUCA	1228	223-243	UGAAGUTGCUUGAUCAUAGGAAA	1540	221-243
AD-1784196.1	GUUUCCUAUGAUCAAGCAACA	1229	220-240	UGUUGCTUGAUCAUAGGAAACAG	1541	218-240
AD-1784197.1	AUGCUGCUUUUAAAACAUAGA	1230	1180-1200	UCUATGTUUUAAAAGCAGCAUUU	1542	1178-1200
AD-1784198.1	CAUUCAGACAAUAUAUCAUAA	1231	1490-1510	UUAUGATAUAUUGUCUGAAUGGA	1543	1488-1510
AD-1784199.1	GACUUCACUAACUUCGAUCCA	1232	595-615	UGGAUCGAAGUUAGUGAAGUCAG	1544	593-615

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3
AD-1784200.1	CCAUUCAGACAA UAUAUCAUA	1233	1489-1509	UAUGAUAUAUUG UCUGAAUGGAA	1545	1487-1509
AD-1784201.1	UCUGUAUCCAAA UAAUGAAUA	1234	872-892	UAUUCATUAUUU GGAUACAGACU	1546	870-892
AD-1784202.1	AAUCAAAGCUUC CUUCAAAUA	1235	837-857	UAUUTGAAGGAA GCUUUGAUUUG	1547	835-857
AD-1784203.1	AUUCAGACAAUA UAUCAUAAA	1236	1491-1511	UUUATGAUAUAU UGUCUGAAUGG	1548	1489-1511
AD-1784204.1	CCGUAAACUUAA CUUCAAUGA	1237	750-770	UCAUUGAAGUUA AGUUUACGGAA	1549	748-770
AD-1784205.1	CCGUAAACUUAA CUUCAAUGA	1237	750-770	UCAUTGAAGUUA AGUUUACGGAA	1550	748-770
AD-1784206.1	GUGCUGACUUCA CUAACUUCA	1238	590-610	UGAAGUTAGUGA AGUCAGCACUC	1551	588-610
AD-1784207.1	AAGCUUCCUUCA AAUAAGAUA	1239	842-862	UAUCUUAUUUGA AGGAAGCUUUG	1552	840-862
AD-1784208.1	AAGCUUCCUUCA AAUAAGAUA	1239	842-862	UAUCTUAUUUGA AGGAAGCUUUG	1553	840-862
AD-1784209.1	AAAUUCCGUAAA CUUAACUUA	1240	745-765	UAAGUUAAGUUU ACGGAAUUUCA	1554	743-765
AD-1784210.1	CUGUCUGUUUCC UAUGAUCAA	1241	214-234	UUGATCAUAGGA AACAGACAGGG	1555	212-234
AD-1784211.1	GUAUCCAAAUAA UGAAUCUUA	1242	875-895	UAAGAUUCAUUA UUUGGAUACAG	1556	873-895
AD-1784212.1	GUAUCCAAAUAA UGAAUCUUA	1242	875-895	UAAGAUTCAUUA UUUGGAUACAG	1557	873-895
AD-1784213.1	CUGACUUCACUA ACUUCGAUA	1243	593-613	UAUCGAAGUUAG UGAAGUCAGCA	1558	591-613
AD-1784214.1	GCUUCCUUCAAA UAAGAUGGA	1244	844-864	UCCAUCUUAUUU GAAGGAAGCUU	1559	842-864
AD-1784215.1	GCUUCCUUCAAA UAAGAUGGA	1244	844-864	UCCATCTUAUUU GAAGGAAGCUU	1560	842-864
AD-1784216.1	AAAUCAAAGCUU CCUUCAAAA	1245	836-856	UUUUGAAGGAAG CUUUGAUUUGC	1561	834-856
AD-1784217.1	AGCUUCCUUCAA AUAAGAUGA	1246	843-863	UCAUCUUAUUUG AAGGAAGCUUU	1562	841-863
AD-1784218.1	UGCUGCUUUUAA AACAUAGGA	1247	1181-1201	UCCUAUGUUUUA AAAGCAGCAUU	1563	1179-1201
AD-1784219.1	AGGCAAAUCAAA GCUUCCUUA	1248	832-852	UAAGGAAGCUUU GAUUUGCCUGU	1564	830-852
AD-1784220.1	AGGCAAAUCAAA GCUUCCUUA	1248	832-852	UAAGGAAGCUUU GAUUUGCCUGU	1564	830-852
AD-1784221.1	GGCAAAUCAAAG CUUCCUUCA	1249	833-853	UGAAGGAAGCUU UGAUUUGCCUG	1565	831-853
AD-1784222.1	AAAGCUUCCUUC AAAUAAGAA	1250	841-861	UUCUUAUUUGAA GGAAGCUUUGA	1566	839-861

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3
AD-1784223.1	AAAGCUUCCUUC AAAUAAGAA	1250	841-861	UUCUTATUUGAA GGAAGCUUUGA	1567	839-861
AD-1784224.1	UAAAAUGCUGCU UUUAAAACA	1251	1176-1196	UGUUUUAAAAGC AGCAUUUUAGU	1568	1174-1196
AD-1784225.1	AAGAAUAAAGUA CCUUGACUA	1252	1113-1133	UAGUCAAGGUAC UUUAUUCUUAU	1569	1111-1133
AD-1784226.1	AGAAUAAAGUAC CUUGACUUA	1253	1114-1134	UAAGUCAAGGUA CUUUAUUCUUA	1570	1112-1134
AD-1784227.1	AGAAUAAAGUAC CUUGACUUA	1253	1114-1134	UAAGTCAAGGUA CUUUAUUCUUA	1571	1112-1134
AD-1784228.1	GUCUGUUUCCUA UGAUCAAGA	1254	216-236	UCUUGATCAUAG GAAACAGACAG	1572	214-236
AD-1784229.1	UCCGUAAACUUA ACUUCAAUA	1255	749-769	UAUUGAAGUUAA GUUUACGGAAU	1573	747-769
AD-1784230.1	CCUCUUCUGGAA UGUGUGACA	1256	676-696	UGUCACACAUUC CAGAAGAGGAG	1574	674-696
AD-1784231.1	UAUCCAAAUAAU GAAUCUUCA	1257	876-896	UGAAGATUCAUU AUUUGGAUACA	1575	874-896
AD-1784232.1	UCUGUUUCCUAU GAUCAAGCA	1258	217-237	UGCUTGAUCAUA GGAAACAGACA	1576	215-237
AD-1784233.1	GUUGACAUCGAC ACUCAUACA	1259	166-186	UGUATGAGUGUC GAUGUCAACAG	1577	164-186
AD-1784234.1	AAGUACCUUGAC UUUGUUCAA	1260	1120-1140	UUGAACAAAGUC AAGGUACUUUA	1578	1118-1140
AD-1784235.1	AAGUACCUUGAC UUUGUUCAA	1260	1120-1140	UUGAACAAAGUC AAGGUACUUUA	1578	1118-1140
AD-1784236.1	CAGAUCUACCUU GGUGAUUUA	1261	919-939	UAAATCACCAAG GUAGAUCUGUG	1579	917-939
AD-1784237.1	CUGGAUUGUGCU CAAGGAACA	1262	696-716	UGUUCCTUGAGC ACAAUCCAGGU	1580	694-716
AD-1784238.1	UGCUUUUAAAAC AUAGGAAAA	1263	1184-1204	UUUUCCTAUGUU UUAAAAGCAGC	1581	1182-1204
AD-1784239.1	UGCUGACUUCAC UAACUUCGA	1264	591-611	UCGAAGUUAGUG AAGUCAGCACU	1582	589-611
AD-1784240.1	UGCUGACUUCAC UAACUUCGA	1264	591-611	UCGAAGTUAGUG AAGUCAGCACU	1583	589-611
AD-1784241.1	GAAAUUCCGUAA ACUUAACUA	1265	744-764	UAGUUAAGUUUA CGGAAUUUCAA	1584	742-764
AD-1784242.1	GAAAUUCCGUAA ACUUAACUA	1265	744-764	UAGUTAAGUUUA CGGAAUUUCAA	1585	742-764
AD-1784243.1	UAAGGCAAAUCA GGUAAAAUA	1266	1252-1272	UAUUUUACCUGA UUUGCCUUAAC	1586	1250-1272
AD-1784244.1	UAAGGCAAAUCA GGUAAAAUA	1266	1252-1272	UAUUTUACCUGA UUUGCCUUAAC	1587	1250-1272
AD-1784245.1	GUUCUAGGUAUU UUUUUGAAA	1267	499-519	UUUCAAAAAAAAU ACCUAGAACGG	1588	497-519

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3
AD-1784246.1	AAGAUAAAUUGA GCUAGUUAA	1268	1234-1254	UUAACUAGCUCA AUUUAUCUUGU	1589	1232-1254
AD-1784247.1	UUAGCUAAGCAC AGAUCUACA	1269	908-928	UGUAGATCUGUG CUUAGCUAAAG	1590	906-928
AD-1784248.1	CUUCACUAACUU CGAUCCUCA	1270	597-617	UGAGGATCGAAG UUAGUGAAGUC	1591	595-617
AD-1784249.1	AAUUCCGUAAAC UUAACUUCA	1271	746-766	UGAAGUTAAGUU UACGGAAUUUC	1592	744-766
AD-1784250.1	CUGCUUUUAAAA CAUAGGAAA	1272	1183-1203	UUUCCUAUGUUU UAAAAGCAGCA	1593	1181-1203
AD-1784251.1	CUGUUGACAUCG ACACUCAUA	1273	164-184	UAUGAGTGUCGA UGUCAACAGGG	1594	162-184
AD-1784252.1	UUCACUAACUUC GAUCCUCGA	1274	598-618	UCGAGGAUCGAA GUUAGUGAAGU	1595	596-618
AD-1784253.1	GCUAAGCACAGA UCUACCUUA	1275	911-931	UAAGGUAGAUCU GUGCUUAGCUA	1596	909-931
AD-1784254.1	UAAAGUACCUUG ACUUUGUUA	1276	1118-1138	UAACAAAGUCAA GGUACUUUAUU	1597	1116-1138
AD-1784255.1	AAAAUGCUGCUU UUAAAACAA	1277	1177-1197	UUGUTUTAAAAG CAGCAUUUUAG	1598	1175-1197
AD-1784256.1	GCUGCUUUUAAA ACAUAGGAA	1278	1182-1202	UUCCUAUGUUUU AAAAGCAGCAU	1599	1180-1202
AD-1784257.1	GCUGCUUUUAAA ACAUAGGAA	1278	1182-1202	UUCCTATGUUUU AAAAGCAGCAU	1600	1180-1202
AD-1784258.1	UCAUGAUUCUAU GUAAUGUAA	1279	1274-1294	UUACAUUACAUA GAAUCAUGACU	1601	1272-1294
AD-1784259.1	UCAUGAUUCUAU GUAAUGUAA	1279	1274-1294	UUACAUTACAUA GAAUCAUGACU	1602	1272-1294
AD-1784260.1	AGUGCUGACUUC ACUAACUUA	1280	589-609	UAAGUUAGUGAA GUCAGCACUCU	1603	587-609
AD-1784261.1	CUAAGCACAGAU CUACCUUGA	1281	912-932	UCAAGGTAGAUC UGUGCUUAGCU	1604	910-932
AD-1784262.1	CACUAACUUCGA UCCUCGUGA	1282	600-620	UCACGAGGAUCG AAGUUAGUGAA	1605	598-620
AD-1784263.1	CUGAAGAACAGG CAAAUCAAA	1283	823-843	UUUGAUTUGCCU GUUCUUCAGUG	1606	821-843
AD-1784264.1	AAAGUACCUUGA CUUUGUUCA	1284	1119-1139	UGAACAAAGUCA AGGUACUUUAU	1607	1117-1139
AD-1784265.1	GCUUUGUUUAUG GUAGUAGUA	1285	1061-1081	UACUACTACCAU AAACAAAGCAC	1608	1059-1081
AD-1784266.1	CAUGAUUCUAUG UAAUGUAAA	1286	1275-1295	UUUACATUACAU AGAAUCAUGAC	1609	1273-1295
AD-1784267.1	CGUUCUAGGUAU UUUUUUGAA	1287	498-518	UUCAAAAAAAAUA CCUAGAACGGC	1610	496-518
AD-1784268.1	UUCUAGGUAUUU UUUUGAAGA	1288	500-520	UCUUCAAAAAAA UACCUAGAACG	1611	498-520

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3
AD-1784269.1	UCCUUCCUGAAUCCUUGGAUA	1289	623-643	UAUCCAAGGAUUCAGGAAGGAGG	1612	621-643
AD-1784270.1	UCCUUCCUGAAUCCUUGGAUA	1289	623-643	UAUCCAAGGAUUCAGGAAGGAGG	1612	621-643
AD-1784271.1	GACUAAAAUGCUGCUUUUAAA	1290	1173-1193	UUUAAAAGCAGCAUUUUAGUCAA	1613	1171-1193
AD-1784272.1	GACUAAAAUGCUGCUUUUAAA	1290	1173-1193	UUUAAAAGCAGCAUUUUAGUCAA	1613	1171-1193
AD-1784273.1	AACAGGCAAAUCAAAGCUUCA	1291	829-849	UGAAGCTUUGAUUUGCCUGUUCU	1614	827-849
AD-1784274.1	CCUUCCUGAAUCCUUGGAUUA	1292	624-644	UAAUCCAAGGAUUCAGGAAGGAG	1615	622-644
AD-1784275.1	UGAUGACUCUCAGGACAAAGA	1293	285-305	UCUUTGTCCUGAGAGUCAUCAAA	1616	283-305
AD-1784276.1	UGGAGUUUGAUGACUCUCAGA	1294	278-298	UCUGAGAGUCAUCAAACUCCACG	1617	276-298
AD-1784277.1	AUCCAAAUAAUGAAUCUUCGA	1295	877-897	UCGAAGAUUCAUUAUUUGGAUAC	1618	875-897
AD-1784278.1	AUCCAAAUAAUGAAUCUUCGA	1295	877-897	UCGAAGAUUCAUUAUUUGGAUAC	1618	875-897
AD-1784279.1	UUGACUUUGUUCACAGCAUGA	1296	1127-1147	UCAUGCTGUGAACAAAGUCAAGG	1619	1125-1147
AD-1784280.1	AGAUCUACCUUGGUGAUUUGA	1297	920-940	UCAAAUCACCAAGGUAGAUCUGU	1620	918-940
AD-1784281.1	AUGGUAGUAGUUUUUCUGUAA	1298	1070-1090	UUACAGAAAAAACUACUACCAUAA	1621	1068-1090
AD-1784282.1	AUGGUAGUAGUUUUUCUGUAA	1298	1070-1090	UUACAGAAAAAACUACUACCAUAA	1621	1068-1090
AD-1784283.1	CCUUGACUUUGUUCACAGCAA	1299	1125-1145	UUGCTGTGAACAAAGUCAAGGUA	1622	1123-1145
AD-1784284.1	CCUGGAUUGUGCUCAAGGAAA	1300	695-715	UUUCCUTGAGCACAAUCCAGGUC	1623	693-715
AD-1784285.1	GAGCUAGUUAAGGCAAAUCAA	1301	1244-1264	UUGATUTGCCUUAACUAGCUCAA	1624	1242-1264
AD-1784286.1	ACUGAAGAACAGGCAAAUCAA	1302	822-842	UUGATUTGCCUGUUCUUCAGUGG	1625	820-842
AD-1784287.1	UGAAGAACAGGCAAAUCAAAA	1303	824-844	UUUUGATUUGCCUGUUCUUCAGU	1626	822-844
AD-1784288.1	CUCCUCUUCUGGAAUGUGUGA	1304	674-694	UCACACAUUCCAGAAGAGGAGGG	1627	672-694
AD-1784289.1	CUCCUCUUCUGGAAUGUGUGA	1304	674-694	UCACACAUUCCAGAAGAGGAGGG	1627	672-694
AD-1784290.1	GCUUUCAACGUGGAGUUUGAA	1305	268-288	UUCAAACUCCACGUUGAAAGCAU	1628	266-288
AD-1784291.1	UGCUUUCAACGUGGAGUUUGA	1306	267-287	UCAAACUCCACGUUGAAAGCAUG	1629	265-287

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3
AD-1784292.1	UGCUUUCAACGUGGAGUUUGA	1306	267-287	UCAAACTCCACGUUGAAAGCAUG	1630	265-287
AD-1784293.1	CAGGUAAAAUAGUCAUGAUUA	1307	1262-1282	UAAUCATGACUAUUUUACCUGAU	1631	1260-1282
AD-1784294.1	CUGUAUCCAAAUAAUGAAUCA	1308	873-893	UGAUTCAUUAUUUGGAUACAGAC	1632	871-893
AD-1784295.1	AAGGCAAAUCAGGUAAAAUAA	1309	1253-1273	UUAUTUTACCUGAUUUGCCUUAA	1633	1251-1273
AD-1784296.1	CCUCCUUCCUGAAUCCUUGGA	1310	621-641	UCCAAGGAUUCAGGAAGGAGGCC	1634	619-641
AD-1784297.1	UUCCUUCAAAUAAGAUGGUCA	1311	846-866	UGACCATCUUAUUUGAAGGAAGC	1635	844-866
AD-1784298.1	UUGAAAUUCCGUAAACUUAAA	1312	742-762	UUUAAGTUUACGGAAUUUCAACA	1636	740-762
AD-1784299.1	ACACUCAUACAGCCAAGUAUA	1313	176-196	UAUACUTGGCUGUAUGAGUGUCG	1637	174-196
AD-1784300.1	GCACAGAUCUACCUUGGUGAA	1314	916-936	UUCACCAAGGUAGAUCUGUGCUU	1638	914-936
AD-1784301.1	CUUUCAACGUGGAGUUUGAUA	1315	269-289	UAUCAAACUCCACGUUGAAAGCA	1639	267-289
AD-1784302.1	UAGCUAAGCACAGAUCUACCA	1316	909-929	UGGUAGAUCUGUGCUUAGCUAAA	1640	907-929
AD-1784303.1	UUGUGAUACAGAGUAUAUUUA	1317	1469-1489	UAAAUAUACUCUGUAUCACAACU	1641	1467-1489
AD-1784304.1	ACUCAUACAGCCAAGUAUGAA	1318	178-198	UUCAUACUUGGCUGUAUGAGUGU	1642	176-198
AD-1784305.1	AGUUAAGGCAAAUCAGGUAAA	1319	1249-1269	UUUACCTGAUUUGCCUUAACUAG	1643	1247-1269
AD-1784306.1	GUUGUGAUACAGAGUAUAUUA	1320	1468-1488	UAAUAUACUCUGUAUCACAACUC	1644	1466-1488
AD-1784307.1	GUUGUGAUACAGAGUAUAUUA	1320	1468-1488	UAAUAUACUCUGUAUCACAACUC	1644	1466-1488
AD-1784308.1	UGACAUCGACACUCAUACAGA	1321	168-188	UCUGUAUGAGUGUCGAUGUCAAC	1645	166-188
AD-1784309.1	AGAUAAAUUGAGCUAGUUAAA	1322	1235-1255	UUUAACTAGCUCAAUUUAUCUUG	1646	1233-1255
AD-1784310.1	UAGGUAUUUUUUUGAAGGUUA	1323	503-523	UAACCUUCAAAAAAAUACCUAGA	1647	501-523
AD-1784311.1	UAGGUAUUUUUUUGAAGGUUA	1324	503-523	UAACCUTCAAAAAAAUACCUAGA	1648	501-523
AD-1784312.1	UGGUGCUUUGUUUAUGGUAGA	1325	1057-1077	UCUACCAUAAACAAAGCACCAAC	1649	1055-1077
AD-1784313.1	UGUGAUACAGAGUAUAUUUCA	1326	1470-1490	UGAAAUAUACUCUGUAUCACAAC	1650	1468-1490
AD-1784314.1	UCUUCUGGAAUGUGUGACCUA	1327	678-698	UAGGTCACACAUUCCAGAAGAGG	1651	676-698

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3
AD-1784315.1	CUGGCCGUUCUAGGUAUUUUA	1328	493-513	UAAAAUACCUAGAACGGCCAGUC	1652	491-513
AD-1784316.1	AUCAGGUAAAAUAGUCAUGAA	1329	1260-1280	UUCATGACUAUUUUACCUGAUUU	1653	1258-1280
AD-1784317.1	UUCCAUUAAAACAAAGGGCAA	1330	567-587	UUGCCCTUUGUUUUAAUGGAAUC	1654	565-587
AD-1784318.1	CAAGAGUGCUGACUUCACUAA	1331	585-605	UUAGTGAAGUCAGCACUCUUGCC	1655	583-605
AD-1784319.1	UUUCAACGUGGAGUUUGAUGA	1332	270-290	UCAUCAAACUCCACGUUGAAAGC	1656	268-290
AD-1784320.1	UUGGUGCUUUGUUUAUGGUAA	1333	1056-1076	UUACCAUAAACAAAGCACCAACC	1657	1054-1076
AD-1784321.1	UUGGUGCUUUGUUUAUGGUAA	1333	1056-1076	UUACCATAAACAAAGCACCAACC	1658	1054-1076
AD-1784322.1	CACUCAUACAGCCAAGUAUGA	1334	177-197	UCAUACUUGGCUGUAUGAGUGUC	1659	175-197
AD-1784323.1	AUAAAGUACCUUGACUUUGUA	1335	1117-1137	UACAAAGUCAAGGUACUUUAUUC	1660	1115-1137
AD-1784324.1	AUGACUUUUGAAUUACAGAGA	1336	1407-1427	UCUCTGTAAUUCAAAAGUCAUUA	1661	1405-1427
AD-1784325.1	GUCAUGAUUCUAUGUAAUGUA	1337	1273-1293	UACAUUACAUAGAAUCAUGACUA	1662	1271-1293
AD-1784326.1	GACCUGGAUUGUGCUCAAGGA	1338	693-713	UCCUTGAGCACAAUCCAGGUCAC	1663	691-713
AD-1784327.1	GACAUCGACACUCAUACAGCA	1339	169-189	UGCUGUAUGAGUGUCGAUGUCAA	1664	167-189
AD-1784328.1	GAAGAACAGGCAAAUCAAAGA	1340	825-845	UCUUTGAUUUGCCUGUUCUUCAG	1665	823-845
AD-1784329.1	CGUAAACUUAACUUCAAUGGA	1341	751-771	UCCAUUGAAGUUAAGUUUACGGA		749-771
AD-1784330.1	AGGUAAAAUAGUCAUGAUUCA	1342	1263-1283	UGAATCAUGACUAUUUUACCUGA	1666	1261-1283
AD-1784331.1	GUACCUUGACUUUGUUCACAA	1343	1122-1142	UUGUGAACAAAGUCAAGGUACUU	1667	1120-1142
AD-1784332.1	CCGUUCUAGGUAUUUUUUUGA	1344	497-517	UCAAAAAAAAUACCUAGAACGGCC	1668	495-517
AD-1784333.1	UUUAUGGUAGUAGUUUUUCUA	1345	1067-1087	UAGAAAAACUACUACCAUAAACA	1669	1065-1087
AD-1784334.1	CGUGGAGUUUGAUGACUCUCA	1346	276-296	UGAGAGTCAUCAAACUCCACGUU	1670	274-296
AD-1784335.1	UUCAACGUGGAGUUUGAUGAA	1347	271-291	UUCATCAAACUCCACGUUGAAAG	1671	269-291
AD-1784336.1	GAGUUGUGAUACAGAGUAUAA	1348	1466-1486	UUAUACTCUGUAUCACAACUCUA	1672	1464-1486
AD-1784337.1	UACCUUGACUUUGUUCACAGA	1349	1123-1143	UCUGUGAACAAAGUCAAGGUACU	1673	1121-1143

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3
AD-1784338.1	UACCUUGACUUU GUUCACAGA	1349	1123-1143	UCUGTGAACAAA GUCAAGGUACU	1674	1121-1143
AD-1784339.1	UAGAGUUGUGAU ACAGAGUAA	1350	1464-1484	UUACTCTGUAUC ACAACUCUAAU	1675	1462-1484
AD-1784340.1	UGAGUGCAAAUC CAUAGCACA	1351	1214-1234	UGUGCUAUGGAU UUGCACUCAAC	1676	1212-1234
AD-1784341.1	CAAAUCAGGUAA AAUAGUCAA	1352	1257-1277	UUGACUAUUUUA CCUGAUUUGCC	1677	1255-1277
AD-1784342.1	AAGCACAGAUCU ACCUUGGUA	1353	914-934	UACCAAGGUAGA UCUGUGCUUAG	1678	912-934
AD-1784343.1	ACUUUGUUCACA GCAUGUAGA	1354	1130-1150	UCUACAUGCUGU GAACAAAGUCA	1679	1128-1150
AD-1784344.1	UGGCCGUUCUAG GUAUUUUUA	1355	494-514	UAAAAAUACCUA GAACGGCCAGU	1680	492-514
AD-1784345.1	GCCAAGUAUGAC CCUUCCCUA	1356	187-207	UAGGGAAGGGUC AUACUUGGCUG	1681	185-207
AD-1784346.1	UAUGGUAGUAGU UUUUCUGUA	1357	1069-1089	UACAGAAAAACU ACUACCAUAAA	1682	1067-1089
AD-1784347.1	AAUUGAGCUAGU UAAGGCAAA	1358	1240-1260	UUUGCCTUAACU AGCUCAAUUUA	1683	1238-1260
AD-1784348.1	ACUAAAAUGCUG CUUUUAAAA	1359	1174-1194	UUUUAAAAGCAG CAUUUUAGUCA	1684	1172-1194
AD-1784349.1	ACUUCACUUGGU UCACUGGAA	1360	426-446	UUCCAGTGAACC AAGUGAAGUUC	1685	424-446
AD-1784350.1	UCUAGGUAUUUU UUUGAAGGA	1361	501-521	UCCUUCAAAAAA AUACCUAGAAC	1686	499-521
AD-1784351.1	AGCACAGAUCUA CCUUGGUGA	1362	915-935	UCACCAAGGUAG AUCUGUGCUUA	1687	913-935
AD-1784352.1	GCCGUUCUAGGU AUUUUUUUA	1363	496-516	UAAAAAAAUACC UAGAACGGCCA	1688	494-516
AD-1784353.1	CUAAAAUGCUGC UUUUAAAAA	1364	1175-1195	UUUUUAAAAGCA GCAUUUUAGUC	1689	1173-1195
AD-1784354.1	GAACAGGCAAAU CAAAGCUUA	1365	828-848	UAAGCUTUGAUU UGCCUGUUCUU	1690	826-848
AD-1784355.1	UGCUUUGUUUAU GGUAGUAGA	1366	1060-1080	UCUACUACCAUA AACAAAGCACC	1691	1058-1080
AD-1784356.1	AAUUAGAGUUGU GAUACAGAA	1367	1461-1481	UUCUGUAUCACA ACUCUAAUUAU	1692	1459-1481
AD-1784357.1	CUGGUUGGUGCU UUGUUUAUA	1368	1052-1072	UAUAAACAAAGC ACCAACCAGCC	1693	1050-1072
AD-1784358.1	UCCUUCAAAUAA GAUGGUCCA	1369	847-867	UGGACCAUCUUA UUUGAAGGAAG	1694	845-867
AD-1784359.1	GCCUCCUUCCUG AAUCCUUGA	1370	620-640	UCAAGGAUUCAG GAAGGAGGCCA	1695	618-640
AD-1784360.1	GAUUCUAUGUAA UGUAAACCA	1371	1278-1298	UGGUTUACAUUA CAUAGAAUCAU	1696	1276-1298

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3
AD-1784361.1	UGGUUGGUGCUU UGUUUAUGA	1372	1053-1073	UCAUAAACAAAG CACCAACCAGC	1697	1051-1073
AD-1784362.1	CUCAUACAGCCA AGUAUGACA	1373	179-199	UGUCAUACUUGG CUGUAUGAGUG	1698	177-199
AD-1784363.1	CUCAUACAGCCA AGUAUGACA	1373	179-199	UGUCAUACUUGG CUGUAUGAGUG	1698	177-199
AD-1784364.1	AUCGACACUCAU ACAGCCAAA	1374	172-192	UUUGGCTGUAUG AGUGUCGAUGU	1699	170-192
AD-1784365.1	GCACUGGCAUAA GGACUUCCA	1375	117-137	UGGAAGTCCUUA UGCCAGUGCUC	1700	115-137
AD-1784366.1	AACGUGGAGUUU GAUGACUCA	1376	274-294	UGAGTCAUCAAA CUCCACGUUGA	1701	272-294
AD-1784367.1	GCAAAUCAGGUA AAAUAGUCA	1377	1256-1276	UGACUAUUUUAC CUGAUUUGCCU	1702	1254-1276
AD-1784368.1	GCAAAUCAGGUA AAAUAGUCA	1377	1256-1276	UGACTATUUUAC CUGAUUUGCCU	1703	1254-1276
AD-1784369.1	CUUCAGAAAGUU GUUGAUGUA	1378	541-561	UACAUCAACAAC UUUCUGAAGGC	1704	539-561
AD-1784370.1	CUUCAGAAAGUU GUUGAUGUA	1378	541-561	UACATCAACAAC UUUCUGAAGGC	1705	539-561
AD-1784371.1	AAAUCAGGUAAA AUAGUCAUA	1379	1258-1278	UAUGACTAUUUU ACCUGAUUUGC	1706	1256-1278
AD-1784372.1	AGGCAAAUCAGG UAAAAUAGA	1380	1254-1274	UCUAUUUUACCU GAUUUGCCUUA	1707	1252-1274
AD-1784373.1	GGGCAAGAGUGC UGACUUCAA	1381	582-602	UUGAAGTCAGCA CUCUUGCCCUU	1708	580-602
AD-1784375.1	GGCCGUUCUAGG UAUUUUUUA	1382	495-515	UAAAAAAUACCU AGAACGGCCAG	1709	493-515
AD-1784377.1	CGGGCCUUCAGA AAGUUGUUA	1383	536-556	UAACAACUUUCU GAAGGCCCGGU	1710	534-556
AD-1784378.1	GGCAAAUCAGGU AAAAUAGUA	1384	1255-1275	UACUAUUUUACC UGAUUUGCCUU	1711	1253-1275
AD-1784379.1	GAGGAUCCUCAA CAAUGGUCA	1385	246-266	UGACCAUUGUUG AGGAUCCUCAG	1712	244-266
AD-1784380.1	GAGGAUCCUCAA CAAUGGUCA	1385	246-266	UGACCATUGUUG AGGAUCCUCAG	1713	244-266
AD-1784381.1	UUCACUUGGUUC ACUGGAACA	1386	428-448	UGUUCCAGUGAA CCAAGUGAAGU	1714	426-448
AD-1784382.1	AGAACUGAUGGU GGACAACUA	1387	786-806	UAGUTGTCCACC AUCAGUUCUUC	1715	784-806
AD-1784383.1	AAUAAAGUACCU UGACUUUGA	1388	1116-1136	UCAAAGUCAAGG UACUUUAUUCU	1716	1114-1136
AD-1784384.1	AAUAAAGUACCU UGACUUUGA	1388	1116-1136	UCAAAGTCAAGG UACUUUAUUCU	1717	1114-1136
AD-1784385.1	CUUUGUUCACAG CAUGUAGGA	1389	1131-1151	UCCUACAUGCUG UGAACAAAGUC	1718	1129-1151

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3
AD-1784386.1	CUUUGUUCACAG CAUGUAGGA	1389	1131-1151	UCCUACAUGCUG UGAACAAAGUC	1718	1129-1151
AD-1784387.1	AAUAAGAAUAAA GUACCUUGA	1390	1110-1130	UCAAGGTACUUU AUUCUUAUUUC	1719	1108-1130
AD-1784388.1	AGUAGUUUUUCU GUAACACAA	1391	1075-1095	UUGUGUTACAGA AAAACUACUAC	1720	1073-1095
AD-1784389.1	CCAAGUAUGACC CUUCCCUGA	1392	188-208	UCAGGGAAGGGU CAUACUUGGCU	1721	186-208
AD-1784390.1	UUGAGUGCAAAU CCAUAGCAA	1393	1213-1233	UUGCTATGGAUU UGCACUCAACC	1722	1211-1233
AD-1784391.1	GGCCUUCAGAAA GUUGUUGAA	1394	538-558	UUCAACAACUUU CUGAAGGCCCG	1723	536-558
AD-1784392.1	AGGAUCCUCAAC AAUGGUCAA	1395	247-267	UUGACCAUUGUU GAGGAUCCUCA	1724	245-267
AD-1784393.1	AUUAGAGUUGUG AUACAGAGA	1396	1462-1482	UCUCTGTAUCAC AACUCUAAUUA	1725	1460-1482
AD-1784394.1	CAACGUGGAGUU UGAUGACUA	1397	273-293	UAGUCATCAAAC UCCACGUUGAA	1726	271-293
AD-1784395.1	GACUUUUGAAUU ACAGAGAUA	1398	1409-1429	UAUCTCTGUAAU UCAAAAGUCAU	1727	1407-1429
AD-1784396.1	UGAGGAUCCUCA ACAAUGGUA	1399	245-265	UACCAUUGUUGA GGAUCCUCAGG	1728	243-265
AD-1784397.1	GAGUUUGAUGAC UCUCAGGAA	1400	280-300	UUCCTGAGAGUC AUCAAACUCCA	1729	278-300
AD-1784398.1	UUUUAAAACAUA GGAAAGUAA	1401	1187-1207	UUACTUTCCUAU GUUUUAAAAGC	1730	1185-1207
AD-1784399.1	UUAUGGUAGUAG UUUUUCUGA	1402	1068-1088	UCAGAAAAACUA CUACCAUAAAC	1731	1066-1088
AD-1784400.1	AACUUCACUUGG UUCACUGGA	1403	425-445	UCCAGUGAACCA AGUGAAGUUCU	1732	423-445
AD-1784401.1	AAAUUGAGCUAG UUAAGGCAA	1404	1239-1259	UUGCCUTAACUA GCUCAAUUUAU	1733	1237-1259
AD-1784402.1	UUUGUUUAUGGU AGUAGUUUA	1405	1063-1083	UAAACUACUACC AUAAACAAAGC	1734	1061-1083
AD-1784403.1	UUUGUUUAUGGU AGUAGUUUA	1405	1063-1083	UAAACUACUACC AUAAACAAAGC	1734	1061-1083
AD-1784404.1	AAGGGCAAGAGU GCUGACUUA	1406	580-600	UAAGTCAGCACU CUUGCCCUUUG	1735	578-600
AD-1784405.1	GGAGUUUGAUGA CUCUCAGGA	1407	279-299	UCCUGAGAGUCA UCAAACUCCAC	1736	277-299
AD-1784406.1	GGGCCUUCAGAA AGUUGUUGA	1408	537-557	UCAACAACUUUC UGAAGGCCCGG	1737	535-557
AD-1784407.1	GCAAGAGUGCUG ACUUCACUA	1409	584-604	UAGUGAAGUCAG CACUCUUGCCC	1738	582-604
AD-1784408.1	AGCCACUGAAGA ACAGGCAAA	1410	818-838	UUUGCCTGUUCU UCAGUGGCUGA	1739	816-838

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3
AD-1784409.1	AUUCCAUUAAAA CAAAGGGCA	1411	566-586	UGCCCUUUGUUU UAAUGGAAUCC	1740	564-586
AD-1784410.1	AUUCCAUUAAAA CAAAGGGCA	1411	566-586	UGCCCUTUGUUU UAAUGGAAUCC	1741	564-586
AD-1784411.1	GUAGUUUUUCUG UAACACAGA	1412	1076-1096	UCUGTGTUACAG AAAAACUACUA	1742	1074-1096
AD-1784412.1	GGUAUUUUUUUG AAGGUUGGA	1413	505-525	UCCAACCUUCAA AAAAAUACCUA	1743	503-525
AD-1784413.1	UCCAAAUAAUGA AUCUUCGGA	1414	878-898	UCCGAAGAUUCA UUAUUUGGAUA	1744	876-898
AD-1784414.1	AAACAUAGGAAA GUAGAAUGA	1415	1192-1212	UCAUTCTACUUU CCUAUGUUUUA	1745	1190-1212
AD-1784415.1	AUGACUCUCAGG ACAAAGCAA	1416	287-307	UUGCTUTGUCCU GAGAGUCAUCA	1746	285-307
AD-1784416.1	AGCUAGUUAAGG CAAAUCAGA	1417	1245-1265	UCUGAUUUGCCU UAACUAGCUCA	1747	1243-1265
AD-1784417.1	CCUGAGGAUCCU CAACAAUGA	1418	243-263	UCAUTGTUGAGG AUCCUCAGGGA	1748	241-263
AD-1784418.1	GGUUGGUGCUUU GUUUAUGGA	1419	1054-1074	UCCAUAAACAAA GCACCAACCAG	1749	1052-1074
AD-1784419.1	AGGUAUUUUUUU GAAGGUUGA	1420	504-524	UCAACCUUCAAA AAAAUACCUAG	1750	502-524
AD-1784420.1	UGAAUCUUCGGG UGUUUCCCA	1421	887-907	UGGGAAACACCC GAAGAUUCAUU	1751	885-907
AD-1784421.1	UGAAUCUUCGGG UGUUUCCCA	1421	887-907	UGGGAAACACCC GAAGAUUCAUU	1751	885-907
AD-1784422.1	UAGUAGUUUUUC UGUAACACA	1422	1074-1094	UGUGUUACAGAA AAACUACUACC	1752	1072-1094
AD-1784423.1	UAGUAGUUUUUC UGUAACACA	1422	1074-1094	UGUGTUACAGAA AAACUACUACC	1753	1072-1094
AD-1784424.1	GUUUGAUGACUC UCAGGACAA	1423	282-302	UUGUCCTGAGAG UCAUCAAACUC	1754	280-302
AD-1784425.1	AAUGAAUCUUCG GGUGUUUCA	1424	885-905	UGAAACACCCGA AGAUUCAUUAU	1755	883-905
AD-1784426.1	CAAAUAAUGAAU CUUCGGGUA	1425	880-900	UACCCGAAGAUU CAUUAUUUGGA	1756	878-900
AD-1784427.1	UUUGUUCACAGC AUGUAGGGA	1426	1132-1152	UCCCUACAUGCU GUGAACAAAGU	1757	1130-1152
AD-1784428.1	AUUGUGCUCAAG GAACCCAUA	1427	700-720	UAUGGGTUCCUU GAGCACAAUCC	1758	698-720
AD-1784429.1	GUUGGUGCUUUG UUUAUGGUA	1428	1055-1075	UACCAUAAACAA AGCACCAACCA	1759	1053-1075
AD-1784430.1	GAAUCUUCGGGU GUUUCCCUA	1429	888-908	UAGGGAAACACC CGAAGAUUCAU	1760	886-908
AD-1784431.1	GGUAGUAGUUUU UCUGUAACA	1430	1072-1092	UGUUACAGAAAA ACUACUACCAU	1761	1070-1092

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3
AD-1784432.1	AGAACAGGCAAA UCAAAGCUA	1431	827-847	UAGCUUUGAUUU GCCUGUUCUUC	1762	825-847
AD-1784433.1	AGAACAGGCAAA UCAAAGCUA	1431	827-847	UAGCTUTGAUUU GCCUGUUCUUC	1763	825-847
AD-1784434.1	AAAAUAGUCAUG AUUCUAUGA	1432	1267-1287	UCAUAGAAUCAU GACUAUUUUAC	1764	1265-1287
AD-1784435.1	ACUGGCCGUUCU AGGUAUUUA	1433	492-512	UAAAUACCUAGA ACGGCCAGUCC	1765	490-512
AD-1784436.1	CCCUGAGGAUCC UCAACAAUA	1434	242-262	UAUUGUTGAGGA UCCUCAGGGAA	1766	240-262
AD-1784437.1	GCUGGUUGGUGC UUUGUUUAA	1435	1051-1071	UUAAACAAAGCA CCAACCAGCCA	1767	1049-1071
AD-1784438.1	CAGAAAGUUGUU GAUGUGCUA	1436	544-564	UAGCACAUCAAC AACUUUCUGAA	1768	542-564
AD-1784439.1	ACUAACUUCGAU CCUCGUGGA	1437	601-621	UCCACGAGGAUC GAAGUUAGUGA	1769	599-621
AD-1784440.1	CCUUCAGAAAGU UGUUGAUGA	1438	540-560	UCAUCAACAACU UUCUGAAGGCC	1770	538-560
AD-1784441.1	UGAGCACUGGCA UAAGGACUA	1439	114-134	UAGUCCTUAUGC CAGUGCUCAGG	1771	112-134
AD-1784442.1	CUAGUUAAGGCA AAUCAGGUA	1440	1247-1267	UACCTGAUUUGC CUUAACUAGCU	1772	1245-1267
AD-1784443.1	CUGAGGAUCCUC AACAAUGGA	1441	244-264	UCCAUUGUUGAG GAUCCUCAGGG	1773	242-264
AD-1784444.1	GUUUAUGGUAGU AGUUUUUCA	1442	1066-1086	UGAAAAACUACU ACCAUAAACAA	1774	1064-1086
AD-1784445.1	UGUGACCUGGAU UGUGCUCAA	1443	690-710	UUGAGCACAAUC CAGGUCACACA	1775	688-710
AD-1784446.1	ACAUCGACACUC AUACAGCCA	1444	170-190	UGGCTGTAUGAG UGUCGAUGUCA	1776	168-190
AD-1784447.1	GAUUGUGCUCAA GGAACCCAA	1445	699-719	UUGGGUTCCUUG AGCACAAUCCA	1777	697-719
AD-1784448.1	UCAUACAGCCAA GUAUGACCA	1446	180-200	UGGUCATACUUG GCUGUAUGAGU	1778	178-200
AD-1784449.1	UAAAAUAGUCAU GAUUCUAUA	1447	1266-1286	UAUAGAAUCAUG ACUAUUUUACC	1779	1264-1286
AD-1784450.1	UAAAAUAGUCAU GAUUCUAUA	1447	1266-1286	UAUAGAAUCAUG ACUAUUUUACC	1779	1264-1286
AD-1784451.1	GUGCUCAAGGAA CCCAUCAGA	1448	703-723	UCUGAUGGGUUC CUUGAGCACAA	1780	701-723
AD-1784452.1	CGAAGAACUGAU GGUGGACAA	1449	783-803	UUGUCCACCAUC AGUUCUUCGGG	1781	781-803
AD-1784453.1	AAUAAAAUGUGA AGACUAGAA	1450	1001-1021	UUCUAGTCUUCA CAUUUUAUUAG	1782	999-1021
AD-1784454.1	GGCUGGUUGGUG CUUUGUUUA	1451	1050-1070	UAAACAAAGCAC CAACCAGCCAC	1783	1048-1070

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3
AD-1784455.1	UUGUUCACAGCA UGUAGGGUA	1452	1133-1153	UACCCUACAUGC UGUGAACAAAG	1784	1131-1153
AD-1784456.1	UUCAAAUAAGAU GGUCCCAUA	1453	850-870	UAUGGGACCAUC UUAUUUGAAGG	1785	848-870
AD-1784457.1	UUUAAAACAUAG GAAAGUAGA	1454	1188-1208	UCUACUUUCCUA UGUUUUAAAAG	1786	1186-1208
AD-1784458.1	UUGUUUAUGGUA GUAGUUUUA	1455	1064-1084	UAAAACUACUAC CAUAAACAAAG	1787	1062-1084
AD-1784459.1	UUGUUUAUGGUA GUAGUUUUA	1455	1064-1084	UAAAACTACUAC CAUAAACAAAG	1788	1062-1084
AD-1784460.1	GCUAGUUAAGGC AAAUCAGGA	1456	1246-1266	UCCUGAUUUGCC UUAACUAGCUC	1789	1244-1266
AD-1784461.1	GUAAAAUAGUCA UGAUUCUAA	1457	1265-1285	UUAGAAUCAUGA CUAUUUUACCU	1790	1263-1285
AD-1784462.1	GUAAAAUAGUCA UGAUUCUAA	1457	1265-1285	UUAGAATCAUGA CUAUUUUACCU	1791	1263-1285
AD-1784463.1	GACUGGCCGUUC UAGGUAUUA	1458	491-511	UAAUACCUAGAA CGGCCAGUCCA	1792	489-511
AD-1784464.1	UCAGCCACUGAA GAACAGGCA	1459	816-836	UGCCTGTUCUUC AGUGGCUGAGC	1793	814-836
AD-1784465.1	UGGAAUGUGUGA CCUGGAUUA	1460	683-703	UAAUCCAGGUCA CACAUUCCAGA	1794	681-703
AD-1784466.1	UCACAGCAUGUA GGGUGAUGA	1461	1137-1157	UCAUCACCCUAC AUGCUGUGAAC	1795	1135-1157
AD-1784467.1	UACAGCCAAGUA UGACCCUUA	1462	183-203	UAAGGGTCAUAC UUGGCUGUAUG	1796	181-203
AD-1784468.1	CUGAGCACUGGC AUAAGGACA	1463	113-133	UGUCCUUAUGCC AGUGCUCAGGU	1797	111-133
AD-1784469.1	CUGAGCACUGGC AUAAGGACA	1463	113-133	UGUCCUTAUGCC AGUGCUCAGGU	1798	111-133
AD-1784470.1	GCUCAAGGAACC CAUCAGCGA	1464	705-725	UCGCTGAUGGGU UCCUUGAGCAC	1799	703-725
AD-1784471.1	UUCUGGAAUGUG UGACCUGGA	1465	680-700	UCCAGGTCACAC AUUCCAGAAGA	1800	678-700
AD-1784472.1	UAAAUUGAGCUA GUUAAGGCA	1466	1238-1258	UGCCUUAACUAG CUCAAUUUAUC	1801	1236-1258
AD-1784473.1	UAUUUUUUUGAA GGUUGGCAA	1467	507-527	UUGCCAACCUUC AAAAAAAUACC	1802	505-527
AD-1784474.1	UAAUUAGAGUUG UGAUACAGA	1468	1460-1480	UCUGUAUCACAA CUCUAAUUAUA	1803	1458-1480
AD-1784475.1	UAAUUAGAGUUG UGAUACAGA	1468	1460-1480	UCUGTATCACAA CUCUAAUUAUA	1804	1458-1480
AD-1784476.1	UGACUCUCAGGA CAAAGCAGA	1469	288-308	UCUGCUUUGUCC UGAGAGUCAUC	1805	286-308
AD-1784477.1	UGACUCUCAGGA CAAAGCAGA	1469	288-308	UCUGCUTUGUCC UGAGAGUCAUC	1806	286-308

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3
AD-1784478.1	CAUACAGCCAAG UAUGACCCA	1470	181-201	UGGGTCAUACUU GGCUGUAUGAG	1807	179-201
AD-1784479.1	GUAUUUUUUUGA AGGUUGGCA	1471	506-526	UGCCAACCUUCA AAAAAAUACCU	1808	504-526
AD-1784480.1	CACAGCAUGUAG GGUGAUGAA	1472	1138-1158	UUCATCACCCUA CAUGCUGUGAA	1809	1136-1158
AD-1784481.1	UAUAAUUAGAGU UGUGAUACA	1473	1458-1478	UGUATCACAACU CUAAUUAUAAC	1810	1456-1478
AD-1784482.1	GAUUUUGGGAAA GCUGUGCAA	1474	460-480	UUGCACAGCUUU CCCAAAAUCCC	1811	458-480
AD-1784483.1	UAAAACAAAGGG CAAGAGUGA	1475	573-593	UCACTCTUGCCC UUUGUUUUAAU	1812	571-593
AD-1784484.1	UCAAGGAACCCA UCAGCGUCA	1476	707-727	UGACGCUGAUGG GUUCCUUGAGC	1813	705-727
AD-1784485.1	UCAAGGAACCCA UCAGCGUCA	1476	707-727	UGACGCTGAUGG GUUCCUUGAGC	1814	705-727
AD-1784486.1	UCAGAAAGUUGU UGAUGUGCA	1477	543-563	UGCACAUCAACA ACUUUCUGAAG	1815	541-563
AD-1784487.1	UCAGAAAGUUGU UGAUGUGCA	1477	543-563	UGCACATCAACA ACUUUCUGAAG	1816	541-563
AD-1784488.1	CCAAAUAAUGAA UCUUCGGGA	1478	879-899	UCCCGAAGAUUC AUUAUUUGGAU	1817	877-899
AD-1784489.1	AGCAUGUAGGGU GAUGAGCAA	1479	1141-1161	UUGCTCAUCACC CUACAUGCUGU	1818	1139-1161
AD-1784490.1	GAUAAAUUGAGC UAGUUAAGA	1480	1236-1256	UCUUAACUAGCU CAAUUUAUCUU	1819	1234-1256
AD-1784491.1	CUCAGCCACUGA AGAACAGGA	1481	815-835	UCCUGUUCUUCA GUGGCUGAGCU	1820	813-835
AD-1784492.1	CUCAGCCACUGA AGAACAGGA	1481	815-835	UCCUGUTCUUCA GUGGCUGAGCU	1821	813-835
AD-1784493.1	CAGCAUGUAGGG UGAUGAGCA	1482	1140-1160	UGCUCATCACCC UACAUGCUGUG	1822	1138-1160
AD-1784494.1	AUAAUGAAUCUU CGGGUGUUA	1483	883-903	UAACACCCGAAG AUUCAUUAUUU	1823	881-903
AD-1784495.1	GGAACCCAUCAG CGUCAGCAA	1484	711-731	UUGCTGACGCUG AUGGGUUCCUU	1824	709-731
AD-1784496.1	UGUUCACAGCAU GUAGGGUGA	1485	1134-1154	UCACCCUACAUG CUGUGAACAAA	1825	1132-1154
AD-1784497.1	AAACAAAGGGCA AGAGUGCUA	1486	575-595	UAGCACTCUUGC CCUUUGUUUUA	1826	573-595
AD-1784498.1	UGUGUGACCUGG AUUGUGCUA	1487	688-708	UAGCACAAUCCA GGUCACACAUU	1827	686-708
AD-1784499.1	UGUGUGACCUGG AUUGUGCUA	1487	688-708	UAGCACAAUCCA GGUCACACAUU	1827	686-708
AD-1784500.1	AAUAAUGAAUCU UCGGGUGUA	1488	882-902	UACACCCGAAGA UUCAUUAUUUG	1828	880-902

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3
AD-1784501.1	AUUUUUUUGAAG GUUGGCAGA	1489	508-528	UCUGCCAACCUU CAAAAAAAUAC	1829	506-528
AD-1784502.1	AUUUUUUUGAAG GUUGGCAGA	1489	508-528	UCUGCCAACCUU CAAAAAAAUAC	1829	506-528
AD-1784503.1	UGCUCAAGGAAC CCAUCAGCA	1490	704-724	UGCUGATGGGUU CCUUGAGCACA	1830	702-724
AD-1784504.1	UAAUGAAUCUUC GGGUGUUUA	1491	884-904	UAAACACCCGAA GAUUCAUUAUU	1831	882-904
AD-1784505.1	GUGGCUGGUUGG UGCUUUGUA	1492	1048-1068	UACAAAGCACCA ACCAGCCACAG	1832	1046-1068
AD-1784506.1	AAGGAACCCAUC AGCGUCAGA	1493	709-729	UCUGACGCUGAU GGGUUCCUUGA	1833	707-729
AD-1784507.1	UUAAAACAAAGG GCAAGAGUA	1494	572-592	UACUCUTGCCCU UUGUUUUAAUG	1834	570-592
AD-1784508.1	CUGUGGCUGGUU GGUGCUUUA	1495	1046-1066	UAAAGCACCAAC CAGCCACAGCA	1835	1044-1066
AD-1784509.1	CAGCUCAGCCAC UGAAGAACA	1496	812-832	UGUUCUTCAGUG GCUGAGCUGGG	1836	810-832
AD-1784510.1	AAAUAAUGAAUC UUCGGGUGA	1497	881-901	UCACCCGAAGAU UCAUUAUUUGG	1837	879-901
AD-1784511.1	GAAUGUGUGACC UGGAUUGUA	1498	685-705	UACAAUCCAGGU CACACAUUCCA	1838	683-705
AD-1784512.1	CAUGUAGGGUGA UGAGCACUA	1499	1143-1163	UAGUGCTCAUCA CCCUACAUGCU	1839	1141-1163
AD-1784513.1	GGACUGGCCGUU CUAGGUAUA	1500	490-510	UAUACCTAGAAC GGCCAGUCCAU	1840	488-510
AD-1784514.1	AUAAAUUGAGCU AGUUAAGGA	1501	1237-1257	UCCUUAACUAGC UCAAUUUAUCU	1841	1235-1257
AD-1784515.1	GAAAGUUGUUGA UGUGCUGGA	1502	546-566	UCCAGCACAUCA ACAACUUUCUG	1842	544-566
AD-1784516.1	GAAAGUUGUUGA UGUGCUGGA	1502	546-566	UCCAGCACAUCA ACAACUUUCUG	1842	544-566
AD-1784517.1	AACAAAGGGCAA GAGUGCUGA	1503	576-596	UCAGCACUCUUG CCCUUUGUUUU	1843	574-596
AD-1784518.1	CCUGAGCACUGG CAUAAGGAA	1504	112-132	UUCCTUAUGCCA GUGCUCAGGUC	1844	110-132
AD-1784519.1	UGAUGGUGGACA ACUGGCGCA	1505	791-811	UGCGCCAGUUGU CCACCAUCAGU	1845	789-811
AD-1784520.1	ACAAAGGGCAAG AGUGCUGAA	1506	577-597	UUCAGCACUCUU GCCCUUUGUUU	1846	575-597
AD-1784521.1	ACGGACCUGAGC ACUGGCAUA	1507	107-127	UAUGCCAGUGCU CAGGUCCGUUG	1847	105-127
AD-1784522.1	UGGGAAAGCUGU GCAGCAACA	1508	465-485	UGUUGCTGCACA GCUUUCCCAAA	1848	463-485
AD-1784523.1	AACCCAUCAGCG UCAGCAGCA	1509	713-733	UGCUGCTGACGC UGAUGGGUUCC	1849	711-733

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3
AD-1784524.1	AGCUCAGCCACU GAAGAACAA	1510	813-833	UUGUTCTUCAGU GGCUGAGCUGG	1850	811-833
AD-1784525.1	UUUUGAAGGUUG GCAGCGCUA	1511	512-532	UAGCGCTGCCAA CCUUCAAAAAA	1851	510-532
AD-1784526.1	GUAUGACCCUUC CCUGAAGCA	1512	192-212	UGCUTCAGGGAA GGGUCAUACUU	1852	190-212
AD-1784527.1	CUACCCAGGCUC ACUGACCAA	1513	651-671	UUGGTCAGUGAG CCUGGGUAGGU	1853	649-671
AD-1784528.1	ACCCAGGCUCAC UGACCACCA	1514	653-673	UGGUGGTCAGUG AGCCUGGGUAG	1854	651-673
AD-1784529.1	AUGGACUGGCCG UUCUAGGUA	1515	488-508	UACCUAGAACGG CCAGUCCAUCA	1855	486-508
AD-1784530.1	ACCUGAGCACUG GCAUAAGGA	1516	111-131	UCCUUAUGCCAG UGCUCAGGUCC	1856	109-131
AD-1784531.1	CCAUCAGCGUCA GCAGCGAGA	1517	716-736	UCUCGCUGCUGA CGCUGAUGGGU	1857	714-736
AD-1784532.1	UGGACUGGCCGU UCUAGGUAA	1518	489-509	UUACCUAGAACG GCCAGUCCAUC	1858	487-509
AD-1784533.1	UUUUGGGAAAGC UGUGCAGCA	1519	462-482	UGCUGCACAGCU UUCCCAAAAUC	1859	460-482
AD-1784534.1	CUGAUGGACUGG CCGUUCUAA	1520	485-505	UUAGAACGGCCA GUCCAUCAGGU	1860	483-505
AD-1784535.1	ACCUACCCAGGC UCACUGACA	1521	649-669	UGUCAGTGAGCC UGGGUAGGUCC	1861	647-669
AD-1784536.1	GGACCUACCCAG GCUCACUGA	1522	647-667	UCAGTGAGCCUG GGUAGGUCCAG	1862	645-667
AD-1784537.1	GAUGGACUGGCC GUUCUAGGA	1523	487-507	UCCUAGAACGGC CAGUCCAUCAG	1863	485-507
AD-1784538.1	AAGGUUGGCAGC GCUAAACCA	1524	517-537	UGGUTUAGCGCU GCCAACCUUCA	1864	515-537
AD-1784539.1	UGAUGGACUGGC CGUUCUAGA	1525	486-506	UCUAGAACGGCC AGUCCAUCAGG	1865	484-506
AD-1784540.1	AACUGAUGGUGG ACAACUGGA	1526	788-808	UCCAGUUGUCCA CCAUCAGUUCU	1866	786-808
AD-1784541.1	AACUGAUGGUGG ACAACUGGA	1526	788-808	UCCAGUTGUCCA CCAUCAGUUCU	1867	786-808
AD-1784542.1	ACAACUGCUGUG GCUGGUUGA	1527	1039-1059	UCAACCAGCCAC AGCAGUUGUGU	1868	1037-1059
AD-1784543.1	ACAACUGCUGUG GCUGGUUGA	1527	1039-1059	UCAACCAGCCAC AGCAGUUGUGU	1868	1037-1059
AD-1784544.1	CAACGGACCUGA GCACUGGCA	1528	105-125	UGCCAGTGCUCA GGUCCGUUGUG	1869	103-125
AD-1784545.1	CAACUGCUGUGG CUGGUUGGA	1529	1040-1060	UCCAACCAGCCA CAGCAGUUGUG	1870	1038-1060
AD-1784546.1	ACUGAUGGUGGA CAACUGGCA	1530	789-809	UGCCAGTUGUCC ACCAUCAGUUC	1871	787-809

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3
AD-1784547.1	CUGCUGUGGCUG GUUGGUGCA	1531	1043-1063	UGCACCAACCAG CCACAGCAGUU	1872	1041-1063

Table 8. Modified Sense and Antisense Strand Sequences of CA2 dsRNA Agents

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1784188.1	usgsuuucCfuAfUf Gfaucaagcasasa	1873	VPusUfsugdCu(Tgn)ga ucauAfgGfaaacasgsa	2183	UCUGUUUCCUAU GAUCAAGCAAC	2541
AD-1784189.1	usgsacuuCfaCfUf Afacuucgauscsa	1874	VPusGfsaucGfaaguuag UfgAfagucasgsc	2184	GCUGACUUCACU AACUUCGAUCC	2542
AD-1784190.1	csasaagcUfuCfCf Ufucaaaauaasgsa	1875	VPusCfsuuaUfuugaagg AfaGfcuuugsasu	2185	AUCAAAGCUUCC UUCAAAUAAGA	2543
AD-1784191.1	uscsaaagCfuUfCf Cfuucaaauasasa	1876	VPusUfsuadTu(Tgn)ga aggaAfgCfuuugasusu	2186	AAUCAAAGCUUC CUUCAAAUAAG	2544
AD-1784192.1	gsuscuguAfuCfCf Afaauaaugasasa	1877	VPusUfsucaUfuauuugg AfuAfcagacsusa	2187	UAGUCUGUAUCC AAAUAAUGAAU	2545
AD-1784193.1	gsuscuguAfuCfCf Afaauaaugasasa	1877	VPusUfsucdAu(Tgn)au uuggAfuAfcagacsusa	2188	UAGUCUGUAUCC AAAUAAUGAAU	2545
AD-1784194.1	asusuccgUfaAfAf Cfuuaacuucsasa	1878	VPusUfsgadAg(Tgn)ua aguuUfaCfggaaususu	2189	AAAUUCCGUAAA CUUAACUUCAA	2546
AD-1784195.1	uscscuauGfaUfCf Afagcaacuuscsa	1879	VPusGfsaadGu(Tgn)gc uugaUfcAfuaggasasa	2190	UUUCCUAUGAUC AAGCAACUUCC	2547
AD-1784196.1	gsusuuccUfaUfGf Afucaagcaascsa	1880	VPusGfsuudGc(Tgn)ug aucaUfaGfgaaacsasg	2191	CUGUUUCCUAUG AUCAAGCAACU	2548
AD-1784197.1	asusgcugCfuUfUf Ufaaaacauasgsa	1881	VPusCfsuadTg(Tgn)uu uaaaAfgCfagcaususu	2192	AAAUGCUGCUUU UAAAACAUAGG	2549
AD-1784198.1	csasuucaGfaCfAf Afuauaucausasa	1882	VPusUfsaudGa(Tgn)au auugUfcUfgaaugsgsa	2193	UCCAUUCAGACA AUAUAUCAUAA	2550
AD-1784199.1	gsascuucAfcUfAf Afcuucgaucscsa	1883	VPusGfsgauCfgaaguua GfuGfaagucsasg	2194	CUGACUUCACUA ACUUCGAUCCU	2551
AD-1784200.1	cscsauucAfgAfCf Afauauaucasusa	1884	VPusAfsugaUfauauugu CfuGfaauggsasa	2195	UUCCAUUCAGAC AAUAUAUCAUA	2552
AD-1784201.1	uscsuguaUfcCfAf Afauaaugaasusa	1885	VPusAfsuudCa(Tgn)ua uuugGfaUfacagascsu	2196	AGUCUGUAUCCA AAUAAUGAAUC	2553
AD-1784202.1	asasucaaAfgCfUf Ufccuucaaasusa	1886	VPusAfsuudTg(Agn)ag gaagCfuUfugauususg	2197	CAAAUCAAAGCU UCCUUCAAAUA	2554
AD-1784203.1	asusucagAfcAfAf Ufauaucauasasa	1887	VPusUfsuadTg(Agn)ua uauuGfuCfugaausgsg	2198	CCAUUCAGACAA UAUAUCAUAAC	2555
AD-1784204.1	cscsguaaAfcUfUf Afacuucaausgsa	1888	VPusCfsauuGfaaguuaa GfuUfuacggsasa	2199	UUCCGUAAACUU AACUUCAAUGG	2556
AD-1784205.1	cscsguaaAfcUfUf Afacuucaausgsa	1888	VPusCfsaudTg(Agn)ag uuaaGfuUfuacggsasa	2200	UUCCGUAAACUU AACUUCAAUGG	2556
AD-1784206.1	gsusgcugAfcUfUf Cfacuaacuusesa	1890	VPusGfsaadGu(Tgn)ag ugaaGfuCfagcacsusc	2201	GAGUGCUGACUU CACUAACUUCG	2557

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1784207.1	asasgcuuCfcUfUfCfaaauaagasusa	1891	VPusAfsucuUfauuugaaGfgAfagcuususg	2202	CAAAGCUUCCUUCAAAUAAGAUG	2558
AD-1784208.1	asasgcuuCfcUfUfCfaaauaagasusa	1891	VPusAfsucdTu(Agn)uuugaaGfgAfagcuususg	2203	CAAAGCUUCCUUCAAAUAAGAUG	2558
AD-1784209.1	asasauucCfgUfAfAfacuuaacususa	1892	VPusAfsaguUfaaguuuaCfgGfaauuuscsa	2204	UGAAAUUCCGUAAACUUAACUUC	2559
AD-1784210.1	csusgucuGfuUfUfCfcuaugaucsasa	1893	VPusUfsgadTc(Agn)uaggaaAfcAfgacagsgsg	2205	CCCUGUCUGUUUCCUAUGAUCAA	2560
AD-1784211.1	gsusauccAfaAfUfAfaugaaucususa	1894	VPusAfsagaUfucauuauUfuGfgauacsasg	2206	CUGUAUCCAAAUAAUGAAUCUUC	2561
AD-1784212.1	gsusauccAfaAfUfAfaugaaucususa	1894	VPusAfsagdAu(Tgn)cauuauUfuGfgauacsasg	2207	CUGUAUCCAAAUAAUGAAUCUUC	2561
AD-1784213.1	csusgacuUfcAfCfUfaacuucgasusa	1895	VPusAfsucgAfaguuaguGfaAfgucagscsa	2208	UGCUGACUUCACUAACUUCGAUC	2562
AD-1784214.1	gscsuuccUfuCfAfAfauaagaugsgsa	1896	VPusCfscauCfuuauuugAfaGfgaagcsusu	2209	AAGCUUCCUUCAAAUAAGAUGGU	2563
AD-1784215.1	gscsuuccUfuCfAfAfauaagaugsgsa	1896	VPusCfscadTc(Tgn)uauuugAfaGfgaagcsusu	2210	AAGCUUCCUUCAAAUAAGAUGGU	2563
AD-1784216.1	asasaucaAfaGfCfUfuccuucaasasa	1897	VPusUfsuudGa(Agn)ggaagcUfuUfgauuusgsc	2211	GCAAAUCAAAGCUUCCUUCAAAU	2564
AD-1784217.1	asgscuucCfuUfCfAfaauaagausgsa	1898	VPusCfsaucUfuauuugaAfgGfaagcususu	2212	AAAGCUUCCUUCAAAUAAGAUGG	2565
AD-1784218.1	usgscugcUfuUfUfAfAfaaacauagsgsa	1899	VPusCfscuaUfguuuuaaAfaGfcagcasusu	2213	AAUGCUGCUUUUAAAACAUAGGA	2566
AD-1784219.1	asgsgcaaAfuCfAfAfAfagcuuccususa	1900	VPusAfsaggAfagcuuugAfuUfugccusgsu	2214	ACAGGCAAAUCAAAGCUUCCUUC	2567
AD-1784220.1	asgsgcaaAfuCfAfAfAfagcuuccususa	1900	VPusAfsagdGa(Agn)gcuuugAfuUfugccusgsu	2215	ACAGGCAAAUCAAAGCUUCCUUC	2567
AD-1784221.1	gsgscaaaUfcAfAfAfAfgcuuccuuscsa	1901	VPusGfsaadGg(Agn)agcuuuGfaUfuugccsusg	2216	CAGGCAAAUCAAAGCUUCCUUCA	2568
AD-1784222.1	asasagcuUfcCfUfUfUfcaaauaagsasa	1902	VPusUfscuuAfuuugaagGfaAfgcuuusgsa	2217	UCAAAGCUUCCUUCAAAUAAGAU	2569
AD-1784223.1	asasagcuUfcCfUfUfUfcaaauaagsasa	1902	VPusUfscudTa(Tgn)uugaagGfaAfgcuuusgsa	2218	UCAAAGCUUCCUUCAAAUAAGAU	2569
AD-1784224.1	usasaaauGfcUfGfCfuuuuaaaascsa	1903	VPusGfsuuuUfaaaagcaGfcAfuuuuasgsu	2219	ACUAAAAUGCUGCUUUUAAAACA	2570
AD-1784225.1	asasgaauAfaAfGfUfaccuugacsusa	1904	VPusAfsgudCa(Agn)gguacuUfuAfuucuusasu	2220	AUAAGAAUAAAGUACCUUGACUU	2571
AD-1784226.1	asgsaauaAfaGfUfAfccuugacususa	1905	VPusAfsaguCfaagguacUfuUfauucususa	2221	UAAGAAUAAAGUACCUUGACUUU	2572
AD-1784227.1	asgsaauaAfaGfUfAfccuugacususa	1905	VPusAfsagdTc(Agn)agguacUfuUfauucususa	2222	UAAGAAUAAAGUACCUUGACUUU	2572
AD-1784228.1	gsuscuguUfuCfCfUfaugaucaasgsa	1906	VPusCfsuudGa(Tgn)cauaggAfaAfcagacsasg	2223	CUGUCUGUUUCCUAUGAUCAAGC	2573
AD-1784229.1	uscscguaAfaCfUfUfUfaacuucaasusa	1907	VPusAfsuudGa(Agn)guuaagUfuUfacggasasu	2224	AUUCCGUAAACUUAACUUCAAUG	2574

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1784230.1	csesucuuCfuGfGfAfaugugugasesa	1908	VPusGfsucdAc(Agn)cauuccAfgAfagaggsasg	2225	CUCCUCUUCUGGAAUGUGUGACC	2575
AD-1784231.1	usasuccaAfaUfAfAfugaaucuuscsa	1909	VPusGfsaadGa(Tgn)ucauuaUfuUfggauascsa	2226	UGUAUCCAAAUAAUGAAUCUUCG	2576
AD-1784232.1	usesuguuUfcCfUfAfugaucaagscsa	1910	VPusGfscudTg(Agn)ucauagGfaAfacagascsa	2227	UGUCUGUUUCCUAUGAUCAAGCA	2577
AD-1784233.1	gsusugacAfuCfGfAfcacucauascsa	1911	VPusGfsuadTg(Agn)gugucgAfuGfucaacsasg	2228	CUGUUGACAUCGACACUCAUACA	2578
AD-1784234.1	asasguacCfuUfGfAfcuuuguucsasa	1912	VPusUfsgaaCfaaagucaAfgGfuacuususa	2229	UAAAGUACCUUGACUUUGUUCAC	2579
AD-1784235.1	asasguacCfuUfGfAfcuuuguucsasa	1912	VPusUfsgadAc(Agn)aagucaAfgGfuacuususa	2230	UAAAGUACCUUGACUUUGUUCAC	2579
AD-1784236.1	csasgaucUfaCfCfUfuggugauususa	1913	VPusAfsaadTc(Agn)ccaaggUfaGfaucugsusg	2231	CACAGAUCUACCUUGGUGAUUUG	2580
AD-1784237.1	csusggauUfgUfGfCfucaaggaasesa	1914	VPusGfsuudCc(Tgn)ugagcaCfaAfuccagsgsu	2232	ACCUGGAUUGUGCUCAAGGAACC	2581
AD-1784238.1	usgscuuuUfaAfAfAfcauaggaasasa	1915	VPusUfsuudCc(Tgn)auguuuUfaAfaagcasgsc	2233	GCUGCUUUUAAAACAUAGGAAAG	2582
AD-1784239.1	usgscugaCfuUfCfAfcuaacuucsgsa	1916	VPusCfsgaaGfuuaugugaAfgUfcagcascsu	2234	AGUGCUGACUUCACUAACUUCGA	2583
AD-1784240.1	usgscugaCfuUfCfAfcuaacuucsgsa	1916	VPusCfsgadAg(Tgn)uagugaAfgUfcagcascsu	2235	AGUGCUGACUUCACUAACUUCGA	2583
AD-1784241.1	gsasaauuCfcGfUfAfaacuuaacsusa	1917	VPusAfsguuAfaguuuacGfgAfauuucsasa	2236	UUGAAAUUCCGUAAACUUAACUU	2584
AD-1784242.1	gsasaauuCfcGfUfAfaacuuaacsusa	1917	VPusAfsgudTa(Agn)guuuacGfgAfauuucsasa	2237	UUGAAAUUCCGUAAACUUAACUU	2584
AD-1784243.1	usasaggcAfaAfUfCfagguaaaasusa	1918	VPusAfsuuuUfaccugauUfuGfccuuasasc	2238	GUUAAGGCAAAUCAGGUAAAAUA	2585
AD-1784244.1	usasaggcAfaAfUfCfagguaaaasusa	1918	VPusAfsuudTu(Agn)ccugauUfuGfccuuasasc	2239	GUUAAGGCAAAUCAGGUAAAAUA	2585
AD-1784245.1	gsusucuaGfgUfAfUfuuuuuugasasa	1919	VPusUfsucaAfaaaaauaCfcUfagaacsgsg	2240	CCGUUCUAGGUAUUUUUUUGAAG	2586
AD-1784246.1	asasgauaAfaUfUfGfagcuaguusasa	1920	VPusUfsaadCu(Agn)gcucaaUfuUfaucuusgsu	2241	ACAAGAUAAAUUGAGCUAGUUAA	2587
AD-1784247.1	ususagcuAfaGfCfAfcagaucuascsa	1921	VPusGfsuadGa(Tgn)cugugcUfuAfgcuaasasg	2242	CUUUAGCUAAGCACAGAUCUACC	2588
AD-1784248.1	csusucacUfaAfCfUfucgauccuscsa	1922	VPusGfsagdGa(Tgn)cgaaguUfaGfugaagsusc	2243	GACUUCACUAACUUCGAUCCUCG	2589
AD-1784249.1	asasuuccGfuAfAfAfcuuaacuuscsa	1923	VPusGfsaadGu(Tgn)aaguuuAfcGfgaauususc	2244	GAAAUUCCGUAAACUUAACUUCA	2590
AD-1784250.1	csusgcuuUfuAfAfAfacauaggasasa	1924	VPusUfsucdCu(Agn)uguuuuAfaAfagcagscsa	2245	UGCUGCUUUUAAAACAUAGGAAA	2591
AD-1784251.1	csusguugAfcAfUfCfgacacucasusa	1925	VPusAfsugdAg(Tgn)gucgauGfuCfaacagsgsg	2246	CCCUGUUGACAUCGACACUCAUA	2592
AD-1784252.1	ususcacuAfaCfUfUfucgauccucsgsa	1926	VPusCfsgadGg(Agn)ucgaagUfuAfgugaasgsu	2247	ACUUCACUAACUUCGAUCCUCGU	2593

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1784253.1	gscsuaagCfaCfAfGfaucuaccususa	1927	VPusAfsagdGu(Agn)gaucugUfgCfuuagcsusa	2248	UAGCUAAGCACAGAUCUACCUUG	2594
AD-1784254.1	usasaaguAfcCfUfUfgacuuugususa	1928	VPusAfsacaAfagucaagGfuAfcuuuasusu	2249	AAUAAAGUACCUUGACUUUGUUC	2595
AD-1784255.1	asasaaugCfuGfCfUfuuuaaaacsasa	1929	VPusUfsgudTu(Tgn)aaaagcAfgCfauuuusasg	2250	CUAAAAUGCUGCUUUUAAAACAU	2596
AD-1784256.1	gscsugcuUfuUfAfAfaacauaggsasa	1930	VPusUfsccuAfuguuuuaAfaAfgcagcsasu	2251	AUGCUGCUUUUAAAACAUAGGAA	2597
AD-1784257.1	gscsugcuUfuUfAfAfaacauaggsasa	1930	VPusUfsccdTa(Tgn)guuuuaAfaAfgcagcsasu	2252	AUGCUGCUUUUAAAACAUAGGAA	2597
AD-1784258.1	uscsaugaUfuCfUfAfuguaaugusasa	1931	VPusUfsacaUfuacauagAfaUfcaugascsu	2253	AGUCAUGAUUCUAUGUAAUGUAA	2598
AD-1784259.1	uscsaugaUfuCfUfAfuguaaugusasa	1931	VPusUfsacdAu(Tgn)acauagAfaUfcaugascsu	2254	AGUCAUGAUUCUAUGUAAUGUAA	2598
AD-1784260.1	asgsugcuGfaCfUfUfucacuaacususa	1932	VPusAfsaguUfagugaagUfcAfgcacuscsu	2255	AGAGUGCUGACUUCACUAACUUC	2599
AD-1784261.1	csusaagcAfcAfGfAfucuaccuusgsa	1933	VPusCfsaadGg(Tgn)agaucuGfuGfcuuagcsesu	2256	AGCUAAGCACAGAUCUACCUUGG	2600
AD-1784262.1	csascuaaCfuUfCfGfauccucgusgsa	1934	VPusCfsacgAfggaucgaAfgUfuagugsasa	2257	UUCACUAACUUCGAUCCUCGUGG	2601
AD-1784263.1	csusgaagAfaCfAfAfgfgcaaaucasasa	1935	VPusUfsugdAu(Tgn)uggcugUfuCfuucagsusg	2258	CACUGAAGAACAGGCAAAUCAAA	2602
AD-1784264.1	asasaguaCfcUfUfGfacuuuguuscsa	1936	VPusGfsaacAfaagucaaGfgUfacuuusasu	2259	AUAAAGUACCUUGACUUUGUUCA	2603
AD-1784265.1	gscsuuugUfuUfAfAfufgguaguagsusa	1937	VPusAfscudAc(Tgn)accauaAfaCfaaagcsasc	2260	GUGCUUUGUUUAUGGUAGUAGUU	2604
AD-1784266.1	csasugauUfcUfAfUfguaauguasasa	1938	VPusUfsuadCa(Tgn)uacauaGfaAfucaugsasc	2261	GUCAUGAUUCUAUGUAAUGUAAA	2605
AD-1784267.1	csgsuucuAfgGfUfAfuuuuuuugsasa	1939	VPusUfscaaAfaaaauacCfuAfgaacgsgsc	2262	GCCGUUCUAGGUAUUUUUUUGAA	2606
AD-1784268.1	ususcuagGfuAfUfUfuuuuugaasgsa	1940	VPusCfsuucAfaaaaaauAfcCfuagaasesg	2263	CGUUCUAGGUAUUUUUUGAAGG	2607
AD-1784269.1	uscscuucCfuGfAfAfufccuuggasusa	1941	VPusAfsuccAfaggauucAfgGfaaggasgsg	2264	CCUCCUUCCUGAAUCCUUGGAUU	2608
AD-1784270.1	uscscuucCfuGfAfAfufccuuggasusa	1941	VPusAfsucdCa(Agn)ggauucAfgGfaaggasgsg	2265	CCUCCUUCCUGAAUCCUUGGAUU	2608
AD-1784271.1	gsascuaaAfaUfGfCfugcuuuuasasa	1942	VPusUfsuaaAfagcagcaUfuUfuagucsasa	2266	UUGACUAAAAAUGCUGCUUUUAAA	2609
AD-1784272.1	gsascuaaAfaUfGfCfugcuuuuasasa	1942	VPusUfsuadAa(Agn)gcagcaUfuUfuagucsasa	2267	UUGACUAAAAAUGCUGCUUUUAAA	2609
AD-1784273.1	asascaggCfaAfAfUfcaaagcuuscsa	1943	VPusGfsaadGc(Tgn)uugauuUfgCfcuguuscsu	2268	AGAACAGGCAAAUCAAAGCUUCC	2610
AD-1784274.1	csesuuccUfgAfAfUfcccuuggaususa	1944	VPusAfsaucCfaaggauuCfaGfgaaggsasg	2269	CUCCUUCCUGAAUCCUUGGAUUA	2611
AD-1784275.1	usgsaugaCfuCfUfCfaggacaaasgsa	1945	VPusCfsuudTg(Tgn)ccugagAfgUfcaucasasa	2270	UUUGAUGACUCUCAGGACAAAGC	2612

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1784276.1	usgsgaguUfuGfAfUfgacucucasgsa	1946	VPusCfsugdAg(Agn)gucaucAfaAfcuccascsg	2271	CGUGGAGUUUGAUGACUCUCAGG	2613
AD-1784277.1	asusccaaAfuAfAfUfgaaucuucsgsa	1947	VPusCfsgaaGfauucauuAfuUfuggausasc	2272	GUAUCCAAAUAAUGAAUCUUCGG	2614
AD-1784278.1	asusccaaAfuAfAfUfgaaucuucsgsa	1947	VPusCfsgadAg(Agn)ucauuAfuUfuggausasc	2273	GUAUCCAAAUAAUGAAUCUUCGG	2614
AD-1784279.1	ususgacuUfuGfUfUfcacagcausgsa	1948	VPusCfsaudGc(Tgn)ggaacAfaAfgucaasgsg	2274	CCUUGACUUUGUUCACAGCAUGU	2615
AD-1784280.1	asgsaucuAfcCfUfUfggugauuusgsa	1949	VPusCfsaaaUfcaccaagGfuAfgaucusgsu	2275	ACAGAUCUACCUUGGUGAUUUGG	2616
AD-1784281.1	asusgguaGfuAfGfUfuuuucugusasa	1950	VPusUfsacaGfaaaaacuAfcUfaccausasa	2276	UUAUGGUAGUAGUUUUUCUGUAA	2617
AD-1784282.1	asusgguaGfuAfGfUfuuuucugusasa	1950	VPusUfsacdAg(Agn)aaaacuAfcUfaccausasa	2277	UUAUGGUAGUAGUUUUUCUGUAA	2617
AD-1784283.1	cscsuugaCfuUfUfGfuucacagcsasa	1951	VPusUfsgcdTg(Tgn)gaacaaAfgUfcaaggsusa	2278	UACCUUGACUUUGUUCACAGCAU	2618
AD-1784284.1	cscsuggaUfuGfUfGfcucaaggasasa	1952	VPusUfsucdCu(Tgn)ggcacAfaUfccaggsusc	2279	GACCUGGAUUGUGCUCAAGGAAC	2619
AD-1784285.1	gsasgcuaGfuUfAfAfgcaaaucsasa	1953	VPusUfsgadTu(Tgn)gccuuaAfcUfagcucsasa	2280	UUGAGCUAGUUAAGGCAAAUCAG	2620
AD-1784286.1	ascsugaaGfaAfCfAfggcaaaucsasa	1954	VPusUfsgadTu(Tgn)gccuguUfcUfucagusgsg	2281	CCACUGAAGAACAGGCAAAUCAA	2621
AD-1784287.1	usgsaagaAfcAfGfGfcaaaucaasasa	1955	VPusUfsuudGa(Tgn)uugccuGfuUfcuucasgsu	2282	ACUGAAGAACAGGCAAAUCAAAG	2622
AD-1784288.1	csusccucUfuCfUfGfgaaugugusgsa	1956	VPusCfsacaCfauuccagAfaGfaggagsgsg	2283	CCCUCCUCUUCUGGAAUGUGUGA	2623
AD-1784289.1	csusccucUfuCfUfGfgaaugugusgsa	1956	VPusCfsacdAc(Agn)uuccagAfaGfaggagsgsg	2284	CCCUCCUCUUCUGGAAUGUGUGA	2623
AD-1784290.1	gscsuuucAfaCfGfUfggaguuugsasa	1957	VPusUfscaaAfcuccacgUfuGfaaagcsasu	2285	AUGCUUUCAACGUGGAGUUUGAU	2624
AD-1784291.1	usgscuuuCfaAfCfGfguggaguuusgsa	1958	VPusCfsaaaCfuccacguUfgAfaagcasusg	2286	CAUGCUUUCAACGUGGAGUUUGA	2625
AD-1784292.1	usgscuuuCfaAfCfGfguggaguuusgsa	1958	VPusCfsaadAc(Tgn)ccacguUfgAfaagcasusg	2287	CAUGCUUUCAACGUGGAGUUUGA	2625
AD-1784293.1	csasgguaAfaAfUfAfgucaugaususa	1959	VPusAfsaudCa(Tgn)gacuauUfuUfaccugsasu	2288	AUCAGGUAAAAUAGUCAUGAUUC	2626
AD-1784294.1	csusguauCfcAfAfAfuaaugaauscsa	1960	VPusGfsaudTc(Agn)uuauuuGfgAfuacagsasc	2289	GUCUGUAUCCAAAUAAUGAAUCU	2627
AD-1784295.1	asasggcaAfaUfCfAfgguaaaausasa	1961	VPusUfsaudTu(Tgn)accugaUfuUfgccuusasa	2290	UUAAGGCAAAUCAGGUAAAAUAG	2628
AD-1784296.1	cscsuccuUfcCfUfGfaauccuugsgsa	1962	VPusCfscaaGfgauucagGfaAfggaggscsc	2291	GGCCUCCUUCCUGAAUCCUUGGA	2629
AD-1784297.1	ususccuuCfaAfAfUfaagauggusgsa	1963	VPusGfsacdCa(Tgn)cuuauuUfgAfaggaasgsc	2292	GCUUCCUUCAAAUAAGAUGGUCC	2630
AD-1784298.1	ususgaaaUfuCfCfGfuaaacuuasasa	1964	VPusUfsuadAg(Tgn)uuacggAfaUfuucaascsa	2293	UGUUGAAAUUCCGUAAACUUAAC	2631

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1784299.1	ascsacucAfuAfCf Afgccaaguasusa	1965	VPusAfsuadCu(Tgn)gg cuguAfuGfagugusesg	2294	CGACACUCAUAC AGCCAAGUAUG	2632
AD-1784300.1	gscsacagAfuCfUf Afccuuggugsasa	1966	VPusUfscacCfaagguag AfuCfugugcsusu	2295	AAGCACAGAUCU ACCUUGGUGAU	2633
AD-1784301.1	csusuucaAfcGfUf Gfgaguuugasusa	1967	VPusAfsucaAfacuccac GfuUfgaaagscsa	2296	UGCUUUCAACGU GGAGUUUGAUG	2634
AD-1784302.1	usasgcuaAfgCfAf Cfagaucuacscsa	1968	VPusGfsgudAg(Agn)u cugugCfuUfagcuasasa	2297	UUUAGCUAAGCA CAGAUCUACCU	2635
AD-1784303.1	ususgugaUfaCfAf Gfaguauauususa	1969	VPusAfsaauAfuacucug UfaUfcacaasesu	2298	AGUUGUGAUACA GAGUAUAUUUC	2636
AD-1784304.1	ascsucauAfcAfGf Cfcaaguaugsasa	1970	VPusUfscauAfcuuggcu GfuAfugagusgsu	2299	ACACUCAUACAG CCAAGUAUGAC	2637
AD-1784305.1	asgsuuaaGfgCfAf Afaucagguasasa	1971	VPusUfsuadCc(Tgn)ga uuugCfcUfuaacusasg	2300	CUAGUUAAGGCA AAUCAGGUAAA	2638
AD-1784306.1	gsusugugAfuAfCf Afgaguauaususa	1972	VPusAfsauaUfacucugu AfuCfacaacsusc	2301	GAGUUGUGAUAC AGAGUAUAUUU	2639
AD-1784307.1	gsusugugAfuAfCf Afgaguauaususa	1972	VPusAfsaudAu(Agn)c ucuguAfuCfacaacsusc	2302	GAGUUGUGAUAC AGAGUAUAUUU	2639
AD-1784308.1	usgsacauCfgAfCf Afcucauacasgsa	1973	VPusCfsuguAfugagugu CfgAfugucasasc	2303	GUUGACAUCGAC ACUCAUACAGC	2640
AD-1784309.1	asgsauaaAfuUfGf Afgcuaguuasasa	1974	VPusUfsuadAc(Tgn)ag cucaAfuUfuaucususg	2304	CAAGAUAAAUUG AGCUAGUUAAG	2641
AD-1784310.1	usasgguaUfuUfUf Ufuugaaggususa	1975	VPusAfsaccUfucaaaaa AfaUfaccuasgsa	2305	UCUAGGUAUUUU UUUGAAGGUUG	2642
AD-1784311.1	usasgguaUfuUfUf Ufuugaaggususa	1975	VPusAfsacdCu(Tgn)ca aaaaAfaUfaccuasgsa	2306	UCUAGGUAUUUU UUUGAAGGUUG	2642
AD-1784312.1	usgsgugcUfuUfGf Ufuuaugguasgsa	1976	VPusCfsuacCfauaaaca AfaGfcaccasasc	2307	GUUGGUGCUUUG UUUAUGGUAGU	2643
AD-1784313.1	usgsugauAfcAfGf Afguauauuuscsa	1977	VPusGfsaaaUfauacucu GfuAfucacasasc	2308	GUUGUGAUACAG AGUAUAUUUCC	2644
AD-1784314.1	uscsuucuGfgAfAf Ufgugugaccsusa	1978	VPusAfsggdTc(Agn)ca cauuCfcAfgaagasgsg	2309	CCUCUUCUGGAA UGUGUGACCUG	2645
AD-1784315.1	csusggccGfuUfCf Ufagguauuususa	1979	VPusAfsaaaUfaccuaga AfcGfgccagsusc	2310	GACUGGCCGUUC UAGGUAUUUUU	2646
AD-1784316.1	asuscaggUfaAfAf Afuagucaugsasa	1980	VPusUfscadTg(Agn)cu auuuUfaCfcugaususu	2311	AAAUCAGGUAAA AUAGUCAUGAU	2647
AD-1784317.1	ususccauUfaAfAf Afcaaagggcsasa	1981	VPusUfsgcdCc(Tgn)uu guuuUfaAfuggaasusc	2312	GAUUCCAUUAAA ACAAAGGGCAA	2648
AD-1784318.1	csasagagUfgCfUf Gfacuucacusasa	1982	VPusUfsagdTg(Agn)ag ucagCfaCfucuugscsc	2313	GGCAAGAGUGCU GACUUCACUAA	2649
AD-1784319.1	ususucaaCfgUfGf Gfaguuugausgsa	1983	VPusCfsaucAfaacucca CfgUfugaaasgsc	2314	GCUUUCAACGUG GAGUUUGAUGA	2650
AD-1784320.1	ususggugCfuUfUf Gfuuuauggusasa	1984	VPusUfsaccAfuaaacaa AfgCfaccaascsc	2315	GGUUGGUGCUUU GUUUAUGGUAG	2651
AD-1784321.1	ususggugCfuUfUf Gfuuuauggusasa	1984	VPusUfsacdCa(Tgn)aa acaaAfgCfaccaascsc	2316	GGUUGGUGCUUU GUUUAUGGUAG	2651

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1784322.1	csascucaUfaCfAfGfccaaguausgsa	1985	VPusCfsauaCfuuggcugUfaUfgagugsusc	2317	GACACUCAUACAGCCAAGUAUGA	2652
AD-1784323.1	asusaaagUfaCfCfUfugacuuugsusa	1986	VPusAfscaaAfgucaaggUfaCfuuuaususc	2318	GAAUAAAGUACCUUGACUUUGUU	2653
AD-1784324.1	asusgacuUfuUfGfAfauuacagasgsa	1987	VPusCfsucdTg(Tgn)aauucaAfaAfgucaususa	2319	UAAUGACUUUUGAAUUACAGAGA	2654
AD-1784325.1	gsuscaugAfuUfCfUfauguaaugsusa	1988	VPusAfscauUfacauagaAfuCfaugacsusa	2320	UAGUCAUGAUUCUAUGUAAUGUA	2655
AD-1784326.1	gsasccugGfaUfUfGfugcucaagsgsa	1989	VPusCfscudTg(Agn)gcacaaUfcCfaggucsasc	2321	GUGACCUGGAUUGUGCUCAAGGA	2656
AD-1784327.1	gsascaucGfaCfAfCfucauacagscsa	1990	VPusGfscudGu(Agn)ugagugUfcGfaugucsasa	2322	UUGACAUCGACACUCAUACAGCC	2657
AD-1784328.1	gsasagaaCfaGfGfCfaaaucaaasgsa	1991	VPusCfsuudTg(Agn)uugccUfgUfucuucsasg	2323	CUGAAGAACAGGCAAAUCAAAGC	2658
AD-1784329.1	csgsuaaaCfuUfAfAfcuucaaugsgsa	1992	VPusCfscauUfgaaguuaAfgUfuuacgsgsa	2324	UCCGUAAACUUAACUUCAAUGGG	2659
AD-1784330.1	asgsguaaAfaUfAfGfucaugauuscsa	1993	VPusGfsaadTc(Agn)ugacuaUfuUfuaccusgsa	2325	UCAGGUAAAAUAGUCAUGAUUCU	2660
AD-1784331.1	gsusaccuUfgAfCfUfuuguucacsasa	1994	VPusUfsgudGa(Agn)caaaguCfaAfgguacsusu	2326	AAGUACCUUGACUUUGUUCACAG	2661
AD-1784332.1	cscsguucUfaGfGfUfauuuuuuusgsa	1995	VPusCfsaaaAfaaauaccUfaGfaacggscsc	2327	GGCCGUUCUAGGUAUUUUUUUGA	2662
AD-1784333.1	ususuaugGfuAfGfUfaguuuuucsusa	1996	VPusAfsgaaAfaacuacuAfcCfauaaascsa	2328	UGUUUAUGGUAGUAGUUUUUCUG	2663
AD-1784334.1	csgsuggaGfuUfUfGfaugacucusesa	1997	VPusGfsagdAg(Tgn)caucaaAfcUfccacgsusu	2329	AACGUGGAGUUUGAUGACUCUCA	2664
AD-1784335.1	ususcaacGfuGfGfAfguuugaugsasa	1998	VPusUfscadTc(Agn)aacuccAfcGfuugaasasg	2330	CUUUCAACGUGGAGUUUGAUGAC	2665
AD-1784336.1	gsasguugUfgAfUfAfcagaguausasa	1999	VPusUfsaudAc(Tgn)cuguauCfaCfaacucsusa	2331	UAGAGUUGUGAUACAGAGUAUAU	2666
AD-1784337.1	usascouuGfaCfUfUfufuguucacasgsa	2000	VPusCfsuguGfaacaaagUfcAfagguascsu	2332	AGUACCUUGACUUUGUUCACAGC	2667
AD-1784338.1	usascouuGfaCfUfUfufuguucacasgsa	2000	VPusCfsugdTg(Agn)acaaagUfcAfagguascsu	2333	AGUACCUUGACUUUGUUCACAGC	2667
AD-1784339.1	usasgaguUfgUfGfAfuacagagusasa	2001	VPusUfsacdTc(Tgn)guaucaCfaAfcucuasasu	2334	AUUAGAGUUGUGAUACAGAGUAU	2668
AD-1784340.1	usgsagugCfaAfAfUfccauagcascsa	2002	VPusGfsugdCu(Agn)uggauuUfgCfacucasasc	2335	GUUGAGUGCAAAUCCAUAGCACA	2669
AD-1784341.1	csasaaucAfgGfUfAfaaauagucsasa	2003	VPusUfsgadCu(Agn)uuuuacCfuGfauuugscsc	2336	GGCAAAUCAGGUAAAAUAGUCAU	2670
AD-1784342.1	asasgcacAfgAfUfCfuaccuuggsusa	2004	VPusAfsccaAfgguagauCfuGfugcuusasg	2337	CUAAGCACAGAUCUACCUUGGUG	2671
AD-1784343.1	ascsuuugUfuCfAfCfagcauguasgsa	2005	VPusCfsuacAfugcugugAfaCfaaaguscsa	2338	UGACUUUGUUCACAGCAUGUAGG	2672
AD-1784344.1	usgsgccgUfuCfUfUfAfgguauuuususa	2006	VPusAfsaaaAfuaccuagAfaCfggccasgsu	2339	ACUGGCCGUUCUAGGUAUUUUUU	2673

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1784345.1	gscscaagUfaUfGfAfccccuuccesusa	2007	VPusAfsggdGa(Agn)ggucaUfaCfuuggcsusg	2340	CAGCCAAGUAUGACCCUUCCCUG	2674
AD-1784346.1	usasugguAfgUfAfGfuuuuuucugsusa	2008	VPusAfscagAfaaaacuaCfuAfccauasasa	2341	UUUAUGGUAGUAGUUUUUCUGUA	2675
AD-1784347.1	asasuugaGfcUfAfGfuuaaggcasasa	2009	VPusUfsugdCc(Tgn)uaacuaGfcUfcaauususa	2342	UAAAUUGAGCUAGUUAAGGCAAA	2676
AD-1784348.1	ascsuaaaAfuGfCfUfgcuuuuaasasa	2010	VPusUfsuuaAfaagcagcAfuUfuuagcscsa	2343	UGACUAAAAUGCUGCUUUUAAAA	2677
AD-1784349.1	ascsuucaCfuUfGfGfuucacuggsasa	2011	VPusUfsccdAg(Tgn)gaaccaAfgUfgaagususc	2344	GAACUUCACUUGGUUCACUGGAA	2678
AD-1784350.1	uscsuaggUfaUfUfUfuuuugaagsgsa	2012	VPusCfscuuCfaaaaaaaUfaCfcuagasasc	2345	GUUCUAGGUAUUUUUUUGAAGGU	2679
AD-1784351.1	asgscacaGfaUfCfUfaccuuggusgsa	2013	VPusCfsaccAfagguagaUfcUfgugcususa	2346	UAAGCACAGAUCUACCUUGGUGA	2680
AD-1784352.1	gscscguuCfuAfGfGfuauuuuuususa	2014	VPusAfsaaaAfaauaccuAfgAfacggcscsa	2347	UGGCCGUUCUAGGUAUUUUUUUG	2681
AD-1784353.1	csusaaaaUfgCfUfGfcuuuuaaasasa	2015	VPusUfsuuuAfaaagcagCfaUfuuuagsusc	2348	GACUAAAAUGCUGCUUUUAAAAC	2682
AD-1784354.1	gsasacagGfcAfAfAfucaaagcususa	2016	VPusAfsagdCu(Tgn)ugauuuGfcCfuguucsusu	2349	AAGAACAGGCAAAUCAAAGCUUC	2683
AD-1784355.1	usgscuuuGfuUfUfUfAfugguaguasgsa	2017	VPusCfsuacUfaccauaaAfcAfaagcascsc	2350	GGUGCUUUGUUUAUGGUAGUAGU	2684
AD-1784356.1	asasuuagAfgUfUfGfGfugauacagsasa	2018	VPusUfscudGu(Agn)ucacaaCfuCfuaauusasu	2351	AUAAUUAGAGUUGUGAUACAGAG	2685
AD-1784357.1	csusgguuGfgUfGfCfCfuuuguuuasusa	2019	VPusAfsuaaAfcaaagcaCfcAfaccagcsgsc	2352	GGCUGGUUGGUGCUUUGUUUAUG	2686
AD-1784358.1	uscscuucAfaAfUfAfAfagauggucscsa	2020	VPusGfsgadCc(Agn)ucuuauUfuGfaaggasasg	2353	CUUCCUUCAAAUAAGAUGGUCCC	2687
AD-1784359.1	gscscuccUfuCfCfUfGfaauccuusgsa	2021	VPusCfsaadGg(Agn)uucaggAfaGfgaggcscsa	2354	UGGCCUCCUUCCUGAAUCCUUGG	2688
AD-1784360.1	gsasuucuAfuGfUfAfAfauguaaacscsa	2022	VPusGfsgudTu(Agn)cauuacAfuAfgaaucsasu	2355	AUGAUUCUAUGUAAUGUAAACCA	2689
AD-1784361.1	usgsguugGfuGfCfUfufuguuuausgsa	2023	VPusCfsauaAfacaaagcAfcCfaaccasgsc	2356	GCUGGUUGGUGCUUUGUUUAUGG	2690
AD-1784362.1	csuscauaCfaGfCfCfCfaaguaugascsa	2024	VPusGfsucaUfacuuggcUfgUfaugagsusg	2357	CACUCAUACAGCCAAGUAUGACC	2691
AD-1784363.1	csuscauaCfaGfCfCfCfaaguaugascsa	2024	VPusGfsucdAu(Agn)ccuuggcUfgUfaugagsusg	2358	CACUCAUACAGCCAAGUAUGACC	2691
AD-1784364.1	asuscgacAfcUfCfAfuacagccasasa	2025	VPusUfsugdGc(Tgn)guaugaGfuGfucgausgsu	2359	ACAUCGACACUCAUACAGCCAAG	2692
AD-1784365.1	gscsacugGfcAfUfAfaggacuucscsa	2026	VPusGfsgadAg(Tgn)ccuuauGfcCfagugcsusc	2360	GAGCACUGGCAUAAGGACUUCCC	2693
AD-1784366.1	asascgugGfaGfUfUfufugaugacuscsa	2027	VPusGfsagdTc(Agn)ucaaacUfcCfacguusgsa	2361	UCAACGUGGAGUUUGAUGACUCU	2694
AD-1784367.1	gscsaaauCfaGfGfUfufaaaauaguscsa	2028	VPusGfsacuAfuuuuaccUfgAfuuugcscsu	2362	AGGCAAAUCAGGUAAAAUAGUCA	2695

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1784368.1	gscsaaauCfaGfGf Ufaaaauaguscsa	2028	VPusGfsacdTa(Tgn)uu uaccUfgAfuuugcscsu	2363	AGGCAAAUCAGG UAAAAUAGUCA	2695
AD-1784369.1	csusucagAfaAfGf Ufuguugaugsusa	2029	VPusAfscauCfaacaacu UfuCfugaagsgsc	2364	GCCUUCAGAAAG UUGUUGAUGUG	2696
AD-1784370.1	csusucagAfaAfGf Ufuguugaugsusa	2029	VPusAfscadTc(Agn)ac aacuUfuCfugaagsgsc	2365	GCCUUCAGAAAG UUGUUGAUGUG	2696
AD-1784371.1	asasaucaGfgUfAf Afaauagucasusa	2030	VPusAfsugdAc(Tgn)au uuuaCfcUfgauuusgsc	2366	GCAAAUCAGGUA AAAUAGUCAUG	2697
AD-1784372.1	asgsgcaaAfuCfAf Gfguaaaauasgsa	2031	VPusCfsuauUfuuaccug AfuUfugccususa	2367	UAAGGCAAAUCA GGUAAAAUAGU	2698
AD-1784373.1	gsgsgcaaGfaGfUf Gfcugacuucsasa	2032	VPusUfsgadAg(Tgn)ca gcacUfcUfugcccsusu	2368	AAGGGCAAGAGU GCUGACUUCAC	2699
AD-1784375.1	gsgsccguUfcUfAf Gfguauuuuususa	2033	VPusAfsaaaAfauaccua GfaAfcggccsasg	2369	CUGGCCGUUCUA GGUAUUUUUUU	2700
AD-1784377.1	csgsggccUfuCfAf Gfaaaguugususa	2034	VPusAfsacaAfcuuucug AfaGfgcccgsgsu	2370	ACCGGGCCUUCA GAAAGUUGUUG	2701
AD-1784378.1	gsgscaaaUfcAfGf Gfuaaaauagsusa	2035	VPusAfscuaUfuuuaccu GfaUfuugccsusu	2371	AAGGCAAAUCAG GUAAAAUAGUC	2702
AD-1784379.1	gsasggauCfcUfCf Afacaaugguscsa	2036	VPusGfsaccAfuuguuga GfgAfuccucsasg	2372	CUGAGGAUCCUC AACAAUGGUCA	2703
AD-1784380.1	gsasggauCfcUfCf Afacaaugguscsa	2036	VPusGfsacdCa(Tgn)ug uugaGfgAfuccucsasg	2373	CUGAGGAUCCUC AACAAUGGUCA	2703
AD-1784381.1	ususcacuUfgGfUf Ufcacuggaasesa	2037	VPusGfsuudCc(Agn)g ugaacCfaAfgugaasgsu	2374	ACUUCACUUGGU UCACUGGAACA	2704
AD-1784382.1	asgsaacuGfaUfGf Gfuggacaacsusa	2038	VPusAfsgudTg(Tgn)cc accaUfcAfguucususc	2375	GAAGAACUGAUG GUGGACAACUG	2705
AD-1784383.1	asasuaaaGfuAfCf Cfuugacuuusgsa	2039	VPusCfsaaaGfucaaggu AfcUfuuauusesu	2376	AGAAUAAAGUAC CUUGACUUUGU	2706
AD-1784384.1	asasuaaaGfuAfCf Cfuugacuuusgsa	2039	VPusCfsaadAg(Tgn)ca agguAfcUfuuauusesu	2377	AGAAUAAAGUAC CUUGACUUUGU	2706
AD-1784385.1	csusuuguUfcAfCf Afgcauguagsgsa	2040	VPusCfscuaCfaugcugu GfaAfcaaagsusc	2378	GACUUUGUUCAC AGCAUGUAGGG	2707
AD-1784386.1	csusuuguUfcAfCf Afgcauguagsgsa	2040	VPusCfscudAc(Agn)ug cuguGfaAfcaaagsusc	2379	GACUUUGUUCAC AGCAUGUAGGG	2707
AD-1784387.1	asasuaagAfaUfAf Afaguaccuusgsa	2041	VPusCfsaadGg(Tgn)ac uuuaUfuCfuuauususc	2380	GAAAUAAGAAUA AAGUACCUUGA	2708
AD-1784388.1	asgsuaguUfuUfUf Cfuguaacacsasa	2042	VPusUfsgudGu(Tgn)ac agaaAfaAfcuacusasc	2381	GUAGUAGUUUUU CUGUAACACAG	2709
AD-1784389.1	csesaaguAfuGfAf Cfccuucccusgsa	2043	VPusCfsaggGfaaggguc AfuAfcuuggscsu	2382	AGCCAAGUAUGA CCCUUCCCUGA	2710
AD-1784390.1	ususgaguGfcAfAf Afuccauagcsasa	2044	VPusUfsgcdTa(Tgn)gg auuuGfcAfcucaascsc	2383	GGUUGAGUGCAA AUCCAUAGCAC	2711
AD-1784391.1	gsgsccuuCfaGfAf Afaguuguugsasa	2045	VPusUfscaaCfaacuuuc UfgAfaggccscsg	2384	CGGGCCUUCAGA AAGUUGUUGAU	2712
AD-1784392.1	asgsgaucCfuCfAf Afcaauggucsasa	2046	VPusUfsgadCc(Agn)uu guugAfgGfauccuscsa	2385	UGAGGAUCCUCA ACAAUGGUCAU	2713

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1784393.1	asusuagaGfuUfGfUfgauacagasgsa	2047	VPusCfsucdTg(Tgn)aucacaAfcUfcuaaususa	2386	UAAUUAGAGUUGUGAUACAGAGU	2714
AD-1784394.1	csasacguGfgAfGfUfuugaugacsusa	2048	VPusAfsgudCa(Tgn)caaacuCfcAfcguugsasa	2387	UUCAACGUGGAGUUUGAUGACUC	2715
AD-1784395.1	gsascuuuUfgAfAfUfuacagagasusa	2049	VPusAfsucdTc(Tgn)guaauuCfaAfaagucsasu	2388	AUGACUUUUGAAUUACAGAGAUA	2716
AD-1784396.1	usgsaggaUfcCfUfCfaacaauggsusa	2050	VPusAfsccaUfuguugagGfaUfccucasgsg	2389	CCUGAGGAUCCUCAACAAUGGUC	2717
AD-1784397.1	gsasguuuGfaUfGfAfcucucaggsasa	2051	VPusUfsccdTg(Agn)gagucaUfcAfaacucscsa	2390	UGGAGUUUGAUGACUCUCAGGAC	2718
AD-1784398.1	ususuuaaAfaCfAfUfaggaaagusasa	2052	VPusUfsacdTu(Tgn)ccuaugUfuUfuaaaasgsc	2391	GCUUUUAAAACAUAGGAAAGUAG	2719
AD-1784399.1	ususauggUfaGfUfAfguuuuucusgsa	2053	VPusCfsagaAfaaacuacUfaCfcauaasasc	2392	GUUUAUGGUAGUAGUUUUUCUGU	2720
AD-1784400.1	asascuucAfcUfUfGfguucacugsgsa	2054	VPusCfscagUfgaaccaaGfuGfaaguuscsu	2393	AGAACUUCACUUGGUUCACUGGA	2721
AD-1784401.1	asasauugAfgCfUfAfguuaaggcsasa	2055	VPusUfsgcdCu(Tgn)aacuagCfuCfaauuusasu	2394	AUAAAUUGAGCUAGUUAAGGCAA	2722
AD-1784402.1	ususuguuUfaUfGfGfuaguaguususa	2056	VPusAfsaacUfacuaccaUfaAfacaaasgsc	2395	GCUUUGUUUAUGGUAGUAGUUUU	2723
AD-1784403.1	ususuguuUfaUfGfGfuaguaguususa	2056	VPusAfsaadCu(Agn)cuaccaUfaAfacaaasgsc	2396	GCUUUGUUUAUGGUAGUAGUUUU	2723
AD-1784404.1	asasgggcAfaGfAfGfugcugacususa	2057	VPusAfsagdTc(Agn)gcacucUfuGfcccuususg	2397	CAAAGGGCAAGAGUGCUGACUUC	2724
AD-1784405.1	gsgsaguuUfgAfUfGfacucucagsgsa	2058	VPusCfscugAfgagucauCfaAfacuccsasc	2398	GUGGAGUUUGAUGACUCUCAGGA	2725
AD-1784406.1	gsgsgccuUfcAfGfAfaaguuguusgsa	2059	VPusCfsaacAfacuuucuGfaAfggcccsgsg	2399	CCGGGCCUUCAGAAAGUUGUUGA	2726
AD-1784407.1	gscsaagaGfuGfCfUfgacuucacsusa	2060	VPusAfsgudGa(Agn)gucagcAfcUfcuugcscsc	2400	GGGCAAGAGUGCUGACUUCACUA	2727
AD-1784408.1	asgsccacUfgAfAfGfaacaggcasasa	2061	VPusUfsugdCc(Tgn)gucuuCfaGfuggcusgsa	2401	UCAGCCACUGAAGAACAGGCAAA	2728
AD-1784409.1	asusuccaUfuAfAfAfacaaagggscsa	2062	VPusGfscccUfuuguuuuAfaUfggaauscsc	2402	GGAUUCCAUUAAAACAAAGGGCA	2729
AD-1784410.1	asusuccaUfuAfAfAfacaaagggscsa	2062	VPusGfsccdCu(Tgn)uguuuuuAfaUfggaauscsc	2403	GGAUUCCAUUAAAACAAAGGGCA	2729
AD-1784411.1	gsusaguuUfuUfCfUfguaacacasgsa	2063	VPusCfsugdTg(Tgn)uacagaAfaAfacuacsusa	2404	UAGUAGUUUUUCUGUAACACAGA	2730
AD-1784412.1	gsgsuauuUfuUfUfUfgaagguugsgsa	2064	VPusCfscaaCfcuucaaaAfaAfauaccsusa	2405	UAGGUAUUUUUUUGAAGGUUGGC	2731
AD-1784413.1	uscscaaaUfaAfUfGfaaucuucgsgsa	2065	VPusCfscgaAfgauucauUfaUfuuggasusa	2406	UAUCCAAAUAAUGAAUCUUCGGG	2732
AD-1784414.1	asasacauAfgGfAfAfafaguagaausgsa	2066	VPusCfsaudTc(Tgn)acuuucCfuAfuguuususa	2407	UAAAACAUAGGAAAGUAGAAUGG	2733
AD-1784415.1	asusgacuCfuCfAfGfgacaaagcsasa	2067	VPusUfsgcdTu(Tgn)gucugAfgAfgucauscsa	2408	UGAUGACUCUCAGGACAAAGCAG	2734

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1784416.1	asgscuagUfuAfAfGfgcaaaucasgsa	2068	VPusCfsugaUfuugccuuAfaCfuagcusesa	2409	UGAGCUAGUUAAGGCAAAUCAGG	2735
AD-1784417.1	cscsugagGfaUfCfCfucaacaausgsa	2069	VPusCfsaudTg(Tgn)uggaggaUfcCfucaggsgsa	2410	UCCCUGAGGAUCCUCAACAAUGG	2736
AD-1784418.1	gsgsuuggUfgCfUfUfuguuuaugsgsa	2070	VPusCfscauAfaacaaagCfaCfcaaccsasg	2411	CUGGUUGGUGCUUUGUUUAUGGU	2737
AD-1784419.1	asgsguauUfuUfUfUfufugaagguusgsa	2071	VPusCfsaacCfuucaaaaAfaAfuaccusasg	2412	CUAGGUAUUUUUUUGAAGGUUGG	2738
AD-1784420.1	usgsaaucUfuCfGfGfguguuuccsesa	2072	VPusGfsggaAfacacccgAfaGfauucasusu	2413	AAUGAAUCUUCGGGUGUUUCCCU	2739
AD-1784421.1	usgsaaucUfuCfGfGfguguuuccsesa	2072	VPusGfsggdAa(Agn)cacccgAfaGfauucasusu	2414	AAUGAAUCUUCGGGUGUUUCCCU	2739
AD-1784422.1	usasguagUfuUfUfUfufcuguaacascsa	2073	VPusGfsuguUfacagaaaAfaCfuacuasesc	2415	GGUAGUAGUUUUUCUGUAACACA	2740
AD-1784423.1	usasguagUfuUfUfUfufcuguaacascsa	2073	VPusGfsugdTu(Agn)cagaaaAfaCfuacuasesc	2416	GGUAGUAGUUUUUCUGUAACACA	2740
AD-1784424.1	gsusuugaUfgAfCfUfcucaggaesasa	2074	VPusUfsgudCc(Tgn)gagaguCfaUfcaaaesusc	2417	GAGUUUGAUGACUCUCAGGACAA	2741
AD-1784425.1	asasugaaUfcUfUfCfggguguuuscsa	2075	VPusGfsaadAc(Agn)cccgaaGfaUfucauusasu	2418	AUAAUGAAUCUUCGGGUGUUUCC	2742
AD-1784426.1	csasaauaAfuGfAfAfAfucuucgggsusa	2076	VPusAfscccGfaagauucAfuUfauuugsgsa	2419	UCCAAAUAAUGAAUCUUCGGGUG	2743
AD-1784427.1	ususuguuCfaCfAfGfcauguaggsgsa	2077	VPusCfsccuAfcaugcugUfgAfacaaasgsu	2420	ACUUUGUUCACAGCAUGUAGGGU	2744
AD-1784428.1	asusugugCfuCfAfAfAfggaaccesasusa	2078	VPusAfsugdGg(Tgn)uccuugAfgCfacaausesc	2421	GGAUUGUGCUCAAGGAACCCAUC	2745
AD-1784429.1	gsusugguGfcUfUfUfufguuuauggsusa	2079	VPusAfsccaUfaaacaaaGfcAfccaacsesa	2422	UGGUUGGUGCUUUGUUUAUGGUA	2746
AD-1784430.1	gsasaucuUfcGfGfGfGfuguuuccesusa	2080	VPusAfsgggAfaacacccGfaAfgauucsasu	2423	AUGAAUCUUCGGGUGUUUCCCUU	2747
AD-1784431.1	gsgsuaguAfgUfUfUfufuucuguaasesa	2081	VPusGfsuudAc(Agn)gaaaaaCfuAfcuacesasu	2424	AUGGUAGUAGUUUUUCUGUAACA	2748
AD-1784432.1	asgsaacaGfgCfAfAfAfaucaaagesusa	2082	VPusAfsgcuUfugauuugCfcUfguucususc	2425	GAAGAACAGGCAAAUCAAAGCUU	2749
AD-1784433.1	asgsaacaGfgCfAfAfAfaucaaagesusa	2082	VPusAfsgcdTu(Tgn)gauuugCfcUfguucususc	2426	GAAGAACAGGCAAAUCAAAGCUU	2749
AD-1784434.1	asasaauaGfuCfAfUfgauucuausgsa	2083	VPusCfsauaGfaaucaugAfcUfauuuusasc	2427	GUAAAAUAGUCAUGAUUCUAUGU	2750
AD-1784435.1	ascsuggcCfgUfUfCfuagguauususa	2084	VPusAfsaauAfccuagaaCfgGfccagusesc	2428	GGACUGGCCGUUCUAGGUAUUUU	2751
AD-1784436.1	cscscugaGfgAfUfCfcucaacaasusa	2085	VPusAfsuudGu(Tgn)ggaggauCfcUfcagggsasa	2429	UUCCCUGAGGAUCCUCAACAAUG	2752
AD-1784437.1	gscsugguUfgGfUfGfgcuuuguuusasa	2086	VPusUfsaaaCfaaagcacCfaAfccagcsesa	2430	UGGCUGGUUGGUGCUUUGUUUAU	2753
AD-1784438.1	csasgaaaGfuUfGfUfufugaugugcsusa	2087	VPusAfsgcdAc(Agn)ucaacaAfcUfuucugsasa	2431	UUCAGAAAGUUGUUGAUGUGCUG	2754

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1784439.1	ascsuaacUfuCfGfAfuccucgugsgsa	2088	VPusCfscacGfaggaucgAfaGfuuagusgsa	2432	UCACUAACUUCGAUCCUCGUGGC	2755
AD-1784440.1	cscsuucaGfaAfAfGfuuguugausgsa	2089	VPusCfsaucAfacaacuuUfcUfgaaggscsc	2433	GGCCUUCAGAAAGUUGUUGAUGU	2756
AD-1784441.1	usgsagcaCfuGfGfCfauaaggacsusa	2090	VPusAfsgudCc(Tgn)uaugccAfgUfgcucasgsg	2434	CCUGAGCACUGGCAUAAGGACUU	2757
AD-1784442.1	csusaguuAfaGfGfCfaaaucaggsusa	2091	VPusAfsccdTg(Agn)uugccUfuAfacuagscsu	2435	AGCUAGUUAAGGCAAAUCAGGUA	2758
AD-1784443.1	csusgaggAfuCfCfUfcaacaaugsgsa	2092	VPusCfscauUfguugaggAfuCfcucagsgsg	2436	CCCUGAGGAUCCUCAACAAUGGU	2759
AD-1784444.1	gsusuuauGfgUfAfGfuaguuuuuscsa	2093	VPusGfsaaaAfacuacuaCfcAfuaaacsasa	2437	UUGUUUAUGGUAGUAGUUUUUCU	2760
AD-1784445.1	usgsugacCfuGfGfAfuugugcucsasa	2094	VPusUfsgadGc(Agn)caauccAfgGfucacascsa	2438	UGUGUGACCUGGAUUGUGCUCAA	2761
AD-1784446.1	ascsaucgAfcAfCfUfcauacagcsesa	2095	VPusGfsgcdTg(Tgn)augaguGfuCfgaugusesa	2439	UGACAUCGACACUCAUACAGCCA	2762
AD-1784447.1	gsasuuguGfcUfCfAfaggaaccesasa	2096	VPusUfsggdGu(Tgn)ccuugaGfcAfcaaucsesa	2440	UGGAUUGUGCUCAAGGAACCCAU	2763
AD-1784448.1	uscsauacAfgCfCfAfaguaugacscsa	2097	VPusGfsgudCa(Tgn)acuuggCfuGfuaugasgsu	2441	ACUCAUACAGCCAAGUAUGACCC	2764
AD-1784449.1	usasaaauAfgUfCfAfugauucuasusa	2098	VPusAfsuagAfaucaugaCfuAfuuuuasesc	2442	GGUAAAAUAGUCAUGAUUCUAUG	2765
AD-1784450.1	usasaaauAfgUfCfAfugauucuasusa	2098	VPusAfsuadGa(Agn)ucaugaCfuAfuuuuasesc	2443	GGUAAAAUAGUCAUGAUUCUAUG	2765
AD-1784451.1	gsusgcucAfaGfGfAfacccaucasgsa	2099	VPusCfsugaUfggguuccUfuGfagcacsasa	2444	UUGUGCUCAAGGAACCCAUCAGC	2766
AD-1784452.1	csgsaagaAfcUfGfAfugguggacsasa	2100	VPusUfsgudCc(Agn)ccaucaGfuUfcuucgsgsg	2445	CCCGAAGAACUGAUGGUGGACAA	2767
AD-1784453.1	asasuaaaAfuGfUfGfaagacuagsasa	2101	VPusUfscudAg(Tgn)cuucacAfuUfuuauusasg	2446	CUAAUAAAAUGUGAAGACUAGAC	2768
AD-1784454.1	gsgscuggUfuGfGfUfgcuuuguususa	2102	VPusAfsaacAfaagcaccAfaCfcagccsasc	2447	GUGGCUGGUUGGUGCUUUGUUUA	2769
AD-1784455.1	ususguucAfcAfGfCfauguagggsusa	2103	VPusAfscccUfacaugcuGfuGfaacaasasg	2448	CUUUGUUCACAGCAUGUAGGGUG	2770
AD-1784456.1	ususcaaaUfaAfGfAfugugcccasusa	2104	VPusAfsugdGg(Agn)ccaucuUfaUfuugaasgsg	2449	CCUUCAAAUAAGAUGGUCCCAUA	2771
AD-1784457.1	ususuaaaAfcAfUfAfggaaaguasgsa	2105	VPusCfsuacUfuuccuauGfuUfuuaaasasg	2450	CUUUUAAAACAUAGGAAAGUAGA	2772
AD-1784458.1	ususguuuAfuGfGfUfaguaguuususa	2106	VPusAfsaaaCfuacuaccAfuAfaacaasasg	2451	CUUUGUUUAUGGUAGUAGUUUUU	2773
AD-1784459.1	ususguuuAfuGfGfUfaguaguuususa	2106	VPusAfsaadAc(Tgn)acuaccAfuAfaacaasasg	2452	CUUUGUUUAUGGUAGUAGUUUUU	2773
AD-1784460.1	gscsuaguUfaAfGfGfcaaaucagsgsa	2107	VPusCfscugAfuuugccuUfaAfcuagcsusc	2453	GAGCUAGUUAAGGCAAAUCAGGU	2774
AD-1784461.1	gsusaaaaUfaGfUfCfaugauucusasa	2108	VPusUfsagaAfucaugacUfaUfuuuacscsu	2454	AGGUAAAAUAGUCAUGAUUCUAU	2775

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1784462.1	gsusaaaaUfaGfUfCfaugauucusasa	2108	VPusUfsagdAa(Tgn)caugacUfaUfuuuacsesu	2455	AGGUAAAAUAGUCAUGAUUCUAU	2775
AD-1784463.1	gsascuggCfcGfUfUfcuagguaususa	2109	VPusAfsauaCfcuagaacGfgCfcagucscsa	2456	UGGACUGGCCGUUCUAGGUAUUU	2776
AD-1784464.1	uscsagccAfcUfGfAfagaacaggscsa	2110	VPusGfscccdTg(Tgn)ucuucaGfuGfgcugasgsc	2457	GCUCAGCCACUGAAGAACAGGCA	2777
AD-1784465.1	usgsgaauGfuGfUfGfaccuggaususa	2111	VPusAfsaudCc(Agn)ggucacAfcAfuuccasgsa	2458	UCUGGAAUGUGUGACCUGGAUUG	2778
AD-1784466.1	uscsacagCfaUfGfUfagggugausgsa	2112	VPusCfsaucAfcccuacaUfgCfugugasasc	2459	GUUCACAGCAUGUAGGGUGAUGA	2779
AD-1784467.1	usascagcCfaAfGfUfaugacccususa	2113	VPusAfsagdGg(Tgn)cauacuUfgGfcuguasusg	2460	CAUACAGCCAAGUAUGACCCUUC	2780
AD-1784468.1	csusgagcAfcUfGfGfcauaaggascsa	2114	VPusGfsuccUfuaugccaGfuGfcucagsgsu	2461	ACCUGAGCACUGGCAUAAGGACU	2781
AD-1784469.1	csusgagcAfcUfGfGfcauaaggascsa	2114	VPusGfsucdCu(Tgn)augccaGfuGfcucagsgsu	2462	ACCUGAGCACUGGCAUAAGGACU	2781
AD-1784470.1	gscsucaaGfgAfAfCfccaucagcsgsa	2115	VPusCfsgcdTg(Agn)uggguuCfcUfugagcsasc	2463	GUGCUCAAGGAACCCAUCAGCGU	2782
AD-1784471.1	ususcuggAfaUfGfUfgugaccugsgsa	2116	VPusCfscadGg(Tgn)cacacaUfuCfcagaasgsa	2464	UCUUCUGGAAUGUGUGACCUGGA	2783
AD-1784472.1	usasaauuGfaGfCfUfaguuaaggscsa	2117	VPusGfsccuUfaacuagcUfcAfauuuasusc	2465	GAUAAAUUGAGCUAGUUAAGGCA	2784
AD-1784473.1	usasuuuuUfuUfGfAfagguuggcsasa	2118	VPusUfsgcdCa(Agn)ccuucaAfaAfaaauascsc	2466	GGUAUUUUUUUGAAGGUUGGCAG	2785
AD-1784474.1	usasauuaGfaGfUfUfgugauacasgsa	2119	VPusCfsuguAfucacaacUfcUfaauuasusa	2467	UAUAAUUAGAGUUGUGAUACAGA	2786
AD-1784475.1	usasauuaGfaGfUfUfgugauacasgsa	2119	VPusCfsugdTa(Tgn)ccaacUfcUfaauuasusa	2468	UAUAAUUAGAGUUGUGAUACAGA	2786
AD-1784476.1	usgsacucUfcAfGfGfacaaagcasgsa	2120	VPusCfsugcUfuuguccuGfaGfagucasusc	2469	GAUGACUCUCAGGACAAAGCAGU	2787
AD-1784477.1	usgsacucUfcAfGfGfacaaagcasgsa	2120	VPusCfsugdCu(Tgn)uguccuGfaGfagucasusc	2470	GAUGACUCUCAGGACAAAGCAGU	2787
AD-1784478.1	csasuacaGfcCfAfAfguaugaccscsa	2121	VPusGfsggdTc(Agn)uacuugGfcUfguaugsasg	2471	CUCAUACAGCCAAGUAUGACCCU	2788
AD-1784479.1	gsusauuuUfuUfUfGfaagguuggcsa	2122	VPusGfsccaAfccuucaaAfaAfaauacscsu	2472	AGGUAUUUUUUUGAAGGUUGGCA	2789
AD-1784480.1	csascagcAfuGfUfAfgggugaugsasa	2123	VPusUfscadTc(Agn)ccuacAfuGfcugugsasa	2473	UUCACAGCAUGUAGGGUGAUGAG	2790
AD-1784481.1	usasuaauUfaGfAfGfuugugauascsa	2124	VPusGfsuadTc(Agn)caacucUfaAfuuauasasc	2474	GUUAUAAUUAGAGUUGUGAUACA	2791
AD-1784482.1	gsasuuuuGfgGfAfAfagcugugcsasa	2125	VPusUfsgcdAc(Agn)gcuuucCfcAfaaaucscsc	2475	GGGAUUUUGGGAAAGCUGUGCAG	2792
AD-1784483.1	usasaaacAfaAfGfGfgcaagagusgsa	2126	VPusCfsacdTc(Tgn)ugcccuUfuGfuuuuasasu	2476	AUUAAAACAAAGGGCAAGAGUGC	2793
AD-1784484.1	uscsaaggAfaCfCfCfcaucagcgusesa	2127	VPusGfsacgCfugauggguUfuCfcuugasgsc	2477	GCUCAAGGAACCCAUCAGCGUCA	2794

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1784485.1	uscsaaggAfaCfCfCfaucagcgcuscsa	2127	VPusGfsacdGc(Tgn)gaugggUfuCfcuugasgsc	2478	GCUCAAGGAACCCAUCAGCGUCA	2794
AD-1784486.1	uscsagaaAfgUfUfGfuugaugugscsa	2128	VPusGfscacAfucaacaaCfuUfucugasasg	2479	CUUCAGAAAGUUGUUGAUGUGCU	2795
AD-1784487.1	uscsagaaAfgUfUfGfuugaugugscsa	2128	VPusGfscadCa(Tgn)caacaaCfuUfucugasasg	2480	CUUCAGAAAGUUGUUGAUGUGCU	2795
AD-1784488.1	cscsaaauAfaUfGfAfaucuucggsgsa	2129	VPusCfsccgAfagauucaUfuAfuuuggsasu	2481	AUCCAAAUAAUGAAUCUUCGGGU	2796
AD-1784489.1	asgscaugUfaGfGfGfugaugagcsasa	2130	VPusUfsgcdTc(Agn)ucacccUfaCfaugcusgsu	2482	ACAGCAUGUAGGGUGAUGAGCAC	2797
AD-1784490.1	gsasuaaaUfuGfAfGfcuaguuaasgsa	2131	VPusCfsuuaAfcuagcucAfaUfuuaucsusu	2483	AAGAUAAAUUGAGCUAGUUAAGG	2798
AD-1784491.1	csuscagcCfaCfUfGfaagaacagsgsa	2132	VPusCfscugUfucuucagUfgGfcugagcsu	2484	AGCUCAGCCACUGAAGAACAGGC	2799
AD-1784492.1	csuscagcCfaCfUfGfaagaacagsgsa	2132	VPusCfscudGu(Tgn)cuucagUfgGfcugagcsu	2485	AGCUCAGCCACUGAAGAACAGGC	2799
AD-1784493.1	csasgcauGfuAfGfGfgugaugagcsca	2133	VPusGfscudCa(Tgn)cacccuAfcAfugcugsusg	2486	CACAGCAUGUAGGGUGAUGAGCA	2800
AD-1784494.1	asusaaugAfaUfCfUfucgggugususa	2134	VPusAfsacaCfccgaagaUfuCfauuaususu	2487	AAAUAAUGAAUCUUCGGGUGUUU	2801
AD-1784495.1	gsgsaacccCfaUfCfAfgcgucagcsasa	2135	VPusUfsgcdTg(Agn)cgcugaUfgGfguuccsusu	2488	AAGGAACCCAUCAGCGUCAGCAG	2802
AD-1784496.1	usgsuucaCfaGfCfAfuguagggusgsa	2136	VPusCfsaccCfuacaugcUfgUfgaacasasa	2489	UUUGUUCACAGCAUGUAGGGUGA	2803
AD-1784497.1	asasacaaAfgGfGfCfaagagugcsusa	2137	VPusAfsgcdAc(Tgn)cuugccCfuUfuguuususa	2490	UAAAACAAAGGGCAAGAGUGCUG	2804
AD-1784498.1	usgsugugAfcCfUfGfgauugugcsusa	2138	VPusAfsgcaCfaauccagGfuCfacacasusu	2491	AAUGUGUGACCUGGAUUGUGCUC	2805
AD-1784499.1	usgsugugAfcCfUfGfgauugugcsusa	2138	VPusAfsgcdAc(Agn)auccagGfuCfacacasusu	2492	AAUGUGUGACCUGGAUUGUGCUC	2805
AD-1784500.1	asasuaauGfaAfUfCfuucgggugsusa	2139	VPusAfscacCfcgaagauUfcAfuuauususg	2493	CAAAUAAUGAAUCUUCGGGUGUU	2806
AD-1784501.1	asusuuuuUfuGfAfAfgguuggcasgsa	2140	VPusCfsugcCfaaccuucAfaAfaaaausasc	2494	GUAUUUUUUUGAAGGUUGGCAGC	2807
AD-1784502.1	asusuuuuUfuGfAfAfgguuggcasgsa	2140	VPusCfsugdCc(Agn)accuucAfaAfaaaausasc	2495	GUAUUUUUUUGAAGGUUGGCAGC	2807
AD-1784503.1	usgscucaAfgGfAfAfcccaucagcsca	2141	VPusGfscudGa(Tgn)gggguucCfuUfgagcascsa	2496	UGUGCUCAAGGAACCCAUCAGCG	2808
AD-1784504.1	usasaugaAfuCfUfUfcggguguususa	2142	VPusAfsaacAfcccgaagAfuUfcauuasusu	2497	AAUAAUGAAUCUUCGGGUGUUUC	2809
AD-1784505.1	gsusggcuGfgUfUfGfgugcuuugsusa	2143	VPusAfscaaAfgcaccaaCfcAfgccacsasg	2498	CUGUGGCUGGUUGGUGCUUUGUU	2810
AD-1784506.1	asasggaaCfcCfAfUfcagcgucasgsa	2144	VPusCfsugaCfgcugaugGfgUfuccuusgsa	2499	UCAAGGAACCCAUCAGCGUCAGC	2811
AD-1784507.1	ususaaaaCfaAfAfGfggcaagagsusa	2145	VPusAfscudCu(Tgn)gccuuUfgUfuuuaasusg	2500	CAUUAAAACAAAGGGCAAGAGUG	2812

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1784508.1	csusguggCfuGfGfUfugugcuususa	2146	VPusAfsaadGc(Agn)ccaaccAfgCfcacagscsa	2501	UGCUGUGGCUGGUUGGUGCUUUG	2813
AD-1784509.1	csasgcucAfgCfCfAfcugaagaascsa	2147	VPusGfsuudCu(Tgn)caguggCfuGfagcugsgsg	2502	CCCAGCUCAGCCACUGAAGAACA	2814
AD-1784510.1	asasauaaUfgAfAfUfcuucgggusgsa	2148	VPusCfsaccCfgaagauuCfaUfuauuusgsg	2503	CCAAAUAAUGAAUCUUCGGGUGU	2815
AD-1784511.1	gsasauguGfuGfAfCfcuggauugsusa	2149	VPusAfscaaUfccaggucAfcAfcauucscsa	2504	UGGAAUGUGUGACCUGGAUUGUG	2816
AD-1784512.1	csasuguaGfgGfUfGfaugagcacsusa	2150	VPusAfsgudGc(Tgn)caucacCfcUfacaugscsu	2505	AGCAUGUAGGGUGAUGAGCACUC	2817
AD-1784513.1	gsgsacugGfcCfGfUfucuagguasusa	2151	VPusAfsuadCc(Tgn)agaacgGfcCfaguccsasu	2506	AUGGACUGGCCGUUCUAGGUAUU	2818
AD-1784514.1	asusaaauUfgAfGfCfuaguuaagsgsa	2152	VPusCfscuuAfacuagcuCfaAfuuuausCsu	2507	AGAUAAAAUUGAGCUAGUUAAGGC	2819
AD-1784515.1	gsasaaguUfgUfUfGfaugugcugsgsa	2153	VPusCfscagCfacaucaaCfaAfcuuucsusg	2508	CAGAAAGUUGUUGAUGUGCUGGA	2820
AD-1784516.1	gsasaaguUfgUfUfGfaugugcugsgsa	2153	VPusCfscadGc(Agn)caucaaCfaAfcuuucsusg	2509	CAGAAAGUUGUUGAUGUGCUGGA	2820
AD-1784517.1	asascaaaGfgGfCfAfagagugcusgsa	2154	VPusCfsagcAfcucuugcCfcUfuuguususu	2510	AAAACAAAGGGCAAGAGUGCUGA	2821
AD-1784518.1	cscsugagCfaCfUfGfgcauaaggsasa	2155	VPusUfsccdTu(Agn)ugccagUfgCfucaggsusc	2511	GACCUGAGCACUGGCAUAAGGAC	2822
AD-1784519.1	usgsauggUfgGfAfCfaacuggcgscsa	2156	VPusGfscgdCc(Agn)guugucCfaCfcaucasgsu	2512	ACUGAUGGUGGACAACUGGCGCC	2823
AD-1784520.1	ascsaaagGfgCfAfAfgagugcugsasa	2157	VPusUfscadGc(Agn)cucuugCfcCfuuugususu	2513	AAACAAAGGGCAAGAGUGCUGAC	2824
AD-1784521.1	ascsggacCfuGfAfGfcacuggcasusa	2158	VPusAfsugdCc(Agn)gugcucAfgGfuccgususg	2514	CAACGGACCUGAGCACUGGCAUA	2825
AD-1784522.1	usgsggaaAfgCfUfGfugcagcaascsa	2159	VPusGfsuudGc(Tgn)gcacagCfuUfucccasasa	2515	UUUGGGAAAGCUGUGCAGCAACC	2826
AD-1784523.1	asascccaUfcAfGfCfgucagcagscsa	2160	VPusGfscudGc(Tgn)gacgcuGfaUfggguuscsc	2516	GGAACCCAUCAGCGUCAGCAGCG	2827
AD-1784524.1	asgscucaGfcCfAfCfugaagaacsasa	2161	VPusUfsgudTc(Tgn)ucagugGfcUfgagcusgsg	2517	CCAGCUCAGCCACUGAAGAACAG	2828
AD-1784525.1	ususuugaAfgGfUfUfggcagcgcsusa	2162	VPusAfsgcdGc(Tgn)gccaacCfuUfcaaaasasa	2518	UUUUUUGAAGGUUGGCAGCGCUA	2829
AD-1784526.1	gsusaugaCfcCfUfUfcccugaagscsa	2163	VPusGfscudTc(Agn)gggaagGfgUfcauacsusu	2519	AAGUAUGACCCUUCCCUGAAGCC	2830
AD-1784527.1	csusacccAfgGfCfUfcacugaccsasa	2164	VPusUfsggdTc(Agn)gugagcCfuGfgguagsgsu	2520	ACCUACCCAGGCUCACUGACCAC	2831
AD-1784528.1	ascsccagGfcUfCfAfcugaccacscsa	2165	VPusGfsgudGg(Tgn)cagugaGfcCfugggusasg	2521	CUACCCAGGCUCACUGACCACCC	2832
AD-1784529.1	asusggacUfgGfCfCfguucuaggsusa	2166	VPusAfsccuAfgaacggcCfaGfuccausCsa	2522	UGAUGGACUGGCCGUUCUAGGUA	2833
AD-1784530.1	ascscugaGfcAfCfUfggcauaagsgsa	2167	VPusCfscuuAfugccaguGfcUfcaggusCsc	2523	GGACCUGAGCACUGGCAUAAGGA	2834

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1784531.1	cscsaucaGfcGfUfCfagcagcgasgsa	2168	VPusCfsucgCfugcugacGfcUfgauggsgsu	2524	ACCCAUCAGCGUCAGCAGCGAGC	2835
AD-1784532.1	usgsgacuGfgCfCfGfuucuaggusasa	2169	VPusUfsacdCu(Agn)gaacggCfcAfguccasusc	2525	GAUGGACUGGCCGUUCUAGGUAU	2836
AD-1784533.1	ususuuggGfaAfAfGfcugugcagscsa	2170	VPusGfscudGc(Agn)cagcuuUfcCfcaaaasusc	2526	GAUUUUGGGAAAGCUGUGCAGCA	2837
AD-1784534.1	csusgaugGfaCfUfGfgccguucusasa	2171	VPusUfsagaAfcggccagUfcCfaucagsgsu	2527	ACCUGAUGGACUGGCCGUUCUAG	2838
AD-1784535.1	ascscuacCfcAfGfGfcucacugascsa	2172	VPusGfsucdAg(Tgn)gagccuGfgGfuaggusesc	2528	GGACCUACCCAGGCUCACUGACC	2839
AD-1784536.1	gsgsaccuAfcCfCfAfggcucacusgsa	2173	VPusCfsagdTg(Agn)gccuggGfuAfgguccsasg	2529	CUGGACCUACCCAGGCUCACUGA	2840
AD-1784537.1	gsasuggaCfuGfGfCfcguucuagsgsa	2174	VPusCfscuaGfaacggccAfgUfccaucsasg	2530	CUGAUGGACUGGCCGUUCUAGGU	2841
AD-1784538.1	asasgguuGfgCfAfGfcgcuaaacsesa	2175	VPusGfsgudTu(Agn)gcgcugCfcAfaccuuscsa	2531	UGAAGGUUGGCAGCGCUAAACCG	2842
AD-1784539.1	usgsauggAfcUfGfGfccguucuasgsa	2176	VPusCfsuagAfacggccaGfuCfcaucasgsg	2532	CCUGAUGGACUGGCCGUUCUAGG	2843
AD-1784540.1	asascugaUfgGfUfGfgacaacugsgsa	2177	VPusCfscagUfuguccacCfaUfcaguuscsu	2533	AGAACUGAUGGUGGACAACUGGC	2844
AD-1784541.1	asascugaUfgGfUfGfgacaacugsgsa	2177	VPusCfscadGu(Tgn)guccacCfaUfcaguuscsu	2534	AGAACUGAUGGUGGACAACUGGC	2844
AD-1784542.1	ascsaacuGfcUfGfUfggcugguusgsa	2178	VPusCfsaacCfagccacaGfcAfguugusgsu	2535	ACACAACUGCUGUGGCUGGUUGG	2845
AD-1784543.1	ascsaacuGfcUfGfUfggcugguusgsa	2178	VPusCfsaadCc(Agn)gccacaGfcAfguugusgsu	2536	ACACAACUGCUGUGGCUGGUUGG	2845
AD-1784544.1	csasacggAfcCfUfGfagcacuggscsa	2179	VPusGfsccdAg(Tgn)gcucagGfuCfcguugsusg	2537	CACAACGGACCUGAGCACUGGCA	2846
AD-1784545.1	csasacugCfuGfUfGfgcugguugsgsa	2180	VPusCfscaaCfcagccacAfgCfaguugsusg	2538	CACAACUGCUGUGGCUGGUUGGU	2847
AD-1784546.1	ascsugauGfgUfGfGfgacaacuggscsa	2181	VPusGfsccdAg(Tgn)uguccaCfcAfucagususc	2539	GAACUGAUGGUGGACAACUGGCG	2848
AD-1784547.1	csusgcugUfgGfCfUfgguuggugscsa	2182	VPusGfscacCfaaccagcCfaCfagcagsusu	2540	AACUGCUGUGGCUGGUUGGUGCU	2849

Table 9. Unmodified Sense and Antisense Strand Sequences of CA2 dsRNA Agents for C16 Modification

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000067.3
AD-1962343	ACCUGAGCACUGGCAUAAGGU	2850	111-131	ACCUUAUGCCAGUGCUCAGGUCC	3210	109-131
AD-1962345	CUGAGCACUGGCAUAAGGACU	2851	113-133	AGUCCUUAUGCCAGUGCUCAGGU	3211	111-133
AD-1962360	UGACAUCGACACUCAUACAGU	2852	168-188	ACUGUAUGAGUGUCGAUGUCAAC	3212	166-188

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3
AD-1962369	CACUCAUACAGC CAAGUAUGU	2853	177-197	ACAUACUUGGCUG UAUGAGUGUC	3213	175-197
AD-1962370	ACUCAUACAGCC AAGUAUGAU	2854	178-198	AUCAUACUUGGCU GUAUGAGUGU	3214	176-198
AD-1962371	CUCAUACAGCCA AGUAUGACU	2855	179-199	AGUCAUACUUGGC UGUAUGAGUG	3215	177-199
AD-1962380	CCAAGUAUGACC CUUCCCUGU	2856	188-208	ACAGGGAAGGGUC AUACUUGGCU	3216	186-208
AD-1962416	CUGAGGAUCCUC AACAAUGGU	2857	244-264	ACCAUUGUUGAGG AUCCUCAGGG	3217	242-264
AD-1962417	UGAGGAUCCUCA ACAAUGGUU	2858	245-265	AACCAUUGUUGAG GAUCCUCAGG	3218	243-265
AD-1962418	GAGGAUCCUCAA CAAUGGUCU	2859	246-266	AGACCAUUGUUGA GGAUCCUCAG	3219	244-266
AD-1962439	UGCUUUCAACGU GGAGUUUGU	2860	267-287	ACAAACUCCACGU UGAAAGCAUG	3220	265-287
AD-1962440	GCUUUCAACGUG GAGUUUGAU	2861	268-288	AUCAAACUCCACG UUGAAAGCAU	3221	266-288
AD-1962441	CUUUCAACGUGG AGUUUGAUU	2862	269-289	AAUCAAACUCCAC GUUGAAAGCA	3222	267-289
AD-1962442	UUUCAACGUGGA GUUUGAUGU	2863	270-290	ACAUCAAACUCCA CGUUGAAAGC	3223	268-290
AD-1962451	GGAGUUUGAUGA CUCUCAGGU	2864	279-299	ACCUGAGAGUCAU CAAACUCCAC	3224	277-299
AD-1962460	UGACUCUCAGGA CAAAGCAGU	2865	288-308	ACUGCUUUGUCCU GAGAGUCAUC	3225	286-308
AD-1962557	AACUUCACUUGG UUCACUGGU	2866	425-445	ACCAGUGAACCAA GUGAAGUUCU	3226	423-445
AD-1962597	CUGAUGGACUGG CCGUUCUAU	2867	485-505	AUAGAACGGCCAG UCCAUCAGGU	3227	483-505
AD-1962598	UGAUGGACUGGC CGUUCUAGU	2868	486-506	ACUAGAACGGCCA GUCCAUCAGG	3228	484-506
AD-1962599	GAUGGACUGGCC GUUCUAGGU	2869	487-507	ACCUAGAACGGCC AGUCCAUCAG	3229	485-507
AD-1962600	AUGGACUGGCCG UUCUAGGUU	2870	488-508	AACCUAGAACGGC CAGUCCAUCA	3230	486-508
AD-1962603	GACUGGCCGUUC UAGGUAUUU	2871	491-511	AAAUACCUAGAAC GGCCAGUCCA	3231	489-511
AD-1962604	ACUGGCCGUUCU AGGUAUUUU	2872	492-512	AAAAUACCUAGAA CGGCCAGUCC	3232	490-512
AD-1962605	CUGGCCGUUCUA GGUAUUUUU	2873	493-513	AAAAAUACCUAGA ACGGCCAGUC	3233	491-513
AD-1962606	UGGCCGUUCUAG GUAUUUUUU	2874	494-514	AAAAAAUACCUAG AACGGCCAGU	3234	492-514
AD-1962607	GGCCGUUCUAGG UAUUUUUUU	2875	495-515	AAAAAAAUACCUA GAACGGCCAG	3235	493-515

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3
AD-1962608	GCCGUUCUAGGUAUUUUUUUU	2876	496-516	AAAAAAAAUACCUAGAACGGCCA	3236	494-516
AD-1962609	CCGUUCUAGGUAUUUUUUUGU	2877	497-517	ACAAAAAAAUACCUAGAACGGCC	3237	495-517
AD-1962610	CGUUCUAGGUAUUUUUUUGAU	2878	498-518	AUCAAAAAAAAUACCUAGAACGGC	3238	496-518
AD-1962611	GUUCUAGGUAUUUUUUUGAAU	2879	499-519	AUUCAAAAAAAAUACCUAGAACGG	3239	497-519
AD-1962612	UUCUAGGUAUUUUUUUGAAGU	2880	500-520	ACUUCAAAAAAAAUACCUAGAACG	3240	498-520
AD-1962613	UCUAGGUAUUUUUUUGAAGGU	2881	501-521	ACCUUCAAAAAAAAUACCUAGAAC	3241	499-521
AD-1962615	UAGGUAUUUUUUUGAAGGUUU	2882	503-523	AAACCUUCAAAAAAAUACCUAGA	3242	501-523
AD-1962616	AGGUAUUUUUUUGAAGGUUGU	2883	504-524	ACAACCUUCAAAAAAUACCUAG	3243	502-524
AD-1962617	GGUAUUUUUUUGAAGGUUGGU	2884	505-525	ACCAACCUUCAAAAAAUACCUA	3244	503-525
AD-1962618	GUAUUUUUUUGAAGGUUGGCU	2885	506-526	AGCCAACCUUCAAAAAAUACCU	3245	504-526
AD-1962620	AUUUUUUUGAAGGUUGGCAGU	2886	508-528	ACUGCCAACCUUCAAAAAAUAC	3246	506-528
AD-1962648	CGGGCCUUCAGAAAGUUGUUU	2887	536-556	AAACAACUUUCUGAAGGCCCGGU	3247	534-556
AD-1962649	GGGCCUUCAGAAAGUUGUUGU	2888	537-557	ACAACAACUUUCUGAAGGCCCGG	3248	535-557
AD-1962650	GGCCUUCAGAAAGUUGUUGAU	2889	538-558	AUCAACAACUUUCUGAAGGCCCG	3249	536-558
AD-1962652	CCUUCAGAAAGUUGUUGAUGU	2890	540-560	ACAUCAACAACUUUCUGAAGGCC	3250	538-560
AD-1962653	CUUCAGAAAGUUGUUGAUGUU	2891	541-561	AACAUCAACAACUUUCUGAAGGC	3251	539-561
AD-1962655	UCAGAAAGUUGUUGAUGUGCU	2892	543-563	AGCACAUCAACAACUUUCUGAAG	3252	541-563
AD-1962658	GAAAGUUGUUGAUGUGCUGGU	2893	546-566	ACCAGCACAUCAACAACUUUCUG	3253	544-566
AD-1962678	AUUCCAUUAAAACAAAGGGCU	2894	566-586	AGCCCUUUGUUUUAAUGGAAUCC	3254	564-586
AD-1962688	AACAAAGGGCAAGAGUGCUGU	2895	576-596	ACAGCACUCUUGCCCUUUGUUUU	3255	574-596
AD-1962701	AGUGCUGACUUCACUAACUUU	2896	589-609	AAAGUUAGUGAAGUCAGCACUCU	3256	587-609
AD-1962703	UGCUGACUUCACUAACUUCGU	2897	591-611	ACGAAGUUAGUGAAGUCAGCACU	3257	589-611
AD-1962705	CUGACUUCACUAACUUCGAUU	2898	593-613	AAUCGAAGUUAGUGAAGUCAGCA	3258	591-613

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3
AD-1962706	UGACUUCACUAA CUUCGAUCU	2899	594-614	AGAUCGAAGUUAG UGAAGUCAGC	3259	592-614
AD-1962707	GACUUCACUAAC UUCGAUCCU	2900	595-615	AGGAUCGAAGUUA GUGAAGUCAG	3260	593-615
AD-1962712	CACUAACUUCGA UCCUCGUGU	2901	600-620	ACACGAGGAUCGA AGUUAGUGAA	3261	598-620
AD-1962713	ACUAACUUCGAU CCUCGUGGU	2902	601-621	ACCACGAGGAUCG AAGUUAGUGA	3262	599-621
AD-1962733	CCUCCUUCCUGA AUCCUUGGU	2903	621-641	ACCAAGGAUUCAG GAAGGAGGCC	3263	619-641
AD-1962735	UCCUUCCUGAAU CCUUGGAUU	2904	623-643	AAUCCAAGGAUUC AGGAAGGAGG	3264	621-643
AD-1962736	CCUUCCUGAAUC CUUGGAUUU	2905	624-644	AAAUCCAAGGAUU CAGGAAGGAG	3265	622-644
AD-1962766	CUCCUCUUCUGG AAUGUGUGU	2906	674-694	ACACACAUUCCAG AAGAGGAGGG	3266	672-694
AD-1962777	GAAUGUGUGACC UGGAUUGUU	2907	685-705	AACAAUCCAGGUC ACACAUUCCA	3267	683-705
AD-1962780	UGUGUGACCUGG AUUGUGCUU	2908	688-708	AAGCACAAUCCAG GUCACACAUU	3268	686-708
AD-1962795	GUGCUCAAGGAA CCCAUCAGU	2909	703-723	ACUGAUGGGUUCC UUGAGCACAA	3269	701-723
AD-1962799	UCAAGGAACCCA UCAGCGUCU	2910	707-727	AGACGCUGAUGGG UUCCUUGAGC	3270	705-727
AD-1962801	AAGGAACCCAUC AGCGUCAGU	2911	709-729	ACUGACGCUGAUG GGUUCCUUGA	3271	707-729
AD-1962808	CCAUCAGCGUCA GCAGCGAGU	2912	716-736	ACUCGCUGCUGAC GCUGAUGGGU	3272	714-736
AD-1962836	GAAAUUCCGUAA ACUUAACUU	2913	744-764	AAGUUAAGUUUAC GGAAUUUCAA	3273	742-764
AD-1962837	AAAUUCCGUAAA CUUAACUUU	2914	745-765	AAAGUUAAGUUUA CGGAAUUUCA	3274	743-765
AD-1962842	CCGUAAACUUAA CUUCAAUGU	2915	750-770	ACAUUGAAGUUAA GUUUACGGAA	3275	748-770
AD-1962843	CGUAAACUUAAC UUCAAUGGU	2916	751-771	ACCAUUGAAGUUA AGUUUACGGA	3276	749-771
AD-1962860	AACUGAUGGUGG ACAACUGGU	2917	788-808	ACCAGUUGUCCAC CAUCAGUUCU	3277	786-808
AD-1962885	CUCAGCCACUGA AGAACAGGU	2918	815-835	ACCUGUUCUUCAG UGGCUGAGCU	3278	813-835
AD-1962897	AGAACAGGCAAA UCAAAGCUU	2919	827-847	AAGCUUUGAUUUG CCUGUUCUUC	3279	825-847
AD-1962902	AGGCAAAUCAAA GCUUCCUUU	2920	832-852	AAAGGAAGCUUUG AUUUGCCUGU	3280	830-852
AD-1962910	CAAAGCUUCCUU CAAAUAAGU	2921	840-860	ACUUAUUUGAAGG AAGCUUUGAU	3281	838-860

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3
AD-1962911	AAAGCUUCCUUC AAAUAAGAU	2922	841-861	AUCUUAUUUGAAG GAAGCUUUGA	3282	839-861
AD-1962912	AAGCUUCCUUCA AAUAAGAUU	2923	842-862	AAUCUUAUUUGAA GGAAGCUUUG	3283	840-862
AD-1962913	AGCUUCCUUCAA AUAAGAUGU	2924	843-863	ACAUCUUAUUUGA AGGAAGCUUU	3284	841-863
AD-1962914	GCUUCCUUCAAA UAAGAUGGU	2925	844-864	ACCAUCUUAUUUG AAGGAAGCUU	3285	842-864
AD-1962941	GUCUGUAUCCAA AUAAUGAAU	2926	871-891	AUUCAUUAUUUGG AUACAGACUA	3286	869-891
AD-1962945	GUAUCCAAAUAA UGAAUCUUU	2927	875-895	AAAGAUUCAUUAU UUGGAUACAG	3287	873-895
AD-1962947	AUCCAAAUAAUG AAUCUUCGU	2928	877-897	ACGAAGAUUCAUU AUUUGGAUAC	3288	875-897
AD-1962948	UCCAAAUAAUGA AUCUUCGGU	2929	878-898	ACCGAAGAUUCAU UAUUUGGAUA	3289	876-898
AD-1962949	CCAAAUAAUGAA UCUUCGGGU	2930	879-899	ACCCGAAGAUUCA UUAUUUGGAU	3290	877-899
AD-1962950	CAAAUAAUGAAU CUUCGGGUU	2931	880-900	AACCCGAAGAUUC AUUAUUUGGA	3291	878-900
AD-1962951	AAAUAAUGAAUC UUCGGGUGU	2932	881-901	ACACCCGAAGAUU CAUUAUUUGG	3292	879-901
AD-1962952	AAUAAUGAAUCU UCGGGUGUU	2933	882-902	AACACCCGAAGAU UCAUUAUUUG	3293	880-902
AD-1962953	AUAAUGAAUCUU CGGGUGUUU	2934	883-903	AAACACCCGAAGA UUCAUUAUUU	3294	881-903
AD-1962954	UAAUGAAUCUUC GGGUGUUUU	2935	884-904	AAAACACCCGAAG AUUCAUUAUU	3295	882-904
AD-1962957	UGAAUCUUCGGG UGUUUCCCU	2936	887-907	AGGGAAACACCCG AAGAUUCAUU	3296	885-907
AD-1962958	GAAUCUUCGGGU GUUUCCCUU	2937	888-908	AAGGGAAACACCC GAAGAUUCAU	3297	886-908
AD-1962984	AAGCACAGAUCU ACCUUGGUU	2938	914-934	AACCAAGGUAGAU CUGUGCUUAG	3298	912-934
AD-1962985	AGCACAGAUCUA CCUUGGUGU	2939	915-935	ACACCAAGGUAGA UCUGUGCUUA	3299	913-935
AD-1962986	GCACAGAUCUAC CUUGGUGAU	2940	916-936	AUCACCAAGGUAG AUCUGUGCUU	3300	914-936
AD-1962990	AGAUCUACCUUG GUGAUUUGU	2941	920-940	ACAAAUCACCAAG GUAGAUCUGU	3301	918-940
AD-1963114	ACAACUGCUGUG GCUGGUUGU	2942	1039-1059	ACAACCAGCCACA GCAGUUGUGU	3302	1037-1059
AD-1963115	CAACUGCUGUGG CUGGUUGGU	2943	1040-1060	ACCAACCAGCCAC AGCAGUUGUG	3303	1038-1060
AD-1963118	CUGCUGUGGCUG GUUGGUGCU	2944	1043-1063	AGCACCAACCAGC CACAGCAGUU	3304	1041-1063

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3
AD-1963123	GUGGCUGGUUGGUGCUUUGUU	2945	1048-1068	AACAAAGCACCAACCAGCCACAG	3305	1046-1068
AD-1963125	GGCUGGUUGGUGCUUUGUUUU	2946	1050-1070	AAAACAAAGCACCAACCAGCCAC	3306	1048-1070
AD-1963126	GCUGGUUGGUGCUUUGUUUAU	2947	1051-1071	AUAAACAAAGCACCAACCAGCCA	3307	1049-1071
AD-1963127	CUGGUUGGUGCUUUGUUUAUU	2948	1052-1072	AAUAAACAAAGCACCAACCAGCC	3308	1050-1072
AD-1963128	UGGUUGGUGCUUUGUUUAUGU	2949	1053-1073	ACAUAAACAAAGCACCAACCAGC	3309	1051-1073
AD-1963129	GGUUGGUGCUUUGUUUAUGGU	2950	1054-1074	ACCAUAAACAAAGCACCAACCAG	3310	1052-1074
AD-1963130	GUUGGUGCUUUGUUUAUGGUU	2951	1055-1075	AACCAUAAACAAAGCACCAACCA	3311	1053-1075
AD-1963131	UUGGUGCUUUGUUUAUGGUAU	2952	1056-1076	AUACCAUAAACAAAGCACCAACC	3312	1054-1076
AD-1963132	UGGUGCUUUGUUUAUGGUAGU	2953	1057-1077	ACUACCAUAAACAAAGCACCAAC	3313	1055-1077
AD-1963135	UGCUUUGUUUAUGGUAGUAGU	2954	1060-1080	ACUACUACCAUAAACAAAGCACC	3314	1058-1080
AD-1963138	UUUGUUUAUGGUAGUAGUUUU	2955	1063-1083	AAAACUACUACCAUAAACAAAGC	3315	1061-1083
AD-1963139	UUGUUUAUGGUAGUAGUUUUU	2956	1064-1084	AAAAACUACUACCAUAAACAAAG	3316	1062-1084
AD-1963140	GUUUAUGGUAGUAGUUUUUCU	2957	1066-1086	AGAAAAACUACUACCAUAAACAA	3317	1064-1086
AD-1963141	UUUAUGGUAGUAGUUUUUCUU	2958	1067-1087	AAGAAAAACUACUACCAUAAACA	3318	1065-1087
AD-1963142	UUAUGGUAGUAGUUUUUCUGU	2959	1068-1088	ACAGAAAAACUACUACCAUAAAC	3319	1066-1088
AD-1963143	UAUGGUAGUAGUUUUUCUGUU	2960	1069-1089	AACAGAAAAACUACUACCAUAAA	3320	1067-1089
AD-1963144	AUGGUAGUAGUUUUUCUGUAU	2961	1070-1090	AUACAGAAAAACUACUACCAUAA	3321	1068-1090
AD-1963148	UAGUAGUUUUUCUGUAACACU	2962	1074-1094	AGUGUUACAGAAAAACUACUACC	3322	1072-1094
AD-1963202	AGAAUAAAGUACCUUGACUUU	2963	1114-1134	AAAGUCAAGGUACUUUAUUCUUA	3323	1112-1134
AD-1963204	AAUAAAGUACCUUGACUUUGU	2964	1116-1136	ACAAAGUCAAGGUACUUUAUUCU	3324	1114-1136
AD-1963205	AUAAAGUACCUUGACUUUGUU	2965	1117-1137	AACAAAGUCAAGGUACUUUAUUC	3325	1115-1137
AD-1963206	UAAAGUACCUUGACUUUGUUU	2966	1118-1138	AAACAAAGUCAAGGUACUUUAUU	3326	1116-1138
AD-1963207	AAAGUACCUUGACUUUGUUCU	2967	1119-1139	AGAACAAAGUCAAGGUACUUUAU	3327	1117-1139

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3
AD-1963208	AAGUACCUUGACUUUGUUCAU	2968	1120-1140	AUGAACAAAGUCAAGGUACUUUA	3328	1118-1140
AD-1963211	UACCUUGACUUUGUUCACAGU	2969	1123-1143	ACUGUGAACAAAGUCAAGGUACU	3329	1121-1143
AD-1963218	ACUUUGUUCACAGCAUGUAGU	2970	1130-1150	ACUACAUGCUGUGAACAAAGUCA	3330	1128-1150
AD-1963219	CUUUGUUCACAGCAUGUAGGU	2971	1131-1151	ACCUACAUGCUGUGAACAAAGUC	3331	1129-1151
AD-1963220	UUUGUUCACAGCAUGUAGGGU	2972	1132-1152	ACCCUACAUGCUGUGAACAAAGU	3332	1130-1152
AD-1963221	UUGUUCACAGCAUGUAGGGUU	2973	1133-1153	AACCCUACAUGCUGUGAACAAAG	3333	1131-1153
AD-1963222	UGUUCACAGCAUGUAGGGUGU	2974	1134-1154	ACACCCUACAUGCUGUGAACAAA	3334	1132-1154
AD-1963225	UCACAGCAUGUAGGGUGAUGU	2975	1137-1157	ACAUCACCCUACAUGCUGUGAAC	3335	1135-1157
AD-1963237	CAACGGACCUGAGCACUGGCU	2976	105-125	AGCCAGTGCUCAGGUCCGUUGUG	3336	103-125
AD-1963239	ACGGACCUGAGCACUGGCAUU	2977	107-127	AAUGCCAGUGCUCAGGUCCGUUG	3337	105-127
AD-1963244	CCUGAGCACUGGCAUAAGGAU	2978	112-132	AUCCTUAUGCCAGUGCUCAGGUC	3338	110-132
AD-1963245	CUGAGCACUGGCAUAAGGACU	2979	113-133	AGUCCUTAUGCCAGUGCUCAGGU	3339	111-133
AD-1963246	UGAGCACUGGCAUAAGGACUU	2980	114-134	AAGUCCTUAUGCCAGUGCUCAGG	3340	112-134
AD-1963249	GCACUGGCAUAAGGACUUCCU	2981	117-137	AGGAAGTCCUUAUGCCAGUGCUC	3341	115-137
AD-1963287	GACUAAAAUGCUGCUUUUAAU	2982	1173-1193	AUUAAAAGCAGCAUUUUAGUCAA	3342	1171-1193
AD-1963288	ACUAAAAUGCUGCUUUUAAAU	2983	1174-1194	AUUUAAAAGCAGCAUUUUAGUCA	3343	1172-1194
AD-1963289	CUAAAAUGCUGCUUUUAAAAU	2984	1175-1195	AUUUUAAAAGCAGCAUUUUAGUC	3344	1173-1195
AD-1963290	UAAAAUGCUGCUUUUAAAACU	2985	1176-1196	AGUUUUAAAAGCAGCAUUUUAGU	3345	1174-1196
AD-1963295	UGCUGCUUUUAAAACAUAGGU	2986	1181-1201	ACCUAUGUUUUAAAAGCAGCAUU	3346	1179-1201
AD-1963296	GCUGCUUUUAAAACAUAGGAU	2987	1182-1202	AUCCUAUGUUUUAAAAGCAGCAU	3347	1180-1202
AD-1963302	UUUAAAACAUAGGAAAGUAGU	2988	1188-1208	ACUACUUUCCUAUGUUUUAAAAG	3348	1186-1208
AD-1963306	CUGUUGACAUCGACACUCAUU	2989	164-184	AAUGAGTGUCGAUGUCAACAGGG	3349	162-184
AD-1963308	GUUGACAUCGACACUCAUACU	2990	166-186	AGUATGAGUGUCGAUGUCAACAG	3350	164-186

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3
AD-1963311	GACAUCGACACU CAUACAGCU	2991	169-189	AGCUGUAUGAGUG UCGAUGUCAA	3351	167-189
AD-1963312	ACAUCGACACUC AUACAGCCU	2992	170-190	AGGCTGTAUGAGU GUCGAUGUCA	3352	168-190
AD-1963314	AUCGACACUCAU ACAGCCAAU	2993	172-192	AUUGGCTGUAUGA GUGUCGAUGU	3353	170-192
AD-1963318	ACACUCAUACAG CCAAGUAUU	2994	176-196	AAUACUTGGCUGU AUGAGUGUCG	3354	174-196
AD-1963321	CUCAUACAGCCA AGUAUGACU	2995	179-199	AGUCAUACUUGGC UGUAUGAGUG	3355	177-199
AD-1963322	UCAUACAGCCAA GUAUGACCU	2996	180-200	AGGUCATACUUGG CUGUAUGAGU	3356	178-200
AD-1963323	CAUACAGCCAAG UAUGACCCU	2997	181-201	AGGGTCAUACUUG GCUGUAUGAG	3357	179-201
AD-1963325	UACAGCCAAGUA UGACCCUUU	2998	183-203	AAAGGGTCAUACU UGGCUGUAUG	3358	181-203
AD-1963329	GCCAAGUAUGAC CCUUCCCUU	2999	187-207	AAGGGAAGGGUCA UACUUGGCUG	3359	185-207
AD-1963375	GAUAAAUUGAGC UAGUUAAGU	3000	1236-1256	ACUUAACUAGCUC AAUUUAUCUU	3360	1234-1256
AD-1963376	AUAAAUUGAGCU AGUUAAGGU	3001	1237-1257	ACCUUAACUAGCU CAAUUUAUCU	3361	1235-1257
AD-1963377	UAAAUUGAGCUA GUUAAGGCU	3002	1238-1258	AGCCUUAACUAGC UCAAUUUAUC	3362	1236-1258
AD-1963384	GUAUGACCCUUC CCUGAAGCU	3003	192-212	AGCUTCAGGGAAG GGUCAUACUU	3363	190-212
AD-1963386	CUGUCUGUUUCC UAUGAUCAU	3004	214-234	AUGATCAUAGGAA ACAGACAGGG	3364	212-234
AD-1963388	GUCUGUUUCCUA UGAUCAAGU	3005	216-236	ACUUGATCAUAGG AAACAGACAG	3365	214-236
AD-1963389	UCUGUUUCCUAU GAUCAAGCU	3006	217-237	AGCUTGAUCAUAG GAAACAGACA	3366	215-237
AD-1963391	UGUUUCCUAUGA UCAAGCAAU	3007	219-239	AUUGCUTGAUCAU AGGAAACAGA	3367	217-239
AD-1963392	GUUUCCUAUGAU CAAGCAACU	3008	220-240	AGUUGCTUGAUCA UAGGAAACAG	3368	218-240
AD-1963395	UCCUAUGAUCAA GCAACUUCU	3009	223-243	AGAAGUTGCUUGA UCAUAGGAAA	3369	221-243
AD-1963410	AGCUAGUUAAGG CAAAUCAGU	3010	1245-1265	ACUGAUUUGCCUU AACUAGCUCA	3370	1243-1265
AD-1963411	GCUAGUUAAGGC AAAUCAGGU	3011	1246-1266	ACCUGAUUUGCCU UAACUAGCUC	3371	1244-1266
AD-1963417	UAAGGCAAAUCA GGUAAAAUU	3012	1252-1272	AAUUUUACCUGAU UUGCCUUAAC	3372	1250-1272
AD-1963419	AGGCAAAUCAGG UAAAAUAGU	3013	1254-1274	ACUAUUUUACCUG AUUUGCCUUA	3373	1252-1274

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3
AD-1963420	GGCAAAUCAGGUAAAAUAGUU	3014	1255-1275	AACUAUUUUACCUGAUUUGCCUU	3374	1253-1275
AD-1963421	GCAAAUCAGGUAAAAUAGUCU	3015	1256-1276	AGACUAUUUUACCUGAUUUGCCU	3375	1254-1276
AD-1963430	GUAAAAUAGUCAUGAUUCUAU	3016	1265-1285	AUAGAAUCAUGACUAUUUUACCU	3376	1263-1285
AD-1963431	UAAAAUAGUCAUGAUUCUAUU	3017	1266-1286	AAUAGAAUCAUGACUAUUUUACC	3377	1264-1286
AD-1963432	AAAAUAGUCAUGAUUCUAUGU	3018	1267-1287	ACAUAGAAUCAUGACUAUUUUAC	3378	1265-1287
AD-1963437	AGUCAUGAUUCUAUGUAAUGU	3019	1272-1292	ACAUUACAUAGAAUCAUGACUAU	3379	1270-1292
AD-1963438	GUCAUGAUUCUAUGUAAUGUU	3020	1273-1293	AACAUUACAUAGAAUCAUGACUA	3380	1271-1293
AD-1963439	UCAUGAUUCUAUGUAAUGUAU	3021	1274-1294	AUACAUUACAUAGAAUCAUGACU	3381	1272-1294
AD-1963464	CCCUGAGGAUCCUCAACAAUU	3022	242-262	AAUUGUTGAGGAUCCUCAGGGAA	3382	240-262
AD-1963465	CCUGAGGAUCCUCAACAAUGU	3023	243-263	ACAUTGTUGAGGAUCCUCAGGGA	3383	241-263
AD-1963468	GAGGAUCCUCAACAAUGGUCU	3024	246-266	AGACCATUGUUGAGGAUCCUCAG	3384	244-266
AD-1963469	AGGAUCCUCAACAAUGGUCAU	3025	247-267	AUGACCAUUGUUGAGGAUCCUCA	3385	245-267
AD-1963539	UGCUUUCAACGUGGAGUUUGU	3026	267-287	ACAAACTCCACGUUGAAAGCAUG	3386	265-287
AD-1963543	UUCAACGUGGAGUUUGAUGAU	3027	271-291	AUCATCAAACUCCACGUUGAAAG	3387	269-291
AD-1963545	CAACGUGGAGUUUGAUGACUU	3028	273-293	AAGUCATCAAACUCCACGUUGAA	3388	271-293
AD-1963546	AACGUGGAGUUUGAUGACUCU	3029	274-294	AGAGTCAUCAAACUCCACGUUGA	3389	272-294
AD-1963548	CGUGGAGUUUGAUGACUCUCU	3030	276-296	AGAGAGTCAUCAAACUCCACGUU	3390	274-296
AD-1963550	UGGAGUUUGAUGACUCUCAGU	3031	278-298	ACUGAGAGUCAUCAAACUCCACG	3391	276-298
AD-1963552	GAGUUUGAUGACUCUCAGGAU	3032	280-300	AUCCTGAGAGUCAUCAAACUCCA	3392	278-300
AD-1963554	GUUUGAUGACUCUCAGGACAU	3033	282-302	AUGUCCTGAGAGUCAUCAAACUC	3393	280-302
AD-1963557	UGAUGACUCUCAGGACAAAGU	3034	285-305	ACUUTGTCCUGAGAGUCAUCAAA	3394	283-305
AD-1963582	UAAUUAGAGUUGUGAUACAGU	3035	1460-1480	ACUGUAUCACAACUCUAAUUAUA	3395	1458-1480
AD-1963590	GUUGUGAUACAGAGUAUAUUU	3036	1468-1488	AAAUAUACUCUGUAUCACAACUC	3396	1466-1488

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3
AD-1963591	UUGUGAUACAGAGUAUAUUUU	3037	1469-1489	AAAAUAUACUCUGUAUCACAACU	3397	1467-1489
AD-1963592	UGUGAUACAGAGUAUAUUUCU	3038	1470-1490	AGAAAUAUACUCUGUAUCACAAC	3398	1468-1490
AD-1963609	AUGACUCUCAGGACAAAGCAU	3039	287-307	AUGCTUTGUCCUGAGAGUCAUCA	3399	285-307
AD-1963610	UGACUCUCAGGACAAAGCAGU	3040	288-308	ACUGCUTUGUCCUGAGAGUCAUC	3400	286-308
AD-1963618	CCAUUCAGACAAUAUAUCAUU	3041	1489-1509	AAUGAUAUAUUGUCUGAAUGGAA	3401	1487-1509
AD-1963719	ACUUCACUUGGUUCACUGGAU	3042	426-446	AUCCAGTGAACCAAGUGAAGUUC	3402	424-446
AD-1963721	UUCACUUGGUUCACUGGAACU	3043	428-448	AGUUCCAGUGAACCAAGUGAAGU	3403	426-448
AD-1963733	GAUUUUGGGAAAGCUGUGCAU	3044	460-480	AUGCACAGCUUUCCCAAAAUCCC	3404	458-480
AD-1963735	UUUUGGGAAAGCUGUGCAGCU	3045	462-482	AGCUGCACAGCUUUCCCAAAAUC	3405	460-482
AD-1963738	UGGGAAAGCUGUGCAGCAACU	3046	465-485	AGUUGCTGCACAGCUUUCCCAAA	3406	463-485
AD-1963762	UGGACUGGCCGUUCUAGGUAU	3047	489-509	AUACCUAGAACGGCCAGUCCAUC	3407	487-509
AD-1963763	GGACUGGCCGUUCUAGGUAUU	3048	490-510	AAUACCTAGAACGGCCAGUCCAU	3408	488-510
AD-1963776	UAGGUAUUUUUUUGAAGGUUU	3049	503-523	AAACCUTCAAAAAAAUACCUAGA	3409	501-523
AD-1963780	UAUUUUUUUGAAGGUUGGCAU	3050	507-527	AUGCCAACCUUCAAAAAAAUACC	3410	505-527
AD-1963781	AUUUUUUUGAAGGUUGGCAGU	3051	508-528	ACUGCCAACCUUCAAAAAAAUAC	3411	506-528
AD-1963785	UUUUGAAGGUUGGCAGCGCUU	3052	512-532	AAGCGCTGCCAACCUUCAAAAAA	3412	510-532
AD-1963790	AAGGUUGGCAGCGCUAAACCU	3053	517-537	AGGUTUAGCGCUGCCAACCUUCA	3413	515-537
AD-1963814	CUUCAGAAAGUUGUUGAUGUU	3054	541-561	AACATCAACAACUUUCUGAAGGC	3414	539-561
AD-1963816	UCAGAAAGUUGUUGAUGUGCU	3055	543-563	AGCACATCAACAACUUUCUGAAG	3415	541-563
AD-1963817	CAGAAAGUUGUUGAUGUGCUU	3056	544-564	AAGCACAUCAACAACUUUCUGAA	3416	542-564
AD-1963819	GAAAGUUGUUGAUGUGCUGGU	3057	546-566	ACCAGCACAUCAACAACUUUCUG	3417	544-566
AD-1963839	AUUCCAUUAAAACAAAGGGCU	3058	566-586	AGCCCUTUGUUUUAAUGGAAUCC	3418	564-586
AD-1963840	UUCCAUUAAAACAAAGGGCAU	3059	567-587	AUGCCCTUUGUUUUAAUGGAAUC	3419	565-587

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3
AD-1963845	UUAAAACAAAGG GCAAGAGUU	3060	572-592	AACUCUTGCCCUU UGUUUUAAUG	3420	570-592
AD-1963846	UAAAACAAAGGG CAAGAGUGU	3061	573-593	ACACTCTUGCCCUU UGUUUUAAU	3421	571-593
AD-1963848	AAACAAAGGGCA AGAGUGCUU	3062	575-595	AAGCACTCUUGCC CUUUGUUUUA	3422	573-595
AD-1963850	ACAAAGGGCAAG AGUGCUGAU	3063	577-597	AUCAGCACUCUUG CCCUUUGUUU	3423	575-597
AD-1963853	AAGGGCAAGAGU GCUGACUUU	3064	580-600	AAAGTCAGCACUC UUGCCCUUUG	3424	578-600
AD-1963855	GGGCAAGAGUGC UGACUUCAU	3065	582-602	AUGAAGTCAGCAC UCUUGCCCUU	3425	580-602
AD-1963857	GCAAGAGUGCUG ACUUCACUU	3066	584-604	AAGUGAAGUCAGC ACUCUUGCCC	3426	582-604
AD-1963858	CAAGAGUGCUGA CUUCACUAU	3067	585-605	AUAGTGAAGUCAG CACUCUUGCC	3427	583-605
AD-1963860	AGAGUGCUGACU UCACUAACU	3068	587-607	AGUUAGTGAAGUC AGCACUCUUG	3428	585-607
AD-1963863	GUGCUGACUUCA CUAACUUCU	3069	590-610	AGAAGUTAGUGAA GUCAGCACUC	3429	588-610
AD-1963864	UGCUGACUUCAC UAACUUCGU	3070	591-611	ACGAAGTUAGUGA AGUCAGCACU	3430	589-611
AD-1963870	CUUCACUAACUU CGAUCCUCU	3071	597-617	AGAGGATCGAAGU UAGUGAAGUC	3431	595-617
AD-1963871	UUCACUAACUUC GAUCCUCGU	3072	598-618	ACGAGGAUCGAAG UUAGUGAAGU	3432	596-618
AD-1963893	GCCUCCUUCCUG AAUCCUUGU	3073	620-640	ACAAGGAUUCAGG AAGGAGGCCA	3433	618-640
AD-1963896	UCCUUCCUGAAU CCUUGGAUU	3074	623-643	AAUCCAAGGAUUC AGGAAGGAGG	3434	621-643
AD-1963920	GGACCUACCCAG GCUCACUGU	3075	647-667	ACAGTGAGCCUGG GUAGGUCCAG	3435	645-667
AD-1963922	ACCUACCCAGGC UCACUGACU	3076	649-669	AGUCAGTGAGCCU GGGUAGGUCC	3436	647-669
AD-1963924	CUACCCAGGCUC ACUGACCAU	3077	651-671	AUGGTCAGUGAGC CUGGGUAGGU	3437	649-671
AD-1963926	ACCCAGGCUCAC UGACCACCU	3078	653-673	AGGUGGTCAGUGA GCCUGGGUAG	3438	651-673
AD-1963927	CUCCUCUUCUGG AAUGUGUGU	3079	674-694	ACACACAUUCCAG AAGAGGAGGG	3439	672-694
AD-1963929	CCUCUUCUGGAA UGUGUGACU	3080	676-696	AGUCACACAUUCC AGAAGAGGAG	3440	674-696
AD-1963931	UCUUCUGGAAUG UGUGACCUU	3081	678-698	AAGGTCACACAUU CCAGAAGAGG	3441	676-698
AD-1963933	UUCUGGAAUGUG UGACCUGGU	3082	680-700	ACCAGGTCACACA UUCCAGAAGA	3442	678-700

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3
AD-1963936	UGGAAUGUGUGACCUGGAUUU	3083	683-703	AAAUCCAGGUCACACAUUCCAGA	3443	681-703
AD-1963941	UGUGUGACCUGGAUUGUGCUU	3084	688-708	AAGCACAAUCCAGGUCACACAUU	3444	686-708
AD-1963943	UGUGACCUGGAUUGUGCUCAU	3085	690-710	AUGAGCACAAUCCAGGUCACACA	3445	688-710
AD-1963946	GACCUGGAUUGUGCUCAAGGU	3086	693-713	ACCUTGAGCACAAUCCAGGUCAC	3446	691-713
AD-1963948	CCUGGAUUGUGCUCAAGGAAU	3087	695-715	AUUCCUTGAGCACAAUCCAGGUC	3447	693-715
AD-1963949	CUGGAUUGUGCUCAAGGAACU	3088	696-716	AGUUCCTUGAGCACAAUCCAGGU	3448	694-716
AD-1963952	GAUUGUGCUCAAGGAACCCAU	3089	699-719	AUGGGUTCCUUGAGCACAAUCCA	3449	697-719
AD-1963953	AUUGUGCUCAAGGAACCCAUU	3090	700-720	AAUGGGTUCCUUGAGCACAAUCC	3450	698-720
AD-1963957	UGCUCAAGGAACCCAUCAGCU	3091	704-724	AGCUGATGGGUUCCUUGAGCACA	3451	702-724
AD-1963958	GCUCAAGGAACCCAUCAGCGU	3092	705-725	ACGCTGAUGGGUUCCUUGAGCAC	3452	703-725
AD-1963960	UCAAGGAACCCAUCAGCGUCU	3093	707-727	AGACGCTGAUGGGUUCCUUGAGC	3453	705-727
AD-1963964	GGAACCCAUCAGCGUCAGCAU	3094	711-731	AUGCTGACGCUGAUGGGUUCCUU	3454	709-731
AD-1963966	AACCCAUCAGCGUCAGCAGCU	3095	713-733	AGCUGCTGACGCUGAUGGGUUCC	3455	711-733
AD-1963995	UUGAAAUUCCGUAAACUUAAU	3096	742-762	AUUAAGTUUACGGAAUUUCAACA	3456	740-762
AD-1963997	GAAAUUCCGUAAACUUAACUU	3097	744-764	AAGUTAAGUUUACGGAAUUUCAA	3457	742-764
AD-1963999	AAUUCCGUAAACUUAACUUCU	3098	746-766	AGAAGUTAAGUUUACGGAAUUUC	3458	744-766
AD-1964000	AUUCCGUAAACUUAACUUCAU	3099	747-767	AUGAAGTUAAGUUUACGGAAUUU	3459	745-767
AD-1964002	UCCGUAAACUUAACUUCAAUU	3100	749-769	AAUUGAAGUUAAGUUUACGGAAU	3460	747-769
AD-1964003	CCGUAAACUUAACUUCAAUGU	3101	750-770	ACAUTGAAGUUAAGUUUACGGAA	3461	748-770
AD-1964016	CGAAGAACUGAUGGUGGACAU	3102	783-803	AUGUCCACCAUCAGUUCUUCGGG	3462	781-803
AD-1964019	AGAACUGAUGGUGGACAACUU	3103	786-806	AAGUTGTCCACCAUCAGUUCUUC	3463	784-806
AD-1964021	AACUGAUGGUGGACAACUGGU	3104	788-808	ACCAGUTGUCCACCAUCAGUUCU	3464	786-808
AD-1964022	ACUGAUGGUGGACAACUGGCU	3105	789-809	AGCCAGTUGUCCACCAUCAGUUC	3465	787-809

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3
AD-1964024	UGAUGGUGGACA ACUGGCGCU	3106	791-811	AGCGCCAGUUGUC CACCAUCAGU	3466	789-811
AD-1964043	CAGCUCAGCCAC UGAAGAACU	3107	812-832	AGUUCUTCAGUGG CUGAGCUGGG	3467	810-832
AD-1964044	AGCUCAGCCACU GAAGAACAU	3108	813-833	AUGUTCTUCAGUG GCUGAGCUGG	3468	811-833
AD-1964046	CUCAGCCACUGA AGAACAGGU	3109	815-835	ACCUGUTCUUCAG UGGCUGAGCU	3469	813-835
AD-1964047	UCAGCCACUGAA GAACAGGCU	3110	816-836	AGCCTGTUCUUCA GUGGCUGAGC	3470	814-836
AD-1964049	AGCCACUGAAGA ACAGGCAAU	3111	818-838	AUUGCCTGUUCUU CAGUGGCUGA	3471	816-838
AD-1964053	ACUGAAGAACAG GCAAAUCAU	3112	822-842	AUGATUTGCCUGU UCUUCAGUGG	3472	820-842
AD-1964054	CUGAAGAACAGG CAAAUCAAU	3113	823-843	AUUGAUTUGCCUG UUCUUCAGUG	3473	821-843
AD-1964055	UGAAGAACAGGC AAAUCAAAU	3114	824-844	AUUUGATUUGCCU GUUCUUCAGU	3474	822-844
AD-1964056	GAAGAACAGGCA AAUCAAAGU	3115	825-845	ACUUTGAUUUGCC UGUUCUUCAG	3475	823-845
AD-1964058	AGAACAGGCAAA UCAAAGCUU	3116	827-847	AAGCTUTGAUUUG CCUGUUCUUC	3476	825-847
AD-1964059	GAACAGGCAAAU CAAAGCUUU	3117	828-848	AAAGCUTUGAUUU GCCUGUUCUU	3477	826-848
AD-1964060	AACAGGCAAAUC AAAGCUUCU	3118	829-849	AGAAGCTUUGAUU UGCCUGUUCU	3478	827-849
AD-1964063	AGGCAAAUCAAA GCUUCCUUU	3119	832-852	AAAGGAAGCUUUG AUUUGCCUGU	3479	830-852
AD-1964064	GGCAAAUCAAAG CUUCCUUCU	3120	833-853	AGAAGGAAGCUUU GAUUUGCCUG	3480	831-853
AD-1964067	AAAUCAAAGCUU CCUUCAAAU	3121	836-856	AUUUGAAGGAAGC UUUGAUUUGC	3481	834-856
AD-1964068	AAUCAAAGCUUC CUUCAAAUU	3122	837-857	AAUUTGAAGGAAG CUUUGAUUUG	3482	835-857
AD-1964070	UCAAAGCUUCCU UCAAAUAAU	3123	839-859	AUUATUTGAAGGA AGCUUUGAUU	3483	837-859
AD-1964072	AAAGCUUCCUUC AAAUAAGAU	3124	841-861	AUCUTATUUGAAG GAAGCUUUGA	3484	839-861
AD-1964073	AAGCUUCCUUCA AAUAAGAUU	3125	842-862	AAUCTUAUUUGAA GGAAGCUUUG	3485	840-862
AD-1964075	GCUUCCUUCAAA UAAGAUGGU	3126	844-864	ACCATCTUAUUUG AAGGAAGCUU	3486	842-864
AD-1964077	UUCCUUCAAAUA AGAUGGUCU	3127	846-866	AGACCATCUUAUU UGAAGGAAGC	3487	844-866
AD-1964078	UCCUUCAAAUAA GAUGGUCCU	3128	847-867	AGGACCAUCUUAU UUGAAGGAAG	3488	845-867

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3
AD-1964081	UUCAAAUAAGAUGGUCCCAUU	3129	850-870	AAUGGGACCAUCUUAUUUGAAGG	3489	848-870
AD-1964102	GUCUGUAUCCAAAUAAUGAAU	3130	871-891	AUUCAUTAUUUGGAUACAGACUA	3490	869-891
AD-1964103	UCUGUAUCCAAAUAAUGAAUU	3131	872-892	AAUUCATUAUUUGGAUACAGACU	3491	870-892
AD-1964104	CUGUAUCCAAAUAAUGAAUCU	3132	873-893	AGAUTCAUUAUUUGGAUACAGAC	3492	871-893
AD-1964106	GUAUCCAAAUAAUGAAUCUUU	3133	875-895	AAAGAUTCAUUAUUUGGAUACAG	3493	873-895
AD-1964107	UAUCCAAAUAAUGAAUCUUCU	3134	876-896	AGAAGATUCAUUAUUUGGAUACA	3494	874-896
AD-1964108	AUCCAAAUAAUGAAUCUUCGU	3135	877-897	ACGAAGAUUCAUUAUUUGGAUAC	3495	875-897
AD-1964116	AAUGAAUCUUCGGGUGUUUCU	3136	885-905	AGAAACACCCGAAGAUUCAUUAU	3496	883-905
AD-1964118	UGAAUCUUCGGGUGUUUCCCU	3137	887-907	AGGGAAACACCCGAAGAUUCAUU	3497	885-907
AD-1964139	UUAGCUAAGCACAGAUCUACU	3138	908-928	AGUAGATCUGUGCUUAGCUAAAG	3498	906-928
AD-1964140	UAGCUAAGCACAGAUCUACCU	3139	909-929	AGGUAGAUCUGUGCUUAGCUAAA	3499	907-929
AD-1964142	GCUAAGCACAGAUCUACCUUU	3140	911-931	AAAGGUAGAUCUGUGCUUAGCUA	3500	909-931
AD-1964143	CUAAGCACAGAUCUACCUUGU	3141	912-932	ACAAGGTAGAUCUGUGCUUAGCU	3501	910-932
AD-1964150	CAGAUCUACCUUGGUGAUUUU	3142	919-939	AAAATCACCAAGGUAGAUCUGUG	3502	917-939
AD-1964229	AAUAAAAUGUGAAGACUAGAU	3143	1001-1021	AUCUAGTCUUCACAUUUUAUUAG	3503	999-1021
AD-1964267	ACAACUGCUGUGGCUGGUUGU	3144	1039-1059	ACAACCAGCCACAGCAGUUGUGU	3504	1037-1059
AD-1964274	CUGUGGCUGGUUGGUGCUUUU	3145	1046-1066	AAAAGCACCAACCAGCCACAGCA	3505	1044-1066
AD-1964284	UUGGUGCUUUGUUUAUGGUAU	3146	1056-1076	AUACCATAAACAAAGCACCAACC	3506	1054-1076
AD-1964289	GCUUUGUUUAUGGUAGUAGUU	3147	1061-1081	AACUACTACCAUAAACAAAGCAC	3507	1059-1081
AD-1964291	UUUGUUUAUGGUAGUAGUUUU	3148	1063-1083	AAAACUACUACCAUAAACAAAGC	3508	1061-1083
AD-1964292	UUGUUUAUGGUAGUAGUUUUU	3149	1064-1084	AAAAACTACUACCAUAAACAAAG	3509	1062-1084
AD-1964297	AUGGUAGUAGUUUUUCUGUAU	3150	1070-1090	AUACAGAAAAACUACUACCAUAA	3510	1068-1090
AD-1964299	GGUAGUAGUUUUUCUGUAACU	3151	1072-1092	AGUUACAGAAAAACUACUACCAU	3511	1070-1092

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3
AD-1964301	UAGUAGUUUUUC UGUAACACU	3152	1074-1094	AGUGTUACAGAAA AACUACUACC	3512	1072-1094
AD-1964302	AGUAGUUUUUCU GUAACACAU	3153	1075-1095	AUGUGUTACAGAA AAACUACUAC	3513	1073-1095
AD-1964303	GUAGUUUUUCUG UAACACAGU	3154	1076-1096	ACUGTGTUACAGA AAAACUACUA	3514	1074-1096
AD-1964325	AAUAAGAAUAAA GUACCUUGU	3155	1110-1130	ACAAGGTACUUUA UUCUUAUUUC	3515	1108-1130
AD-1964328	AAGAAUAAAGUA CCUUGACUU	3156	1113-1133	AAGUCAAGGUACU UUAUUCUUAU	3516	1111-1133
AD-1964329	AGAAUAAAGUAC CUUGACUUU	3157	1114-1134	AAAGTCAAGGUAC UUUAUUCUUA	3517	1112-1134
AD-1964331	AAUAAAGUACCU UGACUUUGU	3158	1116-1136	ACAAAGTCAAGGU ACUUUAUUCU	3518	1114-1136
AD-1964335	AAGUACCUUGAC UUUGUUCAU	3159	1120-1140	AUGAACAAAGUCA AGGUACUUUA	3519	1118-1140
AD-1964337	GUACCUUGACUU UGUUCACAU	3160	1122-1142	AUGUGAACAAAGU CAAGGUACUU	3520	1120-1142
AD-1964338	UACCUUGACUUU GUUCACAGU	3161	1123-1143	ACUGTGAACAAAG UCAAGGUACU	3521	1121-1143
AD-1964340	CCUUGACUUUGU UCACAGCAU	3162	1125-1145	AUGCTGTGAACAA AGUCAAGGUA	3522	1123-1145
AD-1964342	UUGACUUUGUUC ACAGCAUGU	3163	1127-1147	ACAUGCTGUGAAC AAAGUCAAGG	3523	1125-1147
AD-1964346	CUUUGUUCACAG CAUGUAGGU	3164	1131-1151	ACCUACAUGCUGU GAACAAAGUC	3524	1129-1151
AD-1964353	CACAGCAUGUAG GGUGAUGAU	3165	1138-1158	AUCATCACCCUAC AUGCUGUGAA	3525	1136-1158
AD-1964355	CAGCAUGUAGGG UGAUGAGCU	3166	1140-1160	AGCUCATCACCCU ACAUGCUGUG	3526	1138-1160
AD-1964356	AGCAUGUAGGGU GAUGAGCAU	3167	1141-1161	AUGCTCAUCACCC UACAUGCUGU	3527	1139-1161
AD-1964358	CAUGUAGGGUGA UGAGCACUU	3168	1143-1163	AAGUGCTCAUCAC CCUACAUGCU	3528	1141-1163
AD-1964388	GACUAAAAUGCU GCUUUUAAU	3169	1173-1193	AUUAAAAGCAGCA UUUUAGUCAA	3529	1171-1193
AD-1964392	AAAAUGCUGCUU UUAAAACAU	3170	1177-1197	AUGUTUTAAAAGC AGCAUUUUAG	3530	1175-1197
AD-1964395	AUGCUGCUUUUA AAACAUAGU	3171	1180-1200	ACUATGTUUUAAA AGCAGCAUUU	3531	1178-1200
AD-1964397	GCUGCUUUUAAA ACAUAGGAU	3172	1182-1202	AUCCTATGUUUUA AAAGCAGCAU	3532	1180-1202
AD-1964398	CUGCUUUUAAAA CAUAGGAAU	3173	1183-1203	AUUCCUAUGUUUU AAAAGCAGCA	3533	1181-1203
AD-1964399	UGCUUUUAAAAC AUAGGAAAU	3174	1184-1204	AUUUCCTAUGUUU UAAAAGCAGC	3534	1182-1204

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3
AD-1964402	UUUUAAAACAUAGGAAAGUAU	3175	1187-1207	AUACUUTCCUAUGUUUUAAAAGC	3535	1185-1207
AD-1964407	AAACAUAGGAAAGUAGAAUGU	3176	1192-1212	ACAUTCTACUUUCCUAUGUUUUA	3536	1190-1212
AD-1964428	UUGAGUGCAAAUCCAUAGCAU	3177	1213-1233	AUGCTATGGAUUUGCACUCAACC	3537	1211-1233
AD-1964429	UGAGUGCAAAUCCAUAGCACU	3178	1214-1234	AGUGCUAUGGAUUUGCACUCAAC	3538	1212-1234
AD-1964449	AAGAUAAAUUGAGCUAGUUAU	3179	1234-1254	AUAACUAGCUCAAUUUAUCUUGU	3539	1232-1254
AD-1964450	AGAUAAAUUGAGCUAGUUAAU	3180	1235-1255	AUUAACTAGCUCAAUUUAUCUUG	3540	1233-1255
AD-1964454	AAAUUGAGCUAGUUAAGGCAU	3181	1239-1259	AUGCCUTAACUAGCUCAAUUUAU	3541	1237-1259
AD-1964455	AAUUGAGCUAGUUAAGGCAAU	3182	1240-1260	AUUGCCTUAACUAGCUCAAUUUA	3542	1238-1260
AD-1964459	GAGCUAGUUAAGGCAAAUCAU	3183	1244-1264	AUGATUTGCCUUAACUAGCUCAA	3543	1242-1264
AD-1964462	CUAGUUAAGGCAAAUCAGGUU	3184	1247-1267	AACCTGAUUUGCCUUAACUAGCU	3544	1245-1267
AD-1964464	AGUUAAGGCAAAUCAGGUAAU	3185	1249-1269	AUUACCTGAUUUGCCUUAACUAG	3545	1247-1269
AD-1964467	UAAGGCAAAUCAGGUAAAAUU	3186	1252-1272	AAUUTUACCUGAUUUGCCUUAAC	3546	1250-1272
AD-1964468	AAGGCAAAUCAGGUAAAAUAU	3187	1253-1273	AUAUTUTACCUGAUUUGCCUUAA	3547	1251-1273
AD-1964471	GCAAAUCAGGUAAAAUAGUCU	3188	1256-1276	AGACTATUUUACCUGAUUUGCCU	3548	1254-1276
AD-1964472	CAAAUCAGGUAAAAUAGUCAU	3189	1257-1277	AUGACUAUUUUACCUGAUUUGCC	3549	1255-1277
AD-1964473	AAAUCAGGUAAAAUAGUCAUU	3190	1258-1278	AAUGACTAUUUUACCUGAUUUGC	3550	1256-1278
AD-1964475	AUCAGGUAAAAUAGUCAUGAU	3191	1260-1280	AUCATGACUAUUUUACCUGAUUU	3551	1258-1280
AD-1964477	CAGGUAAAAUAGUCAUGAUUU	3192	1262-1282	AAAUCATGACUAUUUUACCUGAU	3552	1260-1282
AD-1964478	AGGUAAAAUAGUCAUGAUUCU	3193	1263-1283	AGAATCAUGACUAUUUUACCUGA	3553	1261-1283
AD-1964480	GUAAAAUAGUCAUGAUUCUAU	3194	1265-1285	AUAGAATCAUGACUAUUUUACCU	3554	1263-1285
AD-1964481	UAAAAUAGUCAUGAUUCUAUU	3195	1266-1286	AAUAGAAUCAUGACUAUUUUACC	3555	1264-1286
AD-1964489	UCAUGAUUCUAUGUAAUGUAU	3196	1274-1294	AUACAUTACAUAGAAUCAUGACU	3556	1272-1294
AD-1964490	CAUGAUUCUAUGUAAUGUAAU	3197	1275-1295	AUUACATUACAUAGAAUCAUGAC	3557	1273-1295

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000 067.3
AD-1964493	GAUUCUAUGUAA UGUAAACCU	3198	1278-1298	AGGUUUACAUUAC AUAGAAUCAU	3558	1276-1298
AD-1964551	AUGACUUUUGAA UUACAGAGU	3199	1407-1427	ACUCUGUAAUUCA AAAGUCAUUA	3559	1405-1427
AD-1964553	GACUUUUGAAUU ACAGAGAUU	3200	1409-1429	AAUCUCUGUAAUU CAAAAGUCAU	3560	1407-1429
AD-1964578	UAUAAUUAGAGU UGUGAUACU	3201	1458-1478	AGUAUCACAACUC UAAUUAUAAC	3561	1456-1478
AD-1964580	UAAUUAGAGUUG UGAUACAGU	3202	1460-1480	ACUGUAUCACAAC UCUAAUUAUA	3562	1458-1480
AD-1964581	AAUUAGAGUUGU GAUACAGAU	3203	1461-1481	AUCUGUAUCACAA CUCUAAUUAU	3563	1459-1481
AD-1964582	AUUAGAGUUGUG AUACAGAGU	3204	1462-1482	ACUCUGUAUCACA ACUCUAAUUA	3564	1460-1482
AD-1964584	UAGAGUUGUGAU ACAGAGUAU	3205	1464-1484	AUACUCUGUAUCA CAACUCUAAU	3565	1462-1484
AD-1964586	GAGUUGUGAUAC AGAGUAUAU	3206	1466-1486	AUAUACUCUGUAU CACAACUCUA	3566	1464-1486
AD-1964588	GUUGUGAUACAG AGUAUAUUU	3207	1468-1488	AAAUAUACUCUGU AUCACAACUC	3567	1466-1488
AD-1964610	CAUUCAGACAAU AUAUCAUAU	3208	1490-1510	AUAUGAUAUAUUG UCUGAAUGGA	3568	1488-1510
AD-1964611	AUUCAGACAAUA UAUCAUAAU	3209	1491-1511	AUUAUGAUAUAUU GUCUGAAUGG	3569	1489-1511

Table 10. Modified Sense and Antisense Strand Sequences of CA2 dsRNA Agents with C16 Modification

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1962343	ascscug(Ahd)GfcAf CfUfggcauaagsgsu	3570	asCfscuuAfugccagu GfcUfcaggcscsc	3930	GGACCUGAGCAC UGGCAUAAGGA	2834
AD-1962345	csusgag(Chd)AfcUf GfGfcauaaggascsu	3571	asGfsucoUfuaugccaG fuGfcucagsgsu	3931	ACCUGAGCACUG GCAUAAGGACU	2781
AD-1962360	usgsaca(Uhd)CfgAf CfAfcucauacasgsu	3572	asCfsuguAfugagugu CfgAfugucasasc	3932	GUUGACAUCGAC ACUCAUACAGC	2640
AD-1962369	csascuc(Ahd)UfaCf AfGfccaaguausgsu	3573	asCfsauaCfuuggcug UfaUfgagugsusc	3933	GACACUCAUACA GCCAAGUAUGA	2652
AD-1962370	ascsuca(Uhd)AfcAf GfCfcaaguaugsasu	3574	asUfscauAfcuuggcu GfuAfugagusgsu	3934	ACACUCAUACAG CCAAGUAUGAC	2637
AD-1962371	csuscau(Ahd)CfaGf CfCfaaguaugascsu	3575	asGfsucaUfacuuggc UfgUfaugagsusg	3935	CACUCAUACAGC CAAGUAUGACC	2691
AD-1962380	cscsaag(Uhd)AfuGf AfCfccuucccusgsu	3576	asCfsaggGfaaggguc AfuAfcuuggscsu	3936	AGCCAAGUAUGA CCCUUCCCUGA	2710

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1962416	csusgag(Ghd)AfuCfCfUfcaacaaugsgsu	3577	asCfscauUfguugaggAfuCfcucagsgsg	3937	CCCUGAGGAUCCUCAACAAUGGU	2759
AD-1962417	usgsagg(Ahd)UfcCfUfCfaacaauggsusu	3578	asAfsccaUfuguugagGfaUfccucasgsg	3938	CCUGAGGAUCCUCAACAAUGGUC	2717
AD-1962418	gsasgga(Uhd)CfcUfCfAfacaaugguscsu	3579	asGfsaccAfuuguugaGfgAfuccucsasg	3939	CUGAGGAUCCUCAACAAUGGUCA	2703
AD-1962439	usgscuu(Uhd)CfaAfCfGfuggaguuusgsu	3580	asCfsaaaCfuccacguUfgAfaagcasusg	3940	CAUGCUUUCAACGUGGAGUUUGA	2625
AD-1962440	gscsuuu(Chd)AfaCfGfUfggaguuugsasu	3581	asUfscaaAfcuccacgUfuGfaaagcsasu	3941	AUGCUUUCAACGUGGAGUUUGAU	2624
AD-1962441	csusuuc(Ahd)AfcGfUfGfgaguuugasusu	3582	asAfsucaAfacuccacGfuUfgaaagcsca	3942	UGCUUUCAACGUGGAGUUUGAUG	2634
AD-1962442	ususuca(Ahd)CfgUfGfGfaguuugausgsu	3583	asCfsaucAfaacuccaCfgUfugaaasgsc	3943	GCUUUCAACGUGGAGUUUGAUGA	2650
AD-1962451	gsgsagu(Uhd)UfgAfUfGfacucucagsgsu	3584	asCfscugAfgagucauCfaAfacuccsasc	3944	GUGGAGUUUGAUGACUCUCAGGA	2725
AD-1962460	usgsacu(Chd)UfcAfGfGfacaaagcasgsu	3585	asCfsugcUfuuguccuGfaGfagucasusc	3945	GAUGACUCUCAGGACAAAGCAGU	2787
AD-1962557	asascuu(Chd)AfcUfUfGfguucacugsgsu	3586	asCfscagUfgaaccaaGfuGfaaguuscsu	3946	AGAACUUCACUUGGUUCACUGGA	2721
AD-1962597	csusgau(Ghd)GfaCfUfGfgccguucusasu	3587	asUfsagaAfcggccagUfcCfaucagsgsu	3947	ACCUGAUGGACUGGCCGUUCUAG	2838
AD-1962598	usgsaug(Ghd)AfcUfGfGfccguucuasgsu	3588	asCfsuagAfacggccaGfuCfcaucasgsg	3948	CCUGAUGGACUGGCCGUUCUAGG	2843
AD-1962599	gsasugg(Ahd)CfuGfGfCfcguucuagsgsu	3589	asCfscuaGfaacggccAfgUfccaucsasg	3949	CUGAUGGACUGGCCGUUCUAGGU	2841
AD-1962600	asusgga(Chd)UfgGfCfCfguucuaggsusu	3590	asAfsccuAfgaacggcCfaGfuccauscsa	3950	UGAUGGACUGGCCGUUCUAGGUA	2833
AD-1962603	gsascug(Ghd)CfcGfUfUfcuagguaususu	3591	asAfsauaCfcuagaacGfgCfcagucscsa	3951	UGGACUGGCCGUUCUAGGUAUUU	2776
AD-1962604	ascsugg(Chd)CfgUfUfCfuagguauususu	3592	asAfsaauAfccuagaaCfgGfccaguscsc	3952	GGACUGGCCGUUCUAGGUAUUUU	2751
AD-1962605	csusggc(Chd)GfuUfCfUfagguauuususu	3593	asAfsaaaUfaccuagaAfcGfgccagsusc	3953	GACUGGCCGUUCUAGGUAUUUUU	2646
AD-1962606	usgsgcc(Ghd)UfuCfUfAfgguauuuususu	3594	asAfsaaaAfuaccuagAfaCfggccasgsu	3954	ACUGGCCGUUCUAGGUAUUUUUU	2673
AD-1962607	gsgsccg(Uhd)UfcUfAfGfguauuuuususu	3595	asAfsaaaAfauaccuaGfaAfcggccsasg	3955	CUGGCCGUUCUAGGUAUUUUUUU	2700
AD-1962608	gscscgu(Uhd)CfuAfGfGfuauuuuuususu	3596	asAfsaaaAfaauaccuAfgAfacggcscsa	3956	UGGCCGUUCUAGGUAUUUUUUUG	2681
AD-1962609	cscsguu(Chd)UfaGfGfUfauuuuuuusgsu	3597	asCfsaaaAfaaauaccUfaGfaacggcsesc	3957	GGCCGUUCUAGGUAUUUUUUUGA	2662
AD-1962610	csgsuuc(Uhd)AfgGfUfAfuuuuuuugsasu	3598	asUfscaaAfaaaauacCfuAfgaacgsgsc	3958	GCCGUUCUAGGUAUUUUUUUGAA	2606
AD-1962611	gsusucu(Ahd)GfgUfAfUfuuuuuugasasu	3599	asUfsucaAfaaaaauaCfcUfagaacsgsg	3959	CCGUUCUAGGUAUUUUUUUGAAG	2586

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1962612	ususcua(Ghd)GfuAf UfUfuuuuugaasgsu	3600	asCfsuucAfaaaaaauA fcCfuagaasesg	3960	CGUUCUAGGUAU UUUUUUGAAGG	2607
AD-1962613	uscsuag(Ghd)UfaUf UfUfuuuugaagsgsu	3601	asCfscuuCfaaaaaaU faCfcuagasasc	3961	GUUCUAGGUAUU UUUUUGAAGGU	2679
AD-1962615	usasggu(Ahd)UfuUf UfUfuugaaggususu	3602	asAfsaccUfucaaaaaA faUfaccuasgsa	3962	UCUAGGUAUUUU UUUGAAGGUUG	2642
AD-1962616	asgsgua(Uhd)UfuUf UfUfugaagguusgsu	3603	asCfsaacCfuucaaaaA faAfuaccusasg	3963	CUAGGUAUUUUU UUGAAGGUUGG	2738
AD-1962617	gsgsuau(Uhd)UfuUf UfUfgaagguugsgsu	3604	asCfscaaCfcuucaaaA faAfauaccsusa	3964	UAGGUAUUUUUU UGAAGGUUGGC	2731
AD-1962618	gsusauu(Uhd)UfuUf UfGfaagguuggscsu	3605	asGfsccaAfccuucaaA faAfaauacscsu	3965	AGGUAUUUUUUU GAAGGUUGGCA	2789
AD-1962620	asususuu(Uhd)UfuGf AfAfgguuggcasgsu	3606	asCfsugcCfaaccuucA faAfaaaausasc	3966	GUAUUUUUUUGA AGGUUGGCAGC	2807
AD-1962648	csgsggc(Chd)UfuCf AfGfaaaguugususu	3607	asAfsacaAfcuuucug AfaGfgcccgsgsu	3967	ACCGGGCCUUCA GAAAGUUGUUG	2701
AD-1962649	gsgsgcc(Uhd)UfcAf GfAfaaguuguusgsu	3608	asCfsaacAfacuuucuG faAfggcccsgsg	3968	CCGGGCCUUCAG AAAGUUGUUGA	2726
AD-1962650	gsgsccu(Uhd)CfaGf AfAfaguuguugsasu	3609	asUfscaaCfaacuuucU fgAfaggccscsg	3969	CGGGCCUUCAGA AAGUUGUUGAU	2712
AD-1962652	cscsuuc(Ahd)GfaAf AfGfuuguugausgsu	3610	asCfsaucAfacaacuuU fcUfgaaggcsc	3970	GGCCUUCAGAAA GUUGUUGAUGU	2756
AD-1962653	csusuca(Ghd)AfaAf GfUfuguugaugsusu	3611	asAfscauCfaacaacuU fuCfugaagsgsc	3971	GCCUUCAGAAAG UUGUUGAUGUG	2696
AD-1962655	uscsaga(Ahd)AfgUf UfGfuugaugugscsu	3612	asGfscacAfucaacaaC fuUfucugasasg	3972	CUUCAGAAAGUU GUUGAUGUGCU	2795
AD-1962658	gsasaag(Uhd)UfgUf UfGfaugugcugsgsu	3613	asCfscagCfacaucaaC faAfcuuucsusg	3973	CAGAAAGUUGUU GAUGUGCUGGA	2820
AD-1962678	asususcc(Ahd)UfuAf AfAfacaaagggscsu	3614	asGfscccUfuuguuuu AfaUfggaauscsc	3974	GGAUUCCAUUAA AACAAAGGGCA	2729
AD-1962688	asascaa(Ahd)GfgGf CfAfagagugcusgsu	3615	asCfsagcAfcucuugcC fcUfuuguususu	3975	AAAACAAAGGGC AAGAGUGCUGA	2821
AD-1962701	asgsugc(Uhd)GfaCf UfUfcacuaacususu	3616	asAfsaguUfagugaag UfcAfgcacuscsu	3976	AGAGUGCUGACU UCACUAACUUC	2599
AD-1962703	usgscug(Ahd)CfuUf CfAfcuaacuucsgsu	3617	asCfsgaaGfuuaguga AfgUfcagcascsu	3977	AGUGCUGACUUC ACUAACUUCGA	2583
AD-1962705	csusgac(Uhd)UfcAf CfUfaacuucgasusu	3618	asAfsucgAfaguuagu GfaAfgucagscsa	3978	UGCUGACUUCAC UAACUUCGAUC	2562
AD-1962706	usgsacu(Uhd)CfaCf UfAfacuucgauscsu	3619	asGfsaucGfaaguuag UfgAfagucasgsc	3979	GCUGACUUCACU AACUUCGAUCC	2542
AD-1962707	gsascuu(Chd)AfcUf AfAfcuucgaucscsu	3620	asGfsgauCfgaaguua GfuGfaagucsasg	3980	CUGACUUCACUA ACUUCGAUCCU	2551
AD-1962712	csascua(Ahd)CfuUf CfGfauccucgusgsu	3621	asCfsacgAfggaucgaA fgUfuagugsasa	3981	UUCACUAACUUC GAUCCUCGUGG	2601
AD-1962713	ascsuaa(Chd)UfuCf GfAfuccucgugsgsu	3622	asCfscacGfaggaucgA faGfuuagusgsa	3982	UCACUAACUUCG AUCCUCGUGGC	2755

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1962733	cscsucc(Uhd)UfcCfUfGfaauccuugsgsu	3623	asCfscaaGfgauucagGfaAfggaggscsc	3983	GGCCUCCUUCCUGAAUCCUUGGA	2629
AD-1962735	uscscuu(Chd)CfuGfAfAfuccuuggasusu	3624	asAfsuccAfaggauucAfgGfaaggasgsg	3984	CCUCCUUCCUGAAUCCUUGGAUU	2608
AD-1962736	cscsuuc(Chd)UfgAfAfUfccuuggaususu	3625	asAfsaucCfaaggauuCfaGfgaaggsasg	3985	CUCCUUCCUGAAUCCUUGGAUUA	2611
AD-1962766	csusccu(Chd)UfuCfUfGfgaaugugusgsu	3626	asCfsacaCfauuccagAfaGfaggagsgsg	3986	CCCUCCUCUUCUGGAAUGUGUGA	2623
AD-1962777	gsasaug(Uhd)GfuGfAfCfcuggauugsusu	3627	asAfscaaUfccaggucAfcAfcauucscsa	3987	UGGAAUGUGUGACCUGGAUUGUG	2816
AD-1962780	usgsugu(Ghd)AfcCfUfGfgauugugcsusu	3628	asAfsgcaCfaauccagGfuCfacacasusu	3988	AAUGUGUGACCUGGAUUGUGCUC	2805
AD-1962795	gsusgcu(Chd)AfaGfGfAfacccaucasgsu	3629	asCfsugaUfggguuceUfuGfagcacsasa	3989	UUGUGCUCAAGGAACCCAUCAGC	2766
AD-1962799	uscsaag(Ghd)AfaCfCfCfaucagcgusesu	3630	asGfsacgCfugaugggUfuCfcuugasgsc	3990	GCUCAAGGAACCCAUCAGCGUCA	2794
AD-1962801	asasgga(Ahd)CfcCfAfUfcagcgucasgsu	3631	asCfsugaCfgcugaugGfgUfuccuusgsa	3991	UCAAGGAACCCAUCAGCGUCAGC	2811
AD-1962808	cscsauc(Ahd)GfcGfUfCfagcagcgasgsu	3632	asCfsucgCfugcugacGfcUfgauggsgsu	3992	ACCCAUCAGCGUCAGCAGCGAGC	2835
AD-1962836	gsasaau(Uhd)CfcGfUfAfaacuuaacsusu	3633	asAfsguuAfaguuuacGfgAfauuucsasa	3993	UUGAAAUUCCGUAAACUUAACUU	2584
AD-1962837	asasauu(Chd)CfgUfAfAfacuuaacususu	3634	asAfsaguUfaaguuuaCfgGfaauuusesa	3994	UGAAAUUCCGUAAACUUAACUUC	2559
AD-1962842	cscsgua(Ahd)AfcUfUfAfacuucaausgsu	3635	asCfsauuGfaaguuaaGfuUfuacggsasa	3995	UUCCGUAAACUUAACUUCAAUGG	2556
AD-1962843	csgsuaa(Ahd)CfuUfAfAfcuucaaugsgsu	3636	asCfscauUfgaaguuaAfgUfuuacgsgsa	3996	UCCGUAAACUUAACUUCAAUGGG	2659
AD-1962860	asascug(Ahd)UfgGfUfGfgacaacugsgsu	3637	asCfscagUfuguccacCfaUfcaguuscsu	3997	AGAACUGAUGGUGGACAACUGGC	2844
AD-1962885	csuscag(Chd)CfaCfUfGfaagaacagsgsu	3638	asCfscugUfucuucagUfgGfcugagscsu	3998	AGCUCAGCCACUGAAGAACAGGC	2799
AD-1962897	asgsaac(Ahd)GfgCfAfAfaucaaagcsusu	3639	asAfsgcuUfugauuugCfcUfguucususc	3999	GAAGAACAGGCAAAUCAAAGCUU	2749
AD-1962902	asgsgca(Ahd)AfuCfAfAfagcuuccususu	3640	asAfsaggAfagcuuugAfuUfugccusgsu	4000	ACAGGCAAAUCAAAGCUUCCUUC	2567
AD-1962910	csasaag(Chd)UfuCfCfUfucaaauaasgsu	3641	asCfsuuaUfuugaaggAfaGfcuuugsasu	4001	AUCAAAGCUUCCUUCAAAUAAGA	2543
AD-1962911	asasagc(Uhd)UfcCfUfUfcaaauaagsasu	3642	asUfscuuAfuuugaagGfaAfgcuuusgsa	4002	UCAAAGCUUCCUUCAAAUAAGAU	2569
AD-1962912	asasgcu(Uhd)CfcUfUfCfaaauaagasusu	3643	asAfsucuUfauuugaaGfgAfagcuususg	4003	CAAAGCUUCCUUCAAAUAAGAUG	2558
AD-1962913	asgscuu(Chd)CfuUfCfAfaauaagausgsu	3644	asCfsaucUfuauuugaAfgGfaagcususu	4004	AAAGCUUCCUUCAAAUAAGAUGG	2565
AD-1962914	gscsuuc(Chd)UfuCfAfAfauaagaugsgsu	3645	asCfscauCfuuauuugAfaGfgaagcsusu	4005	AAGCUUCCUUCAAAUAAGAUGGU	2563

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1962941	gsuscug(Uhd)AfuCfCfAfaauaaugasasu	3646	asUfsucaUfuauuuggAfuAfcagacsusa	4006	UAGUCUGUAUCCAAAUAAUGAAU	2545
AD-1962945	gsusauc(Chd)AfaAfUfAfaugaaucususu	3647	asAfsagaUfucauuauUfuGfgauacsasg	4007	CUGUAUCCAAAUAAUGAAUCUUC	2561
AD-1962947	asuscca(Ahd)AfuAfAfUfgaaucuucsgsu	3648	asCfsgaaGfauucauuAfuUfuggausasc	4008	GUAUCCAAAUAAUGAAUCUUCGG	2614
AD-1962948	uscscaa(Ahd)UfaAfUfGfaaucuucgsgsu	3649	asCfscgaAfgauucauUfaUfuuggasusa	4009	UAUCCAAAUAAUGAAUCUUCGGG	2732
AD-1962949	cscsaaa(Uhd)AfaUfGfAfaucuucggsgsu	3650	asCfsccgAfagauucaUfuAfuuuggsasu	4010	AUCCAAAUAAUGAAUCUUCGGGU	2796
AD-1962950	csasaau(Ahd)AfuGfAfAfucuucgggsusu	3651	asAfscccGfaagauucAfuUfauuugsgsa	4011	UCCAAAUAAUGAAUCUUCGGGUG	2743
AD-1962951	asasaua(Ahd)UfgAfAfUfcuucgggusgsu	3652	asCfsaccCfgaagauuCfaUfuauuusgsg	4012	CCAAAUAAUGAAUCUUCGGGUGU	2815
AD-1962952	asasuaa(Uhd)GfaAfUfCfuucgggugsusu	3653	asAfscacCfcgaagauUfcAfuuauususg	4013	CAAAUAAUGAAUCUUCGGGUGUU	2806
AD-1962953	asusaau(Ghd)AfaUfCfUfucgggugususu	3654	asAfsacaCfccgaagaUfuCfauuaususu	4014	AAAUAAUGAAUCUUCGGGUGUUU	2801
AD-1962954	usasaug(Ahd)AfuCfUfUfcggguguususu	3655	asAfsaacAfcccgaagAfuUfcauuasusu	4015	AAUAAUGAAUCUUCGGGUGUUUC	2809
AD-1962957	usgsaau(Chd)UfuCfGfGfguguuuccscsu	3656	asGfsggaAfacacccgAfaGfauucasusu	4016	AAUGAAUCUUCGGGUGUUUCCCU	2739
AD-1962958	gsasauc(Uhd)UfcGfGfGfuguuucccsusu	3657	asAfsgggAfaacacccGfaAfgauucsasu	4017	AUGAAUCUUCGGGUGUUUCCCUU	2747
AD-1962984	asasgca(Chd)AfgAfUfCfuaccuuggsusu	3658	asAfsccaAfgguagauCfuGfugcuusasg	4018	CUAAGCACAGAUCUACCUUGGUG	2671
AD-1962985	asgscac(Ahd)GfaUfCfUfaccuuggusgsu	3659	asCfsaccAfagguagaUfcUfgugcususa	4019	UAAGCACAGAUCUACCUUGGUGA	2680
AD-1962986	gscsaca(Ghd)AfuCfUfAfccuuggugsasu	3660	asUfscacCfaagguagAfuCfugugcsusu	4020	AAGCACAGAUCUACCUUGGUGAU	2633
AD-1962990	asgsauc(Uhd)AfcCfUfUfggugauuusgsu	3661	asCfsaaaUfcaccaagGfuAfgaucusgsu	4021	ACAGAUCUACCUUGGUGAUUUGG	2616
AD-1963114	ascsaac(Uhd)GfcUfGfUfggcugguusgsu	3662	asCfsaacCfagccacaGfcAfguugusgsu	4022	ACACAACUGCUGUGGCUGGUUGG	2845
AD-1963115	csasacu(Ghd)CfuGfUfGfgcugguugsgsu	3663	asCfscaaCfcagccacAfgCfaguugsusg	4023	CACAACUGCUGUGGCUGGUUGGU	2847
AD-1963118	csusgcu(Ghd)UfgGfCfUfgguuggugscsu	3664	asGfscacCfaaccagcCfaCfagcagsusu	4024	AACUGCUGUGGCUGGUUGGUGCU	2849
AD-1963123	gsusggc(Uhd)GfgUfUfGfgugcuuugsusu	3665	asAfscaaAfgcaccaaCfcAfgccacsasg	4025	CUGUGGCUGGUUGGUGCUUUGUU	2810
AD-1963125	gsgscug(Ghd)UfuGfGfUfgcuuuguususu	3666	asAfsaacAfaagcaccAfaCfcagccsasc	4026	GUGGCUGGUUGGUGCUUUGUUUA	2769
AD-1963126	gscsugg(Uhd)UfgGfUfGfcuuuguuusasu	3667	asUfsaaaCfaaagcacCfaAfccagcscsa	4027	UGGCUGGUUGGUGCUUUGUUUAU	2753
AD-1963127	csusggu(Uhd)GfgUfGfCfuuuguuuasusu	3668	asAfsuaaAfcaaagcaCfcAfaccagcscsc	4028	GGCUGGUUGGUGCUUUGUUUAUG	2686

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1963128	usgsguu(Ghd)GfuGfCfUfuuguuuausgsu	3669	asCfsauaAfacaaagcAfcCfaaccasgsc	4029	GCUGGUUGGUGCUUUGUUUAUGG	2690
AD-1963129	gsgsuug(Ghd)UfgCfUfUfuguuuaugsgsu	3670	asCfscauAfaacaaagCfaCfcaaccsasg	4030	CUGGUUGGUGCUUUGUUUAUGGU	2737
AD-1963130	gsusugg(Uhd)GfcUfUfUfguuuauggsusu	3671	asAfsccaUfaaacaaaGfcAfccaaccsca	4031	UGGUUGGUGCUUUGUUUAUGGUA	2746
AD-1963131	ususggu(Ghd)CfuUfUfGfuuuauggusasu	3672	asUfsaccAfuaaacaaAfgCfaccaascsc	4032	GGUUGGUGCUUUGUUUAUGGUAG	2651
AD-1963132	usgsgug(Chd)UfuUfGfUfuuaugguasgsu	3673	asCfsuacCfauaaacaAfaGfcaccasasc	4033	GUUGGUGCUUUGUUUAUGGUAGU	2643
AD-1963135	usgscuu(Uhd)GfuUfUfAfugguaguasgsu	3674	asCfsuacUfaccauaaAfcAfaagcascsc	4034	GGUGCUUUGUUUAUGGUAGUAGU	2684
AD-1963138	ususugu(Uhd)UfaUfGfGfuaguaguususu	3675	asAfsaacUfacuaccaUfaAfacaaasgsc	4035	GCUUUGUUUAUGGUAGUAGUUUU	2723
AD-1963139	ususguu(Uhd)AfuGfGfUfaguaguuususu	3676	asAfsaaaCfuacuaccAfuAfaacaasasg	4036	CUUUGUUUAUGGUAGUAGUUUUU	2773
AD-1963140	gsusuua(Uhd)GfgUfAfGfuaguuuuuscsu	3677	asGfsaaaAfacuacuaCfcAfuaaacsasa	4037	UUGUUUAUGGUAGUAGUUUUUCU	2760
AD-1963141	ususuau(Ghd)GfuAfGfUfaguuuuucsusu	3678	asAfsgaaAfaacuacuAfcCfauaaascsa	4038	UGUUUAUGGUAGUAGUUUUUCUG	2663
AD-1963142	ususaug(Ghd)UfaGfUfAfguuuuucusgsu	3679	asCfsagaAfaaacuacUfaCfcauaasasc	4039	GUUUAUGGUAGUAGUUUUUCUGU	2720
AD-1963143	usasugg(Uhd)AfgUfAfGfuuuuucugsusu	3680	asAfscagAfaaaacuaCfuAfccauasasa	4040	UUUAUGGUAGUAGUUUUUCUGUA	2675
AD-1963144	asusggu(Ahd)GfuAfGfUfuuuucugusasu	3681	asUfsacaGfaaaaacuAfcUfaccausasa	4041	UUAUGGUAGUAGUUUUUCUGUAA	2617
AD-1963148	usasgua(Ghd)UfuUfUfcuguaacascsu	3682	asGfsuguUfacagaaaAfaCfuacuascsc	4042	GGUAGUAGUUUUUCUGUAACACA	2740
AD-1963202	asgsaau(Ahd)AfaGfUfAfccuugacususu	3683	asAfsaguCfaagguacUfuUfauucususa	4043	UAAGAAUAAAGUACCUUGACUUU	2572
AD-1963204	asasuaa(Ahd)GfuAfCfCfuugacuuusgsu	3684	asCfsaaaGfucaagguAfcUfuuauuscsu	4044	AGAAUAAAGUACCUUGACUUUGU	2706
AD-1963205	asusaaa(Ghd)UfaCfCfUfugacuuugsusu	3685	asAfscaaAfgucaaggUfaCfuuuaususc	4045	GAAUAAAGUACCUUGACUUUGUU	2653
AD-1963206	usasaag(Uhd)AfcCfUfUfgacuuugususu	3686	asAfsacaAfagucaagGfuAfcuuuasusu	4046	AAUAAAGUACCUUGACUUUGUUC	2595
AD-1963207	asasagu(Ahd)CfcUfUfGfacuuuguuscsu	3687	asGfsaacAfaagucaaGfgUfacuuusasu	4047	AUAAAGUACCUUGACUUUGUUCA	2603
AD-1963208	asasgua(Chd)CfuUfGfAfcuuuguucsasu	3688	asUfsgaaCfaaagucaAfgGfuacuususa	4048	UAAAGUACCUUGACUUUGUUCAC	2579
AD-1963211	usasccu(Uhd)GfaCfUfUfuguucacasgsu	3689	asCfsuguGfaacaaagUfcAfagguascsu	4049	AGUACCUUGACUUUGUUCACAGC	2667
AD-1963218	ascsuuu(Ghd)UfuCfAfCfagcauguasgsu	3690	asCfsuacAfugcugugAfaCfaaagusesa	4050	UGACUUUGUUCACAGCAUGUAGG	2672
AD-1963219	csusuug(Uhd)UfcAfCfAfgcauguagsgsu	3691	asCfscuaCfaugcuguGfaAfcaaagsusc	4051	GACUUUGUUCACAGCAUGUAGGG	2707

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1963220	ususugu(Uhd)CfaCfAfGfcauguaggsgsu	3692	asCfsccuAfcaugcugUfgAfacaaasgsu	4052	ACUUUGUUCACAGCAUGUAGGGU	2744
AD-1963221	ususguu(Chd)AfcAfGfCfauguagggsusu	3693	asAfscccUfacaugcuGfuGfaacaasasg	4053	CUUUGUUCACAGCAUGUAGGGUG	2770
AD-1963222	usgsuuc(Ahd)CfaGfCfAfuguagggusgsu	3694	asCfsaccCfuacaugcUfgUfgaacasasa	4054	UUUGUUCACAGCAUGUAGGGUGA	2803
AD-1963225	uscsaca(Ghd)CfaUfGfUfagggugausgsu	3695	asCfsaucAfcccuacaUfgCfugugasasc	4055	GUUCACAGCAUGUAGGGUGAUGA	2779
AD-1963237	csasacg(Ghd)AfcCfUfGfagcacuggscsu	3696	asGfsccdAg(Tgn)gcucagGfuCfcguugsusg	4056	CACAACGGACCUGAGCACUGGCA	2846
AD-1963239	ascsgga(Chd)CfuGfAfGfcacuggcasusu	3697	asAfsugdCc(Agn)gugcucAfgGfuccgususg	4057	CAACGGACCUGAGCACUGGCAUA	2825
AD-1963244	csesuga(Ghd)CfaCfUfGfgcauaaggsasu	3698	asUfsccdTu(Agn)ugccagUfgCfucaggsusc	4058	GACCUGAGCACUGGCAUAAGGAC	2822
AD-1963245	csusgag(Chd)AfcUfGfGfcauaaggascsu	3699	asGfsucdCu(Tgn)augccaGfuGfcucagsgsu	4059	ACCUGAGCACUGGCAUAAGGACU	2781
AD-1963246	usgsagc(Ahd)CfuGfGfCfauaaggacsusu	3700	asAfsgudCc(Tgn)uaugccAfgUfgcucasgsg	4060	CCUGAGCACUGGCAUAAGGACUU	2757
AD-1963249	gscsacu(Ghd)GfcAfUfAfaggacuucscsu	3701	asGfsgadAg(Tgn)ccuuauGfcCfagugcsusc	4061	GAGCACUGGCAUAAGGACUUCCC	2693
AD-1963287	gsascua(Ahd)AfaUfGfCfugcuuuuasasu	3702	asUfsuaaAfagcagcaUfuUfuagucsasa	4062	UUGACUAAAAAUGCUGCUUUUAAA	2609
AD-1963288	ascsuaa(Ahd)AfuGfCfUfgcuuuuaasasu	3703	asUfsuuaAfaagcagcAfuUfuuaguscsa	4063	UGACUAAAAAUGCUGCUUUUAAAA	2677
AD-1963289	csusaaa(Ahd)UfgCfUfGfcuuuuaaasasu	3704	asUfsuuuAfaaagcagCfaUfuuuagsusc	4064	GACUAAAAAUGCUGCUUUUAAAAC	2682
AD-1963290	usasaaa(Uhd)GfcUfGfCfuuuuaaaascsu	3705	asGfsuuuUfaaaagcaGfcAfuuuuasgsu	4065	ACUAAAAAUGCUGCUUUUAAAACA	2570
AD-1963295	usgscug(Chd)UfuUfUfAfaaacauagsgsu	3706	asCfscuaUfguuuuaaAfaGfcagcasusu	4066	AAUGCUGCUUUUAAAACAUAGGA	2566
AD-1963296	gscsugc(Uhd)UfuUfAfAfaacauaggsasu	3707	asUfsccuAfuguuuuaAfaAfgcagcsasu	4067	AUGCUGCUUUUAAAACAUAGGAA	2597
AD-1963302	ususuaa(Ahd)AfcAfUfAfggaaaguasgsu	3708	asCfsuacUfuuccuauGfuUfuuaaasasg	4068	CUUUUAAAACAUAGGAAAGUAGA	2772
AD-1963306	csusguu(Ghd)AfcAfUfCfgacacucasusu	3709	asAfsugdAg(Tgn)gucgauGfuCfaacagsgsg	4069	CCCUGUUGACAUCGACACUCAUA	2592
AD-1963308	gsusuga(Chd)AfuCfGfAfcacucauascsu	3710	asGfsuadTg(Agn)gugucgAfuGfucaacsasg	4070	CUGUUGACAUCGACACUCAUACA	2578
AD-1963311	gsascau(Chd)GfaCfAfCfucauacagsgsu	3711	asGfscudGu(Agn)ugagugUfcGfaugucsasa	4071	UUGACAUCGACACUCAUACAGCC	2657
AD-1963312	ascsauc(Ghd)AfcAfCfUfcauacagcscsu	3712	asGfsgcdTg(Tgn)augaguGfuCfgaugucsca	4072	UGACAUCGACACUCAUACAGCCA	2762
AD-1963314	asuscga(Chd)AfcUfCfAfuacagccasasu	3713	asUfsugdGc(Tgn)guaugaGfuGfucgausgsu	4073	ACAUCGACACUCAUACAGCCAAG	2692
AD-1963318	ascsacu(Chd)AfuAfCfAfgccaaguasusu	3714	asAfsuadCu(Tgn)ggcuguAfuGfaguguscsg	4074	CGACACUCAUACAGCCAAGUAUG	2632

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1963321	csuscau(Ahd)CfaGfCfCfaaguaugascsu	3715	asGfsucdAu(Agn)cuuggcUfgUfaugagsusg	4075	CACUCAUACAGCCAAGUAUGACC	2691
AD-1963322	uscsaua(Chd)AfgCfCfAfaguaugacscsu	3716	asGfsgudCa(Tgn)acuuggCfuGfuaugasgsu	4076	ACUCAUACAGCCAAGUAUGACCC	2764
AD-1963323	csasuac(Ahd)GfcCfAfAfguaugaccscsu	3717	asGfsggdTc(Agn)uacuugGfcUfguaugsasg	4077	CUCAUACAGCCAAGUAUGACCCU	2788
AD-1963325	usascag(Chd)CfaAfGfUfaugacccususu	3718	asAfsagdGg(Tgn)cauacuUfgGfcuguasusg	4078	CAUACAGCCAAGUAUGACCCUUC	2780
AD-1963329	gscscaa(Ghd)UfaUfGfAfcccuucccsusu	3719	asAfsggdGa(Agn)gggucaUfaCfuuggcsusg	4079	CAGCCAAGUAUGACCCUUCCCUG	2674
AD-1963375	gsasuaa(Ahd)UfuGfAfGfcuaguuaasgsu	3720	asCfsuuaAfcuagcucAfaUfuuaucsusu	4080	AAGAUAAAUUGAGCUAGUUAAGG	2798
AD-1963376	asusaaa(Uhd)UfgAfGfCfuaguuaagsgsu	3721	asCfscuuAfacuagcuCfaAfuuuauscsu	4081	AGAUAAAUUGAGCUAGUUAAGGC	2819
AD-1963377	usasaau(Uhd)GfaGfCfUfaguuaaggscsu	3722	asGfsccuUfaacuagcUfcAfauuuasusc	4082	GAUAAAUUGAGCUAGUUAAGGCA	2784
AD-1963384	gsusaug(Ahd)CfcCfUfUfcccugaagscsu	3723	asGfscudTc(Agn)gggaagGfgUfcauacsusu	4083	AAGUAUGACCCUUCCCUGAAGCC	2830
AD-1963386	csusguc(Uhd)GfuUfUfCfcuaugaucsasu	3724	asUfsgadTc(Agn)uaggaaAfcAfgacagsgsg	4084	CCCUGUCUGUUUCCUAUGAUCAA	2560
AD-1963388	gsuscug(Uhd)UfuCfCfUfaugaucaasgsu	3725	asCfsuudGa(Tgn)cauaggAfaAfcagacsasg	4085	CUGUCUGUUUCCUAUGAUCAAGC	2573
AD-1963389	uscsugu(Uhd)UfcCfUfAfugaucaagscsu	3726	asGfscudTg(Agn)ucauagGfaAfacagascsa	4086	UGUCUGUUUCCUAUGAUCAAGCA	2577
AD-1963391	usgsuuu(Chd)CfuAfUfGfaucaagcasasu	3727	asUfsugdCu(Tgn)gaucauAfgGfaaacasgsa	4087	UCUGUUUCCUAUGAUCAAGCAAC	2541
AD-1963392	gsusuuc(Chd)UfaUfGfAfucaagcaascsu	3728	asGfsuudGc(Tgn)ugaucaUfaGfgaaacsasg	4088	CUGUUUCCUAUGAUCAAGCAACU	2548
AD-1963395	uscscua(Uhd)GfaUfCfAfagcaacuuscsu	3729	asGfsaadGu(Tgn)gcuugaUfcAfuaggasasa	4089	UUUCCUAUGAUCAAGCAACUUCC	2547
AD-1963410	asgscua(Ghd)UfuAfAfGfgcaaaucasgsu	3730	asCfsugaUfuugccuuAfaCfuagcuscsa	4090	UGAGCUAGUUAAGGCAAAUCAGG	2735
AD-1963411	gscsuag(Uhd)UfaAfGfUfcaaaucagsgsu	3731	asCfscugAfuuugccuUfaAfcuagcsusc	4091	GAGCUAGUUAAGGCAAAUCAGGU	2774
AD-1963417	usasagg(Chd)AfaAfUfCfagguaaaasusu	3732	asAfsuuuUfaccugauUfuGfccuuasasc	4092	GUUAAGGCAAAUCAGGUAAAAUA	2585
AD-1963419	asgsgca(Ahd)AfuCfAfGfguaaaauasgsu	3733	asCfsuauUfuuaccugAfuUfugccususa	4093	UAAGGCAAAUCAGGUAAAAUAGU	2698
AD-1963420	gsgscaa(Ahd)UfcAfGfGfuaaaauagsusu	3734	asAfscuaUfuuuaccuGfaUfuugccsusu	4094	AAGGCAAAUCAGGUAAAAUAGUC	2702
AD-1963421	gscsaaa(Uhd)CfaGfGfUfaaaauaguscsu	3735	asGfsacuAfuuuuaccUfgAfuuugcscsu	4095	AGGCAAAUCAGGUAAAAUAGUCA	2695
AD-1963430	gsusaaa(Ahd)UfaGfUfCfaugauucusasu	3736	asUfsagaAfucaugacUfaUfuuuacscsu	4096	AGGUAAAAUAGUCAUGAUUCUAU	2775
AD-1963431	usasaaa(Uhd)AfgUfCfAfugauucuasusu	3737	asAfsuagAfaucaugaCfuAfuuuuascsc	4097	GGUAAAAUAGUCAUGAUUCUAUG	2765

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1963432	asasaau(Ahd)GfuCfAfUfgauucuausgsu	3738	asCfsauaGfaaucaugAfcUfauuuusasc	4098	GUAAAAUAGUCAUGAUUCUAUGU	2750
AD-1963437	asgsuca(Uhd)GfaUfUfCfuauguaaausgsu	3739	asCfsauuAfcauagaaUfcAfugacusasu	4099	AUAGUCAUGAUUCUAUGUAAUGU	4290
AD-1963438	gsuscau(Ghd)AfuUfCfUfauguaaaugsusu	3740	asAfscauUfacauagaAfuCfaugacsusa	4100	UAGUCAUGAUUCUAUGUAAUGUA	2655
AD-1963439	uscsaug(Ahd)UfuCfUfAfuguaaaugusasu	3741	asUfsacaUfuacauagAfaUfcaugascsu	4101	AGUCAUGAUUCUAUGUAAUGUAA	2598
AD-1963464	cscscug(Ahd)GfgAfUfCfcucaacaasusu	3742	asAfsuudGu(Tgn)gaggauCfcUfcagggsasa	4102	UUCCCUGAGGAUCCUCAACAAUG	2752
AD-1963465	cscsuga(Ghd)GfaUfCfCfucaacaausgsu	3743	asCfsaudTg(Tgn)ugaggaUfcCfucaggsgsa	4103	UCCCUGAGGAUCCUCAACAAUGG	2736
AD-1963468	gsasgga(Uhd)CfcUfCfAfacaauggusesu	3744	asGfsacdCa(Tgn)ugugaGfgAfuccucsasg	4104	CUGAGGAUCCUCAACAAUGGUCA	2703
AD-1963469	asgsgau(Chd)CfuCfAfAfcaauggucsasu	3745	asUfsgadCc(Agn)uuguugAfgGfauccusesa	4105	UGAGGAUCCUCAACAAUGGUCAU	2713
AD-1963539	usgscuu(Uhd)CfaAfCfGfuggaguuusgsu	3746	asCfsaadAc(Tgn)ccacguUfgAfaagcasusg	4106	CAUGCUUUCAACGUGGAGUUUGA	2625
AD-1963543	ususcaa(Chd)GfuGfGfAfguuugaugsasu	3747	asUfscadTc(Agn)aacuccAfcGfuugaasasg	4107	CUUUCAACGUGGAGUUUGAUGAC	2665
AD-1963545	csasacg(Uhd)GfgAfGfUfuugaugacsusu	3748	asAfsgudCa(Tgn)caaacuCfcAfcguugsasa	4108	UUCAACGUGGAGUUUGAUGACUC	2715
AD-1963546	asascgu(Ghd)GfaGfUfUfugaugacuscsu	3749	asGfsagdTc(Agn)ucaaacUfcCfacguusgsa	4109	UCAACGUGGAGUUUGAUGACUCU	2694
AD-1963548	csgsugg(Ahd)GfuUfUfGfaugacucuscsu	3750	asGfsagdAg(Tgn)caucaaAfcUfccacgsusu	4110	AACGUGGAGUUUGAUGACUCUCA	2664
AD-1963550	usgsgag(Uhd)UfuGfAfUfgacucucasgsu	3751	asCfsugdAg(Agn)gucaucAfaAfcuccasesg	4111	CGUGGAGUUUGAUGACUCUCAGG	2613
AD-1963552	gsasguu(Uhd)GfaUfGfAfcucucaggsasu	3752	asUfsccdTg(Agn)gagucaUfcAfaacucscsa	4112	UGGAGUUUGAUGACUCUCAGGAC	2718
AD-1963554	gsusuug(Ahd)UfgAfCfUfcucaggacsasu	3753	asUfsgudCc(Tgn)gagaguCfaUfcaaacsusc	4113	GAGUUUGAUGACUCUCAGGACAA	2741
AD-1963557	usgsaug(Ahd)CfuCfUfCfaggacaaasgsu	3754	asCfsuudTg(Tgn)ccugagAfgUfcaucasasa	4114	UUUGAUGACUCUCAGGACAAAGC	2612
AD-1963582	usasauu(Ahd)GfaGfUfUfugauacasgsu	3755	asCfsuguAfucacaacUfcUfaauuasusa	4115	UAUAAUUAGAGUUGUGAUACAGA	2786
AD-1963590	gsusugu(Ghd)AfuAfCfAfgaguauaususu	3756	asAfsauaUfacucuguAfuCfacaacsusc	4116	GAGUUGUGAUACAGAGUAUAUUU	2639
AD-1963591	ususgug(Ahd)UfaCfAfGfaguauauususu	3757	asAfsaauAfuacucugUfaUfcacaascsu	4117	AGUUGUGAUACAGAGUAUAUUUC	2636
AD-1963592	usgsuga(Uhd)AfcAfGfAfguauauuusesu	3758	asGfsaaaUfauacucuGfuAfucacasasc	4118	GUUGUGAUACAGAGUAUAUUUCC	2644
AD-1963609	asusgac(Uhd)CfuCfAfGfgacaaagcsasu	3759	asUfsgcdTu(Tgn)guccugAfgAfgucausesa	4119	UGAUGACUCUCAGGACAAAGCAG	2734
AD-1963610	usgsacu(Chd)UfcAfGfGfacaaagcasgsu	3760	asCfsugdCu(Tgn)uguccuGfaGfagucasusc	4120	GAUGACUCUCAGGACAAAGCAGU	2787

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1963618	cscsauu(Chd)AfgAfCfAfauauaucasusu	3761	asAfsugaUfauauugu CfuGfaauggsasa	4121	UUCCAUUCAGACAAUAUAUCAUA	2552
AD-1963719	ascsuuc(Ahd)CfuUfGfGfuucacuggsasu	3762	asUfsccdAg(Tgn)gaaccaAfgUfgaagususc	4122	GAACUUCACUUGGUUCACUGGAA	2678
AD-1963721	ususcac(Uhd)UfgGfUfUfcacuggaascsu	3763	asGfsuudCc(Agn)gugaacCfaAfgugaasgsu	4123	ACUUCACUUGGUUCACUGGAACA	2704
AD-1963733	gsasuuu(Uhd)GfgGfAfAfagcugugcsasu	3764	asUfsgcdAc(Agn)gcuuucCfcAfaaaucscsc	4124	GGGAUUUUGGGAAAGCUGUGCAG	2792
AD-1963735	ususuug(Ghd)GfaAfAfGfcugugcagscsu	3765	asGfscudGc(Agn)cagcuuUfcCfcaaaasusc	4125	GAUUUUGGGAAAGCUGUGCAGCA	2837
AD-1963738	usgsgga(Ahd)AfgCfUfGfugcagcaascsu	3766	asGfsuudGc(Tgn)gcacagCfuUfucccasasa	4126	UUUGGGAAAGCUGUGCAGCAACC	2826
AD-1963762	usgsgac(Uhd)GfgCfCfGfuucuaggusasu	3767	asUfsacdCu(Agn)gaacggCfcAfguccasusc	4127	GAUGGACUGGCCGUUCUAGGUAU	2836
AD-1963763	gsgsacu(Ghd)GfcCfGfUfucuagguasusu	3768	asAfsuadCc(Tgn)agaacgGfcCfaguccsasu	4128	AUGGACUGGCCGUUCUAGGUAUU	2818
AD-1963776	usasggu(Ahd)UfuUfUfUfuugaaggususu	3769	asAfsacdCu(Tgn)caaaaaAfaUfaccuasgsa	4129	UCUAGGUAUUUUUUUGAAGGUUG	2642
AD-1963780	usasuuu(Uhd)UfuUfGfAfagguuggcsasu	3770	asUfsgcdCa(Agn)ccuucaAfaAfaaauascsc	4130	GGUAUUUUUUUGAAGGUUGGCAG	2785
AD-1963781	asususu(Uhd)UfuGfAfAfgguuggcasgsu	3771	asCfsugdCc(Agn)accuucAfaAfaaaausasc	4131	GUAUUUUUUUGAAGGUUGGCAGC	2807
AD-1963785	ususuug(Ahd)AfgGfUfUfggcagcgcsusu	3772	asAfsgcdGc(Tgn)gccaacCfuUfcaaaasasa	4132	UUUUUUGAAGGUUGGCAGCGCUA	2829
AD-1963790	asasggu(Uhd)GfgCfAfGfcgcuaaacscsu	3773	asGfsgudTu(Agn)gcgcugCfcAfaccuuscsa	4133	UGAAGGUUGGCAGCGCUAAACCG	2842
AD-1963814	csusuca(Ghd)AfaAfGfUfuguugaugsusu	3774	asAfscadTc(Agn)acaacuUfuCfugaagsgsc	4134	GCCUUCAGAAAGUUGUUGAUGUG	2696
AD-1963816	uscsaga(Ahd)AfgUfUfGfuugaugugcsu	3775	asGfscadCa(Tgn)caacaaCfuUfucugasasg	4135	CUUCAGAAAGUUGUUGAUGUGCU	2795
AD-1963817	csasgaa(Ahd)GfuUfGfUfugaugugcsusu	3776	asAfsgcdAc(Agn)ucaacaAfcUfuucugsasa	4136	UUCAGAAAGUUGUUGAUGUGCUG	2754
AD-1963819	gsasaag(Uhd)UfgUfUfGfaugugcugsgsu	3777	asCfscadGc(Agn)caucaaCfaAfcuuucsusg	4137	CAGAAAGUUGUUGAUGUGCUGGA	2820
AD-1963839	asususcc(Ahd)UfuAfAfAfacaaagggscsu	3778	asGfsccdCu(Tgn)uguuuuAfaUfggaausesc	4138	GGAUUCCAUUAAAACAAAGGGCA	2729
AD-1963840	ususcca(Uhd)UfaAfAfAfcaaagggcsasu	3779	asUfsgcdCc(Tgn)uuguuuUfaAfuggaasusc	4139	GAUUCCAUUAAAACAAAGGGCAA	2648
AD-1963845	ususaaa(Ahd)CfaAfAfGfggcaagagsusu	3780	asAfscudCu(Tgn)gcccuuUfgUfuuuaasusg	4140	CAUUAAAACAAAGGGCAAGAGUG	2812
AD-1963846	usasaaa(Chd)AfaAfGfGfgcaagagusgsu	3781	asCfsacdTc(Tgn)ugcccuUfuGfuuuuasasu	4141	AUUAAAACAAAGGGCAAGAGUGC	2793
AD-1963848	asasaca(Ahd)AfgGfGfCfaagagugcsusu	3782	asAfsgcdAc(Tgn)cuugccCfuUfuguuususa	4142	UAAAACAAAGGGCAAGAGUGCUG	2804
AD-1963850	ascsaaa(Ghd)GfgCfAfAfgagugcugsasu	3783	asUfscadGc(Agn)cucuugCfcCfuuugususu	4143	AAACAAAGGGCAAGAGUGCUGAC	2824

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1963853	asasggg(Chd)AfaGf AfGfugcugacususu	3784	asAfsagdTc(Agn)gca cucUfuGfcccuususg	4144	CAAAGGGCAAGA GUGCUGACUUC	2724
AD-1963855	gsgsgca(Ahd)GfaGf UfGfcugacuucsasu	3785	asUfsgadAg(Tgn)cag cacUfcUfugcccsusu	4145	AAGGGCAAGAGU GCUGACUUCAC	2699
AD-1963857	gscsaag(Ahd)GfuGf CfUfgacuucacsusu	3786	asAfsgudGa(Agn)gu cagcAfcUfcuugcscsc	4146	GGGCAAGAGUGC UGACUUCACUA	2727
AD-1963858	csasaga(Ghd)UfgCf UfGfacuucacusasu	3787	asUfsagdTg(Agn)agu cagCfaCfucuugcsc	4147	GGCAAGAGUGCU GACUUCACUAA	2649
AD-1963860	asgsagu(Ghd)CfuGf AfCfuucacuaascsu	3788	asGfsuudAg(Tgn)gaa gucAfgCfacucususg	4148	CAAGAGUGCUGA CUUCACUAACU	4291
AD-1963863	gsusgcu(Ghd)AfcUf UfCfacuaacuuscsu	3789	asGfsaadGu(Tgn)agu gaaGfuCfagcacsusc	4149	GAGUGCUGACUU CACUAACUUCG	2557
AD-1963864	usgscug(Ahd)CfuUf CfAfcuaacuucsgsu	3790	asCfsgadAg(Tgn)uag ugaAfgUfcagcascsu	4150	AGUGCUGACUUC ACUAACUUCGA	2583
AD-1963870	csusuca(Chd)UfaAf CfUfucgauccuscsu	3791	asGfsagdGa(Tgn)cga aguUfaGfugaagsusc	4151	GACUUCACUAAC UUCGAUCCUCG	2589
AD-1963871	ususcac(Uhd)AfaCf UfUfcgauccucsgsu	3792	asCfsgadGg(Agn)ucg aagUfuAfgugaasgsu	4152	ACUUCACUAACU UCGAUCCUCGU	2593
AD-1963893	gscscuc(Chd)UfuCf CfUfgaauccuusgsu	3793	asCfsaadGg(Agn)uuc aggAfaGfgaggcscsa	4153	UGGCCUCCUUCC UGAAUCCUUGG	2688
AD-1963896	uscscuu(Chd)CfuGf AfAfuccuuggasusu	3794	asAfsucdCa(Agn)gga uucAfgGfaaggasgsg	4154	CCUCCUUCCUGA AUCCUUGGAUU	2608
AD-1963920	gsgsacc(Uhd)AfcCf CfAfggcucacusgsu	3795	asCfsagdTg(Agn)gcc uggGfuAfgguccsasg	4155	CUGGACCUACCC AGGCUCACUGA	2840
AD-1963922	ascscua(Chd)CfcAf GfGfcucacugascsu	3796	asGfsucdAg(Tgn)gag ccuGfgGfuagguscsc	4156	GGACCUACCCAG GCUCACUGACC	2839
AD-1963924	csusacc(Chd)AfgGf CfUfcacugaccsasu	3797	asUfsggdTc(Agn)gug agcCfuGfgguagsgsu	4157	ACCUACCCAGGC UCACUGACCAC	2831
AD-1963926	ascscca(Ghd)GfcUf CfAfcugaccacscsu	3798	asGfsgudGg(Tgn)cag ugaGfcCfugggusasg	4158	CUACCCAGGCUC ACUGACCACCC	2832
AD-1963927	csusccu(Chd)UfuCf UfGfgaaugugusgsu	3799	asCfsacdAc(Agn)uuc cagAfaGfaggagsgsg	4159	CCCUCCUCUUCU GGAAUGUGUGA	2623
AD-1963929	cscsucu(Uhd)CfuGf GfAfaugugugascsu	3800	asGfsucdAc(Agn)cau uccAfgAfagaggsasg	4160	CUCCUCUUCUGG AAUGUGUGACC	2575
AD-1963931	uscsuuc(Uhd)GfgAf AfUfgugugaccsusu	3801	asAfsggdTc(Agn)cac auuCfcAfgaagasgsg	4161	CCUCUUCUGGAA UGUGUGACCUG	2645
AD-1963933	ususcug(Ghd)AfaUf GfUfgugaccugsgsu	3802	asCfscadGg(Tgn)cac acaUfuCfcagaasgsa	4162	UCUUCUGGAAUG UGUGACCUGGA	2783
AD-1963936	usgsgaa(Uhd)GfuGf UfGfaccuggaususu	3803	asAfsaudCc(Agn)ggu cacAfcAfuuccasgsa	4163	UCUGGAAUGUGU GACCUGGAUUG	2778
AD-1963941	usgsugu(Ghd)AfcCf UfGfgauugugcsusu	3804	asAfsgcdAc(Agn)auc cagGfuCfacacasusu	4164	AAUGUGUGACCU GGAUUGUGCUC	2805
AD-1963943	usgsuga(Chd)CfuGf GfAfuugugcucsasu	3805	asUfsgadGc(Agn)caa uccAfgGfucacascsa	4165	UGUGUGACCUGG AUUGUGCUCAA	2761
AD-1963946	gsasccu(Ghd)GfaUf UfGfugcucaagsgsu	3806	asCfscudTg(Agn)gca caaUfcCfaggucsasc	4166	GUGACCUGGAUU GUGCUCAAGGA	2656

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1963948	cscsugg(Ahd)UfuGf UfGfcucaaggasasu	3807	asUfsucdCu(Tgn)gag cacAfaUfccaggsusc	4167	GACCUGGAUUGU GCUCAAGGAAC	2619
AD-1963949	csusgga(Uhd)UfgUf GfCfucaaggaascsu	3808	asGfsuudCc(Tgn)uga gcaCfaAfuccagsgsu	4168	ACCUGGAUUGUG CUCAAGGAACC	2581
AD-1963952	gsasuug(Uhd)GfcUf CfAfaggaaccccsasu	3809	asUfsggdGu(Tgn)ccu ugaGfcAfcaaucscsa	4169	UGGAUUGUGCUC AAGGAACCCAU	2763
AD-1963953	asusugu(Ghd)CfuCf AfAfggaaccccasusu	3810	asAfsugdGg(Tgn)ucc uugAfgCfacaauscsc	4170	GGAUUGUGCUCA AGGAACCCAUC	2745
AD-1963957	usgscuc(Ahd)AfgGf AfAfccccaucagscsu	3811	asGfscudGa(Tgn)ggg uucCfuUfgagcascsa	4171	UGUGCUCAAGGA ACCCAUCAGCG	2808
AD-1963958	gscsuca(Ahd)GfgAf AfCfccaucagcsgsu	3812	asCfsgcdTg(Agn)ugg guuCfcUfugagcsasc	4172	GUGCUCAAGGAA CCCAUCAGCGU	2782
AD-1963960	uscsaag(Ghd)AfaCf CfCfaucagcgusesu	3813	asGfsacdGc(Tgn)gau gggUfuCfcuugasgsc	4173	GCUCAAGGAACC CAUCAGCGUCA	2794
AD-1963964	gsgsaac(Chd)CfaUf CfAfgcgucagcsasu	3814	asUfsgcdTg(Agn)cgc ugaUfgGfguuccsusu	4174	AAGGAACCCAUC AGCGUCAGCAG	2802
AD-1963966	asascce(Ahd)UfcAf GfCfgucagcagscsu	3815	asGfscudGc(Tgn)gac gcuGfaUfggguusesc	4175	GGAACCCAUCAG CGUCAGCAGCG	2827
AD-1963995	ususgaa(Ahd)UfuCf CfGfuaaacuuasasu	3816	asUfsuadAg(Tgn)uua cggAfaUfuucaascsa	4176	UGUUGAAAUUCC GUAAACUUAAC	2631
AD-1963997	gsasaau(Uhd)CfcGf UfAfaacuuaacsusu	3817	asAfsgudTa(Agn)guu uacGfgAfauuucsasa	4177	UUGAAAUUCCGU AAACUUAACUU	2584
AD-1963999	asasuuc(Chd)GfuAf AfAfcuuaacuuscsu	3818	asGfsaadGu(Tgn)aag uuuAfcGfgaauususc	4178	GAAAUUCCGUAA ACUUAACUUCA	2590
AD-1964000	asususcc(Ghd)UfaAf AfCfuuaacuucsasu	3819	asUfsgadAg(Tgn)uaa guuUfaCfggaaususu	4179	AAAUUCCGUAAA CUUAACUUCAA	2546
AD-1964002	uscscgu(Ahd)AfaCf UfUfaacuucaasusu	3820	asAfsuudGa(Agn)gu uaagUfuUfacggasasu	4180	AUUCCGUAAACU UAACUUCAAUG	2574
AD-1964003	cscsgua(Ahd)AfcUf UfAfacuucaausgsu	3821	asCfsaudTg(Agn)agu uaaGfuUfuacggsasa	4181	UUCCGUAAACUU AACUUCAAUGG	2556
AD-1964016	csgsaag(Ahd)AfcUf GfAfugguggacsasu	3822	asUfsgudCc(Agn)cca ucaGfuUfcuucgsgsg	4182	CCCGAAGAACUG AUGGUGGACAA	2767
AD-1964019	asgsaac(Uhd)GfaUf GfGfuggacaacsusu	3823	asAfsgudTg(Tgn)cca ccaUfcAfguucususc	4183	GAAGAACUGAUG GUGGACAACUG	2705
AD-1964021	asascug(Ahd)UfgGf UfGfgacaacugsgsu	3824	asCfscadGu(Tgn)guc cacCfaUfcaguuscsu	4184	AGAACUGAUGGU GGACAACUGGC	2844
AD-1964022	ascsuga(Uhd)GfgUf GfGfacaacuggscsu	3825	asGfsccdAg(Tgn)ugu ccaCfcAfucagususc	4185	GAACUGAUGGUG GACAACUGGCG	2848
AD-1964024	usgsaug(Ghd)UfgGf AfCfaacuggcgscsu	3826	asGfscgdCc(Agn)guu gucCfaCfcaucasgsu	4186	ACUGAUGGUGGA CAACUGGCGCC	2823
AD-1964043	csasgcu(Chd)AfgCf CfAfcugaagaascsu	3827	asGfsuudCu(Tgn)cag uggCfuGfagcugsgsg	4187	CCCAGCUCAGCC ACUGAAGAACA	2814
AD-1964044	asgscuc(Ahd)GfcCf AfCfugaagaacsasu	3828	asUfsgudTc(Tgn)uca gugGfcUfgagcusgsg	4188	CCAGCUCAGCCA CUGAAGAACAG	2828
AD-1964046	csuscag(Chd)CfaCf UfGfaagaacagsgsu	3829	asCfscudGu(Tgn)cuu cagUfgGfcugagscsu	4189	AGCUCAGCCACU GAAGAACAGGC	2799

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1964047	uscsagc(Chd)AfcUfGfAfagaacaggscsu	3830	asGfscedTg(Tgn)ucuucaGfuGfgcugasgsc	4190	GCUCAGCCACUGAAGAACAGGCA	2777
AD-1964049	asgscca(Chd)UfgAfAfGfaacaggcasasu	3831	asUfsugdCc(Tgn)guucuuCfaGfuggcusgsa	4191	UCAGCCACUGAAGAACAGGCAAA	2728
AD-1964053	ascsuga(Ahd)GfaAfCfAfggcaaaucsasu	3832	asUfsgadTu(Tgn)gccuguUfcUfucagusgsg	4192	CCACUGAAGAACAGGCAAAUCAA	2621
AD-1964054	csusgaa(Ghd)AfaCfAfGfgcaaaucasasu	3833	asUfsugdAu(Tgn)ugccugUfuCfuucagsusg	4193	CACUGAAGAACAGGCAAAUCAAA	2602
AD-1964055	usgsaag(Ahd)AfcAfGfGfcaaaucaasasu	3834	asUfsuudGa(Tgn)uugccuGfuUfcuucasgsu	4194	ACUGAAGAACAGGCAAAUCAAAG	2622
AD-1964056	gsasaga(Ahd)CfaGfGfCfaaaucaaasgsu	3835	asCfsuudTg(Agn)uuugccUfgUfucuucsasg	4195	CUGAAGAACAGGCAAAUCAAAGC	2658
AD-1964058	asgsaac(Ahd)GfgCfAfAfaucaaagcsusu	3836	asAfsgcdTu(Tgn)gauuugCfcUfguucususc	4196	GAAGAACAGGCAAAUCAAAGCUU	2749
AD-1964059	gsasaca(Ghd)GfcAfAfUfcaaagcususu	3837	asAfsagdCu(Tgn)ugauuuGfcCfuguucsusu	4197	AAGAACAGGCAAAUCAAAGCUUC	2683
AD-1964060	asascag(Ghd)CfaAfAfUfcaaagcuuscsu	3838	asGfsaadGc(Tgn)uugauuUfgCfcuguuscsu	4198	AGAACAGGCAAAUCAAAGCUUCC	2610
AD-1964063	asgsgca(Ahd)AfuCfAfAfagcuuccususu	3839	asAfsagdGa(Agn)gcuuugAfuUfugccusgsu	4199	ACAGGCAAAUCAAAGCUUCCUUC	2567
AD-1964064	gsgscaa(Ahd)UfcAfAfAfgcuuccuuscsu	3840	asGfsaadGg(Agn)agcuuuGfaUfuugccsusg	4200	CAGGCAAAUCAAAGCUUCCUUCA	2568
AD-1964067	asasauc(Ahd)AfaGfCfUfuccuucaasasu	3841	asUfsuudGa(Agn)ggaagcUfuUfgauuusgsc	4201	GCAAAUCAAAGCUUCCUUCAAAU	2564
AD-1964068	asasuca(Ahd)AfgCfUfUfccuucaaasusu	3842	asAfsuudTg(Agn)aggaagCfuUfugauususg	4202	CAAAUCAAAGCUUCCUUCAAAUA	2554
AD-1964070	uscsaaa(Ghd)CfuUfCfCfuucaaauasasu	3843	asUfsuadTu(Tgn)gaaggaAfgCfuuugasusu	4203	AAUCAAAGCUUCCUUCAAAUAAG	2544
AD-1964072	asasagc(Uhd)UfcCfUfUfcaaauaagsasu	3844	asUfscudTa(Tgn)uugaagGfaAfgcuuusgsa	4204	UCAAAGCUUCCUUCAAAUAAGAU	2569
AD-1964073	asasgcu(Uhd)CfcUfUfCfaaauaagasusu	3845	asAfsucdTu(Agn)uuugaaGfgAfagcuususg	4205	CAAAGCUUCCUUCAAAUAAGAUG	2558
AD-1964075	gscsuuc(Chd)UfuCfAfAfauaagaugsgsu	3846	asCfscadTc(Tgn)uauuugAfaGfgaagcsusu	4206	AAGCUUCCUUCAAAUAAGAUGGU	2563
AD-1964077	ususccu(Uhd)CfaAfAfUfaagauggucsusu	3847	asGfsacdCa(Tgn)cuuauuUfgAfaggaasgsc	4207	GCUUCCUUCAAAUAAGAUGGUCC	2630
AD-1964078	uscscuu(Chd)AfaAfUfAfagauggucscsu	3848	asGfsgadCc(Agn)ucuuauUfuGfaaggasasg	4208	CUUCCUUCAAAUAAGAUGGUCCC	2687
AD-1964081	ususcaa(Ahd)UfaAfGfAfuggucccasusu	3849	asAfsugdGg(Agn)ccaucuUfaUfuugaasgsg	4209	CCUUCAAAUAAGAUGGUCCCAUA	2771
AD-1964102	gsuscug(Uhd)AfuCfCfAfaauaaugasasu	3850	asUfsucdAu(Tgn)auuuggAfuAfcagacsusa	4210	UAGUCUGUAUCCAAAUAAUGAAU	2545
AD-1964103	uscsugu(Ahd)UfcCfAfAfauaaugaasusu	3851	asAfsuudCa(Tgn)uauuugGfaUfacagascsu	4211	AGUCUGUAUCCAAAUAAUGAAUC	2553
AD-1964104	csusgua(Uhd)CfcAfAfUfaaugaauscsu	3852	asGfsaudTc(Agn)uuauuuGfgAfuacagsasc	4212	GUCUGUAUCCAAAUAAUGAAUCU	2627

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1964106	gsusauc(Chd)AfaAf UfAfaugaaucususu	3853	asAfsagdAu(Tgn)cau uauUfuGfgauacsasg	4213	CUGUAUCCAAAU AAUGAAUCUUC	2561
AD-1964107	usasucc(Ahd)AfaUf AfAfugaaucuuscsu	3854	asGfsaadGa(Tgn)uca uuaUfuUfggauascsa	4214	UGUAUCCAAAUA AUGAAUCUUCG	2576
AD-1964108	asuscca(Ahd)AfuAf AfUfgaaucuucsgsu	3855	asCfsgadAg(Agn)uuc auuAfuUfuggausasc	4215	GUAUCCAAAUAA UGAAUCUUCGG	2614
AD-1964116	asasuga(Ahd)UfcUf UfCfgggugauuscsu	3856	asGfsaadAc(Agn)ccc gaaGfaUfucauusasu	4216	AUAAUGAAUCUU CGGGUGUUUCC	2742
AD-1964118	usgsaau(Chd)UfuCf GfGfguguuuccscsu	3857	asGfsggdAa(Agn)cac ccgAfaGfauucasusu	4217	AAUGAAUCUUCG GGUGUUUCCCU	2739
AD-1964139	ususagc(Uhd)AfaGf CfAfcagaucuascsu	3858	asGfsuadGa(Tgn)cug ugcUfuAfgcuaasasg	4218	CUUUAGCUAAGC ACAGAUCUACC	2588
AD-1964140	usasgcu(Ahd)AfgCf AfCfagaucuacscsu	3859	asGfsgudAg(Agn)uc ugugCfuUfagcuasasa	4219	UUUAGCUAAGCA CAGAUCUACCU	2635
AD-1964142	gscsuaa(Ghd)CfaCf AfGfaucuaccususu	3860	asAfsagdGu(Agn)ga ucugUfgCfuuagcsusa	4220	UAGCUAAGCACA GAUCUACCUUG	2594
AD-1964143	csusaag(Chd)AfcAf GfAfucuaccuusgsu	3861	asCfsaadGg(Tgn)aga ucuGfuGfcuuagscsu	4221	AGCUAAGCACAG AUCUACCUUGG	2600
AD-1964150	csasgau(Chd)UfaCf CfUfuggugauususu	3862	asAfsaadTc(Agn)cca aggUfaGfaucugsusg	4222	CACAGAUCUACC UUGGUGAUUUG	2580
AD-1964229	asasuaa(Ahd)AfuGf UfGfaagacuagsasu	3863	asUfscudAg(Tgn)cuu cacAfuUfuuauusasg	4223	CUAAUAAAAUGU GAAGACUAGAC	2768
AD-1964267	ascsaac(Uhd)GfcUf GfUfggcugguusgsu	3864	asCfsaadCc(Agn)gcc acaGfcAfguugusgsu	4224	ACACAACUGCUG UGGCUGGUUGG	2845
AD-1964274	csusgug(Ghd)CfuGf GfUfuggugcuususu	3865	asAfsaadGc(Agn)cca accAfgCfcacagscsa	4225	UGCUGUGGCUGG UUGGUGCUUUG	2813
AD-1964284	ususggu(Ghd)CfuUf UfGfuuuauggusasu	3866	asUfsacdCa(Tgn)aaa caaAfgCfaccaascsc	4226	GGUUGGUGCUUU GUUUAUGGUAG	2651
AD-1964289	gscsuuu(Ghd)UfuUf AfUfgguaguagsusu	3867	asAfscudAc(Tgn)acc auaAfaCfaaagcsasc	4227	GUGCUUUGUUUA UGGUAGUAGUU	2604
AD-1964291	ususugu(Uhd)UfaUf GfGfuaguaguususu	3868	asAfsaadCu(Agn)cua ccaUfaAfacaaasgsc	4228	GCUUUGUUUAUG GUAGUAGUUUU	2723
AD-1964292	ususguu(Uhd)AfuGf GfUfaguaguuususu	3869	asAfsaadAc(Tgn)acu accAfuAfaacaasasg	4229	CUUUGUUUAUGG UAGUAGUUUUU	2773
AD-1964297	asusggu(Ahd)GfuAf GfUfuuuucugusasu	3870	asUfsacdAg(Agn)aaa acuAfcUfaccausasa	4230	UUAUGGUAGUAG UUUUUCUGUAA	2617
AD-1964299	gsgsuag(Uhd)AfgUf UfUfuucuguaascsu	3871	asGfsuudAc(Agn)gaa aaaCfuAfcuaccsasu	4231	AUGGUAGUAGUU UUUCUGUAACA	2748
AD-1964301	usasgua(Ghd)UfuUf UfUfcuguaacascsu	3872	asGfsugdTu(Agn)cag aaaAfaCfuacuascsc	4232	GGUAGUAGUUUU UCUGUAACACA	2740
AD-1964302	asgsuag(Uhd)UfuUf UfCfuguaacacsasu	3873	asUfsgudGu(Tgn)aca gaaAfaAfcuacusasc	4233	GUAGUAGUUUUU CUGUAACACAG	2709
AD-1964303	gsusagu(Uhd)UfuUf CfUfguaacacasgsu	3874	asCfsugdTg(Tgn)uac agaAfaAfacuacsusa	4234	UAGUAGUUUUUC UGUAACACAGA	2730
AD-1964325	asasuaa(Ghd)AfaUf AfAfaguaccuusgsu	3875	asCfsaadGg(Tgn)acu uuaUfuCfuuauususc	4235	GAAAUAAGAAUA AAGUACCUUGA	2708

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1964328	asasgaa(Uhd)AfaAfGfUfaccuugacsusu	3876	asAfsgudCa(Agn)gguacuUfuAfuucuusasu	4236	AUAAGAAUAAAGUACCUUGACUU	2571
AD-1964329	asgsaau(Ahd)AfaGfUfAfccuugacususu	3877	asAfsagdTc(Agn)agguacUfuUfauucususa	4237	UAAGAAUAAAGUACCUUGACUUU	2572
AD-1964331	asasuaa(Ahd)GfuAfCfCfuugacuuusgsu	3878	asCfsaadAg(Tgn)caaggguAfcUfuuauuscsu	4238	AGAAUAAAGUACCUUGACUUUGU	2706
AD-1964335	asasgua(Chd)CfuUfGfAfcuuuguucsasu	3879	asUfsgadAc(Agn)aagucaAfgGfuacuususa	4239	UAAAGUACCUUGACUUUGUUCAC	2579
AD-1964337	gsusacc(Uhd)UfgAfCfUfuuguucacsasu	3880	asUfsgudGa(Agn)caaaguCfaAfgguacsusu	4240	AAGUACCUUGACUUUGUUCACAG	2661
AD-1964338	usasccu(Uhd)GfaCfUfUfuguucacasgsu	3881	asCfsugdTg(Agn)acaaagUfcAfagguascsu	4241	AGUACCUUGACUUUGUUCACAGC	2667
AD-1964340	csesuug(Ahd)CfuUfUfGfuucacagcsasu	3882	asUfsgcdTg(Tgn)gaacaaAfgUfcaaggsusa	4242	UACCUUGACUUUGUUCACAGCAU	2618
AD-1964342	ususgac(Uhd)UfuGfUfUfcacagcausgsu	3883	asCfsaudGc(Tgn)gugaacAfaAfgucaasgsg	4243	CCUUGACUUUGUUCACAGCAUGU	2615
AD-1964346	csusuug(Uhd)UfcAfCfAfgcauguagsgsu	3884	asCfscudAc(Agn)ugcuguGfaAfcaaagsusc	4244	GACUUUGUUCACAGCAUGUAGGG	2707
AD-1964353	csascag(Chd)AfuGfUfAfggugaugsasu	3885	asUfscadTc(Agn)cccuacAfuGfcugugsasa	4245	UUCACAGCAUGUAGGGUGAUGAG	2790
AD-1964355	csasgca(Uhd)GfuAfGfGfgugaugagscsu	3886	asGfscudCa(Tgn)cacccuAfcAfugcugsusg	4246	CACAGCAUGUAGGGUGAUGAGCA	2800
AD-1964356	asgscau(Ghd)UfaGfGfGfugaugagcsasu	3887	asUfsgcdTc(Agn)ucacccUfaCfaugcusgsu	4247	ACAGCAUGUAGGGUGAUGAGCAC	2797
AD-1964358	csasugu(Ahd)GfgGfUfGfaugagcacsusu	3888	asAfsgudGc(Tgn)caucacCfcUfacaugscsu	4248	AGCAUGUAGGGUGAUGAGCACUC	2817
AD-1964388	gsascua(Ahd)AfaUfGfCfugcuuuuasasu	3889	asUfsuadAa(Agn)gcagcaUfuUfuagucsasa	4249	UUGACUAAAAUGCUGCUUUUAAA	2609
AD-1964392	asasaau(Ghd)CfuGfCfUfuuuaaaacsasu	3890	asUfsgudTu(Tgn)aaaagcAfgCfauuuusasg	4250	CUAAAAUGCUGCUUUUAAAACAU	2596
AD-1964395	asusgcu(Ghd)CfuUfUfAfaaacauasgsu	3891	asCfsuadTg(Tgn)uuuaaaAfgCfagcaususu	4251	AAAUGCUGCUUUUAAAACAUAGG	2549
AD-1964397	gscsugc(Uhd)UfuUfAfAfacauaggsasu	3892	asUfscedTa(Tgn)guuuuaAfaAfgcagcsasu	4252	AUGCUGCUUUUAAAACAUAGGAA	2597
AD-1964398	csusgcu(Uhd)UfuAfAfAfacauaggasasu	3893	asUfsucdCu(Agn)uguuuuAfaAfagcagscsa	4253	UGCUGCUUUUAAAACAUAGGAAA	2591
AD-1964399	usgscuu(Uhd)UfaAfAfAfcauaggaasasu	3894	asUfsuudCc(Tgn)auguuuUfaAfaagcasgsc	4254	GCUGCUUUUAAAACAUAGGAAAG	2582
AD-1964402	ususuua(Ahd)AfaCfAfUfaggaaagusasu	3895	asUfsacdTu(Tgn)ccuaugUfuUfuaaaasgsc	4255	GCUUUUAAAACAUAGGAAAGUAG	2719
AD-1964407	asasaca(Uhd)AfgGfAfAfaguagaausgsu	3896	asCfsaudTc(Tgn)acuuucCfuAfuguuususa	4256	UAAAACAUAGGAAAGUAGAAUGG	2733
AD-1964428	ususgag(Uhd)GfcAfAfAfuccauagcsasu	3897	asUfsgcdTa(Tgn)ggauuuGfcAfcucaascsc	4257	GGUUGAGUGCAAAUCCAUAGCAC	2711
AD-1964429	usgsagu(Ghd)CfaAfAfUfccauagcascsu	3898	asGfsugdCu(Agn)uggauuUfgCfacucasasc	4258	GUUGAGUGCAAAUCCAUAGCACA	2669

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1964449	asasgau(Ahd)AfaUf UfGfagcuaguusasu	3899	asUfsaadCu(Agn)gcu caaUfuUfaucuusgsu	4259	ACAAGAUAAAUU GAGCUAGUUAA	2587
AD-1964450	asgsaua(Ahd)AfuUf GfAfgcuaguuasasu	3900	asUfsuadAc(Tgn)agc ucaAfuUfuaucususg	4260	CAAGAUAAAUUG AGCUAGUUAAG	2641
AD-1964454	asasauu(Ghd)AfgCf UfAfguuaaggcsasu	3901	asUfsgcdCu(Tgn)aac uagCfuCfaauuusasu	4261	AUAAAUUGAGCU AGUUAAGGCAA	2722
AD-1964455	asasuug(Ahd)GfcUf AfGfuuaaggcasasu	3902	asUfsugdCc(Tgn)uaa cuaGfcUfcaauususa	4262	UAAAUUGAGCUA GUUAAGGCAAA	2676
AD-1964459	gsasgcu(Ahd)GfuUf AfAfggcaaaucsasu	3903	asUfsgadTu(Tgn)gcc uuaAfcUfagcucsasa	4263	UUGAGCUAGUUA AGGCAAAUCAG	2620
AD-1964462	csusagu(Uhd)AfaGf GfCfaaaucaggsusu	3904	asAfscdTg(Agn)uuu gccUfuAfacuagscsu	4264	AGCUAGUUAAGG CAAAUCAGGUA	2758
AD-1964464	asgsuua(Ahd)GfgCf AfAfaucagguasasu	3905	asUfsuadCc(Tgn)gau uugCfcUfuaacusasg	4265	CUAGUUAAGGCA AAUCAGGUAAA	2638
AD-1964467	usasagg(Chd)AfaAf UfCfagguaaaasusu	3906	asAfsuudTu(Agn)ccu gauUfuGfccuuasasc	4266	GUUAAGGCAAAU CAGGUAAAAUA	2585
AD-1964468	asasggc(Ahd)AfaUf CfAfgguaaaausasu	3907	asUfsaudTu(Tgn)acc ugaUfuUfgccuusasa	4267	UUAAGGCAAAUC AGGUAAAAUAG	2628
AD-1964471	gscsaaa(Uhd)CfaGf GfUfaaaauagusesu	3908	asGfsacdTa(Tgn)uuu accUfgAfuuugcscsu	4268	AGGCAAAUCAGG UAAAAUAGUCA	2695
AD-1964472	csasaau(Chd)AfgGf UfAfaaauagucsasu	3909	asUfsgadCu(Agn)uu uuacCfuGfauuugscsc	4269	GGCAAAUCAGGU AAAAUAGUCAU	2670
AD-1964473	asasauc(Ahd)GfgUf AfAfaauagucasusu	3910	asAfsugdAc(Tgn)auu uuaCfcUfgauuusgsc	4270	GCAAAUCAGGUA AAAUAGUCAUG	2697
AD-1964475	asuscag(Ghd)UfaAf AfAfuagucaugsasu	3911	asUfscadTg(Agn)cua uuuUfaCfcugaususu	4271	AAAUCAGGUAAA AUAGUCAUGAU	2647
AD-1964477	csasggu(Ahd)AfaAf UfAfgucaugaususu	3912	asAfsaudCa(Tgn)gac uauUfuUfaccugsasu	4272	AUCAGGUAAAAU AGUCAUGAUUC	2626
AD-1964478	asgsgua(Ahd)AfaUf AfGfucaugauuscsu	3913	asGfsaadTc(Agn)uga cuaUfuUfuaccusgsa	4273	UCAGGUAAAAUA GUCAUGAUUCU	2660
AD-1964480	gsusaaa(Ahd)UfaGf UfCfaugauucusasu	3914	asUfsagdAa(Tgn)cau gacUfaUfuuuacscsu	4274	AGGUAAAAUAGU CAUGAUUCUAU	2775
AD-1964481	usasaaa(Uhd)AfgUf CfAfugauucuasusu	3915	asAfsuadGa(Agn)uca ugaCfuAfuuuuascsc	4275	GGUAAAAUAGUC AUGAUUCUAUG	2765
AD-1964489	uscsaug(Ahd)UfuCf UfAfuguaaugusasu	3916	asUfsacdAu(Tgn)aca uagAfaUfcaugascsu	4276	AGUCAUGAUUCU AUGUAAUGUAA	2598
AD-1964490	csasuga(Uhd)UfcUf AfUfguaaauguasasu	3917	asUfsuadCa(Tgn)uac auaGfaAfucaugsasc	4277	GUCAUGAUUCUA UGUAAUGUAAA	2605
AD-1964493	gsasuuc(Uhd)AfuGf UfAfauguaaacscsu	3918	asGfsgudTu(Agn)cau uacAfuAfgaaucsasu	4278	AUGAUUCUAUGU AAUGUAAACCA	2689
AD-1964551	asusgac(Uhd)UfuUf GfAfauuacagasgsu	3919	asCfsucdTg(Tgn)aau ucaAfaAfgucaususa	4279	UAAUGACUUUUG AAUUACAGAGA	2654
AD-1964553	gsascuu(Uhd)UfgAf AfUfuacagagasusu	3920	asAfsucdTc(Tgn)gua auuCfaAfaagucsasu	4280	AUGACUUUUGAA UUACAGAGAUA	2716
AD-1964578	usasuaa(Uhd)UfaGf AfGfuugugauascsu	3921	asGfsuadTc(Agn)caa cucUfaAfuuauasasc	4281	GUUAUAAUUAGA GUUGUGAUACA	2791

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1964580	usasauu(Ahd)GfaGfUfUfgugauacasgsu	3922	asCfsugdTa(Tgn)cacaacUfcUfaauuasusa	4282	UAUAAUUAGAGUUGUGAUACAGA	2786
AD-1964581	asasuua(Ghd)AfgUfUfGfugauacagsasu	3923	asUfscudGu(Agn)ucacaaCfuCfuaauusasu	4283	AUAAUUAGAGUUGUGAUACAGAG	2685
AD-1964582	asusuag(Ahd)GfuUfGfUfgauacagasgsu	3924	asCfsucdTg(Tgn)aucacaAfcUfcuaaususa	4284	UAAUUAGAGUUGUGAUACAGAGU	2714
AD-1964584	usasgag(Uhd)UfgUfGfAfuacagagusasu	3925	asUfsacdTc(Tgn)guaucaCfaAfcucuasasu	4285	AUUAGAGUUGUGAUACAGAGUAU	2668
AD-1964586	gsasguu(Ghd)UfgAfUfAfcagaguausasu	3926	asUfsaudAc(Tgn)cuguauCfaCfaacucsusa	4286	UAGAGUUGUGAUACAGAGUAUAU	2666
AD-1964588	gsusugu(Ghd)AfuAfCfAfgaguauaususu	3927	asAfsaudAu(Agn)cucuguAfuCfacaacsusc	4287	GAGUUGUGAUACAGAGUAUAUUU	2639
AD-1964610	csasuuc(Ahd)GfaCfAfAfuauaucausasu	3928	asUfsaudGa(Tgn)auauugUfcUfgaaugsgsa	4288	UCCAUUCAGACAAUAUAUCAUAA	2550
AD-1964611	asusuca(Ghd)AfcAfAfUfauaucauasasu	3929	asUfsuadTg(Agn)uauauuGfuCfugaausgsg	4289	CCAUUCAGACAAUAUAUCAUAAC	2555

Example 2. *In vitro* screening of CA2 siRNA

Experimental Methods

Cell culture and transfections:

Hep3b or RPE-J cells (ATCC, Manassas, VA) are grown to near confluence at 37°C in an atmosphere of 5% CO_2 in Eagle's Minimum Essential Medium (Gibco) supplemented with 10% FBS (ATCC) before being released from the plate by trypsinization. Transfection is carried out by adding 14.8 µL of Opti-MEM plus 0.2 µL of Lipofectamine RNAiMax per well (Invitrogen, Carlsbad CA. cat # 13778-150) to 5 µL of each siRNA duplex to an individual well in a 96-well plate. The mixture is then incubated at room temperature for 15 minutes. Eighty µL of complete growth media without antibiotic containing ~2 x10^4 Hep3B cells is then added to the siRNA mixture. Cells are incubated for 24 hours prior to RNA purification. Single dose experiments are performed at 10 nM, 1 nM and 0.1 nM final duplex concentration.

Total RNA isolation using DYNABEADS mRNA Isolation Kit:

Cells are lysed in 75 µL of Lysis/Binding Buffer containing 3 µL of beads per well and are mixed for 10 minutes on an electrostatic shaker. The washing steps are automated on a Biotek EL406, using a magnetic plate support. Beads are washed (in 90 µL) once in Buffer A,

once in Buffer B, and twice in Buffer E, with aspiration steps in between. Following a final aspiration, complete 10μL RT mixture is added to each well, as described below.

cDNA synthesis using ABI High capacity cDNA reverse transcription kit (Applied Biosystems, Foster City, CA, Cat #4368813):

A master mix of 1μl 10X Buffer, 0.4μl 25X dNTPs, 1 μL Random primers, 0.5 μL Reverse Transcriptase, 0.5 μL RNase inhibitor and 6.6 μL of H_2O per reaction is added per well. Plates are sealed, are agitated for 10 minutes on an electrostatic shaker, and then are incubated at 37 degrees C for 2 hours. Following this, the plates are agitated at 80 degrees C for 8 minutes.

Real time PCR:

Two microliter (μL) of cDNA is added to a master mix containing 0.5 μL of human GAPDH TaqMan Probe, 0.5 μL human CA2 probe, 2 μL nuclease-free water and 5 μL Lightcycler 480 probe master mix (Roche Cat # 04887301001) per well in a 384 well plate (Roche cat # 04887301001). Real time PCR is done in a LightCycler480 Real Time PCR system (Roche). Each duplex is tested at least two times and data are normalized to cells transfected with a non-targeting control siRNA. To calculate relative fold change, real time data are analyzed using the ΔΔCt method and are normalized to assays performed with cells transfected with a non-targeting control siRNA.

Example 3. Single dose *in vitro* screening of CA siRNAs

Cell culture and transfections:

A253 cells or Hela cells were grown to near confluence at 37°C in an atmosphere of 5% CO_2 in Eagle's Minimum Essential Medium (Gibco) supplemented with 10% FBS (ATCC) before being released from the plate by trypsinization. Transfection was carried out by adding 14.8 μL of Opti-MEM plus 0.2 μL of Lipofectamine RNAiMax per well (Invitrogen, Carlsbad CA. cat # 13778-150) to 5 μL of each siRNA duplex to an individual well in a 96-well plate. The mixture was then incubated at room temperature for 15 minutes. Eighty μL of complete growth media without antibiotic containing ~1.5×10^4 A253 cells was then added to the siRNA mixture. Cells were incubated for 24 hours prior to RNA purification. A single dose experiment was

performed at 10 nM final duplex concentration in A253 cells. For Hela cells, a multi-dose experiment was performed at 0.1 nM, 1 nM, and 10 nM final duplex concentration.

Total RNA isolation using DYNABEADS mRNA Isolation Kit:

Cells were lysed in 75 µL of Lysis/Binding Buffer containing 3 µL of beads per well and were mixed for 10 minutes on an electrostatic shaker. The washing steps were automated on a Biotek EL406, using a magnetic plate support. Beads were washed (in 90 µL) once in Buffer A, once in Buffer B, and twice in Buffer E, with aspiration steps in between. Following a final aspiration, complete 10µL RT mixture was added to each well, as described below.

cDNA synthesis using ABI High capacity cDNA reverse transcription kit (Applied Biosystems, Foster City, CA, Cat #4368813):

A master mix of 1µl 10X Buffer, 0.4µl 25X dNTPs, 1 µL Random primers, 0.5 µL Reverse Transcriptase, 0.5 µL RNase inhibitor and 6.6 µL of H_2O per reaction was added per well. Plates were sealed, were agitated for 10 minutes on an electrostatic shaker, and then were incubated at 37 degrees C for 2 hours. Following this, the plates were agitated at 80 degrees C for 8 minutes.

Real time PCR:

Two microliter (µL) of cDNA was added to a master mix containing 0.5 µL of human GAPDH TaqMan Probe, 0.5 µL human CA2 probe, 2 µL nuclease-free water and 5 µL Lightcycler 480 probe master mix (Roche Cat # 04887301001) per well in a 384 well plate (Roche cat # 04887301001). Real time PCR is done in a LightCycler480 Real Time PCR system (Roche). Each duplex was tested at least two times and data were normalized to cells transfected with a non-targeting control siRNA. To calculate relative fold change, real time data were analyzed using the ΔΔCt method and were normalized to assays performed with cells transfected with a non-targeting control siRNA. The results for A253 cells are shown in Table 11 and the results for Hela cells are shown in Table 12. The results are presented as the pecent message remaining.

Table 11. CA2 Single Dose Screen in A253 Cells

Duplex Name	% CA Message Remaining		Duplex Name	% CA Message Remaining	
	Mean	SD		Mean	SD
AD-1447598	7.20	0.47	AD-1561130	70.78	12.81
AD-1561703	6.89	0.25	AD-1561122	7.10	1.78
AD-1561694	9.47	0.96	AD-1561116	7.00	1.56
AD-1561686	11.90	0.80	AD-1561112	8.15	5.14
AD-1561679	9.05	0.73	AD-1561106	26.09	6.97
AD-1561651	8.50	0.24	AD-1561100	3.10	0.99
AD-1561613	9.92	0.47	AD-1561092	3.09	0.86
AD-1561601	10.70	1.11	AD-1475424	18.12	4.10
AD-1561591	8.82	0.65	AD-1561072	28.20	2.22
AD-1561581	8.17	0.73	AD-1561066	6.47	1.72
AD-1561570	9.46	1.69	AD-1561056	6.94	1.51
AD-1561562	9.92	1.09	AD-1561050	5.54	1.17
AD-1561551	6.50	1.45	AD-1561043	21.07	1.67
AD-1561542	9.21	0.97	AD-1561037	9.53	1.21
AD-1561534	9.59	0.36	AD-1561031	33.42	2.51
AD-1561527	9.25	1.54	AD-1561015	7.38	0.60
AD-1561521	8.37	0.27	AD-1561009	15.37	1.80
AD-1561513	13.07	1.38	AD-1561002	50.31	2.37
AD-1561504	9.70	0.78	AD-1560996	7.63	0.53
AD-1561498	8.73	1.80	AD-1560989	74.31	4.13
AD-1561489	10.24	1.19	AD-1560976	5.17	0.44
AD-1561478	10.18	1.11	AD-1560970	8.59	3.64
AD-1561471	11.22	1.21	AD-1560963	6.77	3.46
AD-1561465	15.01	1.09	AD-1560954	27.23	5.41
AD-1561456	40.43	3.66	AD-1560948	26.42	0.76
AD-1561450	24.74	1.42	AD-1560941	6.44	1.39
AD-1561444	17.51	2.01	AD-1560930	27.16	6.71
AD-1561433	11.61	0.78	AD-1560921	5.44	1.37
AD-1561422	8.20	0.63	AD-1560915	5.44	1.54
AD-1561414	10.20	0.58	AD-1560904	89.40	10.68
AD-1561408	6.88	0.89	AD-1560895	37.15	2.86
AD-1561402	8.58	1.21	AD-1560892	5.67	1.90
AD-1561396	20.33	6.80	AD-1560880	48.60	7.79
AD-1561390	7.95	1.75	AD-1560874	10.82	1.27
AD-1561384	15.34	3.97	AD-1560862	14.92	1.69
AD-1561378	16.76	4.22	AD-1560843	33.98	3.79
AD-1561366	20.14	5.16	AD-1560851	4.79	0.38
AD-1561360	11.28	1.92	AD-1560845	20.26	2.36
AD-1561349	10.47	3.67	AD-1560837	9.58	0.89
AD-1561342	19.22	2.75	AD-1560816	11.19	0.83
AD-1561336	6.48	2.35	AD-1560810	10.58	1.27
AD-1561327	7.80	0.93	AD-1560804	9.93	1.78
AD-1561319	5.93	1.03	AD-1560798	11.16	1.31
AD-1561313	6.39	0.67	AD-1560792	5.26	0.83
AD-1561306	6.03	0.49	AD-1560783	2.91	0.76
AD-1561300	5.62	0.50	AD-1560777	6.73	1.62

AD-1561294	3.77	1.38	AD-1560765	31.74	3.45
AD-1561285	6.79	0.61	AD-1560759	7.85	2.77
AD-1561279	5.80	0.61	AD-1560752	23.53	6.36
AD-1561272	5.68	0.49	AD-1560745	13.34	2.85
AD-1561261	6.74	1.09	AD-1560735	53.63	10.67
AD-1561254	5.60	1.23	AD-1560726	6.10	0.45
AD-1561245	7.01	1.68	AD-1560720	43.72	14.97
AD-1561239	6.15	1.94	AD-1560711	6.65	0.92
AD-1561231	6.36	1.73	AD-1560701	29.81	3.54
AD-1561225	8.26	1.82	AD-1560693	5.41	0.94
AD-1561218	4.88	1.54	AD-1560684	4.00	0.86
AD-1561210	3.65	0.76	AD-1560678	20.06	5.49
AD-1561203	4.31	0.92	AD-1560672	11.26	3.35
AD-1561196	7.63	1.46	AD-1560665	11.82	2.15
AD-1561190	10.83	1.95	AD-1560655	21.40	3.19
AD-1561181	7.36	1.12	AD-1560644	18.35	1.71
AD-1561175	2.23	0.49	AD-1560638	27.36	7.62
AD-1561168	6.44	1.74	AD-1560628	22.60	5.09
AD-1446763	4.73	1.43	AD-1560622	40.19	10.35
AD-1561158	4.31	1.24	AD-1560617	21.41	5.73
AD-1561152	11.35	3.57	AD-1560600	19.85	2.56
AD-1561146	9.71	2.38			

Table 12. CA2 Multi-Dose Screen in Hela Cells

Duplex Name	% CA Message Remaining					
	10 nM Mean	10 nM SD	1 nM Mean	1 nM SD	0.1 nM Mean	0.1 nM SD
AD-1784188.1	7.4	3.9	10.7	1.5	12.3	2.5
AD-1784196.1	13.2	2.7	15.8	6.5	32.2	9.4
AD-1784204.1	15.1	4.8	21	4.8	37.4	7.7
AD-1784211.1	10.4	3.2	10.1	3.7	16.5	3.5
AD-1784218.1	6.4	1.6	13.3	3.2	21.4	2.9
AD-1784226.1	23.8	2	21.9	4.3	46	9.3
AD-1784233.1	15.7	3.2	19.1	5.9	34.6	6
AD-1784241.1	30.1	5.7	39	6.6	48.9	16.8
AD-1784249.1	12.6	3.1	13.9	4	28.2	8.1
AD-1784256.1	15.6	3.3	19.4	4.4	23.8	1.9
AD-1784263.1	22.8	5.4	25	6.5	31.2	11
AD-1784271.1	14.7	4.4	10.8	1.8	15.6	2.3
AD-1784189.1	17.4	4.3	12.2	3.8	25.9	1
AD-1784197.1	24.4	4.7	29	6.7	33	5.5
AD-1784205.1	18	2.7	22.2	9.6	40.1	9.3
AD-1784212.1	23.8	3.8	13.9	2	30.6	6.8
AD-1784219.1	13.1	5.1	12.4	2.4	26.9	4.1
AD-1784227.1	20.3	4.4	15.1	2.9	28.9	9.1
AD-1784234.1	22.1	3.9	24.6	10.6	35.3	12
AD-1784242.1	38	3.1	41.7	8.6	50.6	7.7
AD-1784250.1	18.2	3.5	20.4	8.5	31.7	9.6
AD-1784257.1	15	4.8	14.4	5.9	24.5	9.9

AD-1784264.1	23.5	6.6	22.8	9	30.6	6.1
AD-1784272.1	15.3	5.1	13.8	7.1	26.8	6
AD-1784190.1	8.8	3.4	10.5	1.5	18.2	4.8
AD-1784198.1	24.4	4.1	25.4	5.1	23.4	8.2
AD-1955	79.5	6.1				
AD-1784220.1	25.3	7.3	25.3	6.2	48.8	10.5
AD-1784228.1	20.2	4.6	16.5	3.4	31.8	6.7
AD-1784235.1	23.4	5.9	23.6	5.8	24.3	2.5
AD-1784243.1	23	6.9	26.4	1.6	24.6	5.9
AD-1784265.1	28.5	9.4	24.1	2.9	31.7	2.4
AD-1784273.1	16.4	5.2	14.4	1.1	31.6	6.1
AD-1784191.1	9.1	4.9	8.7	2.2	20.2	1.2
AD-1784199.1	26.6	8.7	18	2.8	44.8	14.2
AD-1784206.1	25.3	6.8	30.1	9.6	74.8	17.3
AD-1784213.1	25.9	9.1	12.7	1.5	33.3	5.8
AD-1784221.1	29.8	6	34.4	7.6	70.4	14.3
AD-1784229.1	39.8	5.5	36.9	8.1	56.2	5.6
AD-1784236.1	26.9	10	24.6	9	39.8	10.6
AD-1784244.1	22.4	4.9	32.7	10.2	30	5.1
AD-1784251.1	72.8	13.6	77.5	12.6	95.7	34
AD-1784258.1	21.6	7.6	20.8	1.8	24	6.7
AD-1784266.1	16.1	3.4	25.6	2.1	19.4	7.5
AD-1784274.1	53.4	6.3	51.4	14.9	51.5	11.2
AD-1784192.1	15.5	6	12.7	2.9	18.1	4.6
AD-1784200.1	25.1	4.2	22	3.6	26.4	7.7
AD-1784207.1	60.8	8.8	48.1	5.8	98.4	18.9
AD-1784214.1	42.6	9.9	50.2	17.4	120.6	40.2
AD-1784222.1	52.6	10.7	56.4	4.1	85.1	17.5
AD-1784230.1	69.9	5.9	63.4	12.5	123.9	38.2
AD-1784237.1	20.8	2.8	26.7	15.9	50.3	13.8
AD-1784245.1	25	3.9	25.8	8.6	70.6	19.9
AD-1784252.1	46.8	8.5	60.2	16.7	101.9	24.6
AD-1784259.1	29.4	4.6	19.1	3.5	23.1	5
AD-1784267.1	32.3	3.4	29.1	4.5	34.3	12.5
AD-1784275.1	24.9	6.8	38.6	9.8	34.9	10.6
AD-1784193.1	19.5	5.2	19	4.1	23.6	9
AD-1784201.1	32.3	1.2	22.8	3.4	34.4	5.3
AD-1784208.1	66.4	7.8	63.2	20.5	90.2	21.9
AD-1784215.1	52.8	10.5	56.7	12.6	72.6	7.7
AD-1784223.1	77.3	25.6	69.2	17.5	87	29.8
AD-1784231.1	29.8	6.5	27.9	4.4	32.1	13.3
AD-1784238.1	13.1	1.8	25.9	8.8	37.9	7.4
AD-1784246.1	35.5	8.8	41.9	15.7	38.3	10.6
AD-1784253.1	23.8	5.2	21.3	2.6	34.7	9.7
AD-1784260.1	33.1	9.8	18.8	6.1	23.1	6.8
AD-1784268.1	25.1	3	18.6	7.5	29.7	13.2
AD-1784276.1	29.1	12.1	24.7	7.8	50	10.4
AD-1784194.1	18.7	6.1	16.1	5.8	29.1	9.3
AD-1784202.1	63	4.5	53.5	5.7	56.6	5.7

AD-1784209.1	19.2	5.4	16.2	2	25.7	3
AD-1784216.1	23.4	4.8	19.9	5.1	33.1	8.1
AD-1784224.1	49.9	6.3	33.8	6	38.7	11
AD-1784232.1	34.9	1.9	60.7	12.4	54.5	12.2
AD-1784239.1	15.9	5.5	17.9	7.2	21.9	7.2
AD-1784247.1	15.8	2.2	17	4.2	28.1	3.6
AD-1784254.1	42.5	10.2	39.8	14.8	46.6	13.5
AD-1784261.1	38.9	6.3	31.5	11.6	35.8	9.1
AD-1784269.1	36.1	8.3	29.6	10.6	40.4	7.7
AD-1784277.1	15.5	4.4	19.8	8.5	20	8.6
AD-1784195.1	13.1	5.3	13	5.1	19.6	2.6
AD-1784203.1	43.5	5.1	24.6	2.5	43.5	13.4
AD-1784210.1	18.7	2.3	17.4	6.4	36.2	8.5
AD-1784217.1	44	7.8	33.4	10.7	61.5	19.7
AD-1784225.1	49.9	9.5	53.3	17.1	59.7	18.9
AD-1784240.1	25	7.5	21.4	11.6	46.1	9
AD-1784248.1	36.8	10.1	20.4	4.5	76.8	12
AD-1784255.1	60.4	14.7	54.7	21.1	65.3	16.7
AD-1784262.1	13.4	3	27.9	8	40	12
AD-1784270.1	39.5	11.6	41.7	12.8	28.2	4.8
AD-1784458.1	26.6	1	22.6	7	22.6	7
AD-1784466.1	26	3.1	18	4.6	24.1	6
AD-1784474.1	12.5	2.3	18.1	5.2	16.5	4
AD-1784481.1	13.8	3.9	17.3	3	25.2	6
AD-1784488.1	10.2	4.6	14.4	5.8	21.4	4.2
AD-1784496.1	24.7	5.8	50.6	4	69.1	14.9
AD-1784503.1	31.4	4.6	64.7	18.4	67.8	10.3
AD-1784511.1	17.8	0.7	23.5	4.8	54	13.8
AD-1784519.1	39.7	9.7	52.2	12.3	56.2	10.2
AD-1784526.1	37	6.1	48.6	12.4	51.2	2.4
AD-1784533.1	12	3.5	16.4	6	38.2	10
AD-1784541.1	59.3	13.2	34.8	5.8	42.1	10.2
AD-1784459.1	42.7	10.2	38.4	3.4	51	7.4
AD-1784467.1	16.9	4.3	27.8	4.5	46.5	13
AD-1784475.1	16.9	1.8	14.4	4.8	21.2	3.9
AD-1784482.1	24.8	4.6	29.8	6.6	59.6	15.2
AD-1784489.1	25.7	5.1	20.6	5	38.5	6.4
AD-1784497.1	66.4	18.4	67.3	7.6	74	15.3
AD-1784504.1	13.5	4.5	25.1	9.6	24.3	3.4
AD-1784512.1	37.7	10.7	41.8	10.5	46.7	15.9
AD-1784520.1	11.1	3.9	22.5	4.7	28.1	7.2
AD-1784527.1	30.6	9.3	36.9	9.6	45.4	22.2
AD-1784534.1	13.9	5.7	20.4	4.7	32.5	8.9
AD-1784542.1	22.2	4.1	13.8	5.1	28.3	11.9
AD-1784460.1	13.5	1.3	21.2	2.6	24.3	5.6
AD-1784468.1	36.4	8.5	44.7	8.5	53.6	13.7
AD-1784490.1	29.2	9.6	24.4	6.3	38.9	5.5
AD-1784498.1	51.8	4.2	71.4	5.6	96.9	3.5
AD-1784505.1	31	9.6	50.9	5.9	46.1	3.5

AD-1784513.1	57.4	14.8	51.5	9.9	63	4.5
AD-1784535.1	42.5	8.8	30.3	5.2	53.9	5.1
AD-1784543.1	14	0.5	28.9	4.1	46.4	4.1
AD-1784461.1	18	5.7	17.5	5.4	23	6.2
AD-1784469.1	72.7	13.2	65.3	10	44.9	8.2
AD-1784476.1	29.9	5.5	36.7	4.8	54.1	7.2
AD-1784483.1	34.4	3.4	52.9	12.9	71.4	10.3
AD-1784491.1	30.9	8.7	44.5	11.3	78.2	16.1
AD-1784499.1	132.2	30.7	91.9	28.5	114.8	20.2
AD-1784506.1	51	16.8	78.8	22	108.9	26.3
AD-1784514.1	26.4	8.4	38.8	4.9	36.9	15.8
AD-1784521.1	58.5	16	71.2	12.6	98.8	18
AD-1784528.1	47.6	6.6	56.7	13	69.4	9
AD-1784536.1	74.9	11.5	43.2	9.4	107.7	31.8
AD-1784544.1	39.1	6.3	74.5	3.5	65.1	21.6
AD-1784462.1	19.1	1.2	22.1	0.5	25.4	2.8
AD-1784470.1	35.1	10	45.4	11.7	64.1	11.1
AD-1784477.1	33.1	7.8	45.5	7.3	60.3	6.7
AD-1784484.1	24.3	2.4	28.7	3.4	39.9	1.8
AD-1784492.1	48.1	13.1	56.6	12	82.4	10.4
AD-1784500.1	40.3	6.9	33.4	16.8	58.6	1
AD-1784507.1	47.2	13.5	62.6	20.5	71.9	13.1
AD-1784515.1	29.1	1.9	59.6	19.7	86.9	25.1
AD-1784522.1	29.6	4.9	38.4	0.8	61.1	20.6
AD-1784529.1	98.4	22.8	88.5	20.4	64.6	15.5
AD-1784537.1	20.5	8.2	18.2	6.6	55.7	5.6
AD-1784545.1	38	10.1	26	2.8	58.3	10.4
AD-1784463.1	50	15.3	58	10.4	52.4	6.6
AD-1784471.1	30.1	2.1	47.8	10.7	50.3	7.1
AD-1784478.1	53.8	8.6	64.9	8.3	68.1	15.6
AD-1784485.1	23.8	7.1	28.5	8.5	32.9	4.9
AD-1784493.1	34.5	10.1	33.5	11.7	48.4	14.7
AD-1784501.1	78.8	20.3	70.4	28.6	89.6	23.1
AD-1784508.1	21.4	5.8	46	9.5	42.5	19.5
AD-1784516.1	31.1	5.7	66.3	17.3	76	24.5
AD-1784523.1	40.9	13	60.2	12.3	70.1	21.4
AD-1784530.1	61.2	18.8	62.2	10.8	63.8	18.8
AD-1784538.1	79.1	26.9	73.2	13.2	73.8	38.3
AD-1784546.1	21.9	7.1	17.3	7.3	40	13.6
AD-1784464.1	44.3	8.1	50.6	15.3	71.4	11.4
AD-1784472.1	26.5	3.8	29.7	8.7	29.5	6.5
AD-1784479.1	26.6	3.9	38.9	6.4	58.9	16.9
AD-1784486.1	26.2	8.9	50.5	10.7	47.6	11.2
AD-1784494.1	25.2	6.6	54.1	16.8	40.7	10.5
AD-1784502.1	93.8	15.5	74.6	20.4	92.5	26.3
AD-1784509.1	45	6.2	41.3	11.5	60.7	15.7
AD-1784517.1	29	7.6	30.4	6.9	48.9	11.3
AD-1784524.1	77	23.1	75	23.6	75.9	26.8
AD-1784531.1	43.8	7.1	38	12.8	92.8	22.1

AD-1784539.1	30.5	4	27.7	22	50	16.9
AD-1784547.1	25.3	1.2	22.8	6.8	46.3	18.8
AD-1784465.1	30.6	7.8	45.5	11.9	46.5	15.2
AD-1784473.1	27.4	5.4	26.3	7.3	44.9	6.6
AD-1784480.1	47.5	9.9	67.9	13.8	60.1	13.6
AD-1784487.1	34	12.8	37.3	7.1	45.5	13
AD-1784495.1	37	6.7	79.2	22.2	74.7	6
AD-1784510.1	26.5	6.6	23	4.8	36.1	11.5
AD-1784518.1	48.2	13.8	82.2	12.4	82.7	23.5
AD-1784525.1	78.7	25.6	103	34.2	88.9	21.9
AD-1784532.1	29.5	4.2	32.4	8.7	53.5	24.5
AD-1784540.1	106.9	27.5	86.8	21	94.4	31.8
AD-1784278.1	15	3.3	15	8.5	23.3	7.1
AD-1784286.1	12.7	4.1	16.3	5.2	24.7	2.7
AD-1784294.1	31.7	2.9	41.4	6.9	36.7	6.6
AD-1784301.1	60.4	9.6	73.2	11.8	71.4	13
AD-1784308.1	11	3.4	18	3.2	38.8	10
AD-1784316.1	15.4	4.2	20.5	3.3	40.3	2.7
AD-1784323.1	21.2	7.5	36.4	7.3	33.9	6.6
AD-1784331.1	17.2	7.4	31.7	8.2	31	4.5
AD-1784339.1	17.6	5.5	19.4	2.8	8.4	3.2
AD-1784346.1	13.1	3.3	13.6	3	23.4	6.1
AD-1784353.1	12.1	8.1	10.2	3.6	13.3	3.2
AD-1784361.1	14.9	5.8	12.1	2.5	24.5	7.5
AD-1784279.1	12.3	3.6	20.4	6.3	31.4	7
AD-1784287.1	47.8	10.5	45.7	1.1	45.4	7.3
AD-1784295.1	13.3	4	14.5	6.5	15.5	4.9
AD-1784302.1	19.3	2.7	20.5	3.4	22.7	6.8
AD-1784309.1	26.9	4.8	26.6	4.2	39.7	8.7
AD-1784317.1	14.4	7.6	20	3	64.2	16.2
AD-1784324.1	30.4	7.3	53.2	11.4	24.8	6.9
AD-1784332.1	9.6	4.1	23	9.5	37.7	8
AD-1784340.1	29.8	10.4	38.4	14	43.4	28.7
AD-1784347.1	14.4	4	17.4	7.3	37.9	15
AD-1784354.1	28.4	11.4	29.5	7.4	31.9	5.5
AD-1784362.1	12.1	8.6	22.4	10.6	29.3	12.1
AD-1784280.1	19.6	6.7	22.4	3.1	33.9	11.5
AD-1784288.1	26.4	6.3	44.4	8.1	60.3	12.2
AD-1784310.1	19.6	5.7	51.2	12.8	60.7	14.6
AD-1784318.1	53	9.7	114.8	43.9	84.4	10.1
AD-1784325.1	26.7	5.8	36.3	11.1	38.3	12.7
AD-1784333.1	18.6	5.9	35.7	4.7	38.1	7.4
AD-1784355.1	23.2	6.1	28.6	6.8	50.3	8.3
AD-1784363.1	11.2	5.6	19.2	7.6	28.5	4.7
AD-1784281.1	15.1	5.9	16.4	4.3	23.1	3.1
AD-1784289.1	53.4	10.1	43.7	7.6	60.6	12.1
AD-1784296.1	60.6	10.9	36.5	9.4	85.8	22
AD-1784303.1	32.1	6.8	38.6	1	38.6	4.1
AD-1784311.1	40.2	4	43.2	13.1	81.6	8.8

AD-1784319.1	28.7	2.4	26.5	0.3	50	17.6
AD-1784326.1	35.8	8.3	41.8	5.9	65.1	16.4
AD-1784334.1	36	9	55.2	12.1	46.5	10.9
AD-1784341.1	38.6	8.8	40.7	8.4	40.2	8.8
AD-1784348.1	23	9.2	28.2	3	44.5	7.6
AD-1784356.1	18.1	8.1	23	7.4	39.7	6.8
AD-1784364.1	14.2	6.5	18.3	10.7	36.7	21.7
AD-1784282.1	20.5	3.7	24.7	2	25	4.1
AD-1784290.1	32.9	6.2	34	7.9	36.1	6
AD-1784297.1	56.2	6.6	52.3	8.1	50.5	13.6
AD-1784304.1	98.2	9.8	101.8	9.5	103.8	13.7
AD-1784312.1	42.8	2.3	43.7	9.7	72.8	15
AD-1784320.1	41.8	4.3	39.3	7.5	83.3	18.2
AD-1784327.1	26.3	2.8	32.9	6.2	59.8	4.9
AD-1784335.1	21.6	2	48.9	9.4	46.4	11.9
AD-1784342.1	24.9	9.4	36.3	6.1	34.4	8.4
AD-1784349.1	19.7	7.5	22.5	3.5	35.8	7.1
AD-1784357.1	17	4.8	31	8.8	51.7	14.1
AD-1784365.1	31.2	1.9	59.4	3.9	58.6	5.5
AD-1784283.1	25.7	4.6	27.4	10.2	22.1	6.4
AD-1784291.1	24.8	5.1	19.6	7.4	34.5	10.2
AD-1784298.1	23.1	6.2	29.6	11.7	27.2	4.1
AD-1784305.1	28.8	7.3	23.2	2.8	27.8	9.7
AD-1784313.1	34.9	7.8	31.9	7.4	43.1	6.1
AD-1784321.1	31.1	9.4	39.2	2.6	55.4	8.6
AD-1784328.1	40.5	9.9	50.2	8.3	60.2	11.1
AD-1784336.1	20	5.8	36	5.3	33.7	9.5
AD-1784343.1	20.7	1.8	30.4	9.1	61.8	7.4
AD-1784350.1	17.4	9.9	34.4	7.8	84.8	9.2
AD-1784358.1	20.2	11	19.2	1.7	42.8	11.8
AD-1784366.1	20.4	10.9	19.2	4.6	38	13.3
AD-1784284.1	33.2	9.7	32	1.1	33.5	0.6
AD-1784292.1	23.7	6.8	31.7	6.1	38.5	12.6
AD-1784299.1	30.4	6.8	34.9	10.4	36.9	1.9
AD-1784306.1	34.2	8.6	45.3	8.1	52.9	6.8
AD-1784314.1	46.2	11.5	87.7	7.7	54.5	3.2
AD-1784322.1	43	9.2	83.4	10	94.9	20.4
AD-1784329.1	15.8	6.1	30.4	10.4	39.8	11.8
AD-1784337.1	29.3	7.8	42.1	10.5	46.3	15.9
AD-1784344.1	45.4	15.2	33.3	1.3	50.7	22.5
AD-1784351.1	20.5	10.4	28.2	8.4	47.8	12.7
AD-1784359.1	14.2	1.3	42.2	12.6	33.8	4.8
AD-1784367.1	16.3	7.9	25.2	9	27.4	5.7
AD-1784285.1	24	3.7	19.1	1.5	21.5	3.3
AD-1784293.1	26.2	5.4	21.3	5	18	3.7
AD-1784300.1	24.3	6.9	38.7	6	36.8	7.1
AD-1784307.1	32.9	8.2	52.5	8.6	44.3	10.1
AD-1784315.1	25	12.1	64.4	10.2	69.2	18.3
AD-1784330.1	27.8	8.9	35.1	2.7	45.7	1.2

AD-1784338.1	24.4	10.8	36	7.2	49.5	13.8
AD-1784345.1	23.7	9.6	45.3	10.6	64.7	19
AD-1784352.1	16.5	7.1	26.5	7.6	46.6	12.4
AD-1784360.1	23.4	1.2	66.1	14.9	66.1	21
AD-1784368.1	8.6	2.2	12.6	3.6	21.5	2.2
AD-1784384.1	14.5	5.4	37.3	9.8	34	1
AD-1784391.1	16.2	1.8	24.6	5.6	22.9	4.1
AD-1784398.1	18.9	4.3	18.8	2.3	8.4	2.1
AD-1784406.1	36.1	9.8	45	18.6	38.2	7.6
AD-1784413.1	23	3.3	16	3	36.4	7.9
AD-1784421.1	22.8	3.3	16.1	3.3	25	1.9
AD-1784429.1	16.9	3.4	18.1	5	34	6.9
AD-1784436.1	13.5	6.2	35.1	3.6	32.5	9.4
AD-1784443.1	22	9	28.9	6.6	50.3	11.5
AD-1784451.1	16.9	7.2	19.3	5.7	21.4	4.2
AD-1784369.1	15	2.7	12.4	1.8	22.6	2.8
AD-1784377.1	32.5	2.8	33.4	8	33.1	9.4
AD-1784385.1	25.6	3.2	65.1	20.8	41.5	11.3
AD-1784392.1	20.2	4.1	59.2	11.1	43.3	18.8
AD-1784399.1	30.8	9.1	31.2	3.8	19.9	4.9
AD-1784407.1	35.6	9.6	35.1	2.8	31.5	4.6
AD-1784414.1	35.5	7.8	30.7	3.5	34	13
AD-1784422.1	10.8	1.4	17.8	3.2	21.8	8.1
AD-1784430.1	13.5	3.5	21.2	7.5	21.2	4.9
AD-1784437.1	25.3	8.1	37.8	5.8	35.1	8.3
AD-1784444.1	11.2	5.6	18.3	3	15.4	3.5
AD-1784452.1	10.7	4.9	12.4	6.2	22.5	9.2
AD-1784370.1	24.4	6.4	24.3	3.1	34.7	11
AD-1784378.1	14.2	5.7	41.9	13.1	32.7	7.7
AD-1784400.1	55.7	12.3	87.4	16.5	66.6	14
AD-1784408.1	81.7	21.8	88	18.2	46.2	1.5
AD-1784415.1	74.8	15.3	74.9	18.4	89	12.7
AD-1784423.1	30.1	5	30.7	4.7	43.6	6.3
AD-1784445.1	25.5	2.7	39.5	11.1	39.3	10.9
AD-1784453.1	31.2	6.5	26.4	11.6	17.6	7
AD-1784371.1	24.2	1.9	25.7	7.1	36.4	5
AD-1784379.1	32.9	3.3	60	13.9	59.7	12.1
AD-1784386.1	32.7	2.9	54.2	15.7	48.7	21.5
AD-1784393.1	33.8	3.6	46.8	15.6	34.8	7.6
AD-1784401.1	51.3	15.2	63.4	28.2	45.8	7
AD-1784409.1	72.2	8.5	79.6	20.1	54.6	12.5
AD-1784416.1	42.4	12.3	55.9	16.2	48.9	2.7
AD-1784424.1	22.9	7.1	49.6	21.5	50.4	10.4
AD-1784431.1	20.1	3.5	36.3	6.3	52.1	10.2
AD-1784438.1	34.1	9.1	36.6	9.3	39.7	8.4
AD-1784446.1	43.4	8.7	63.9	10.2	88	24.2
AD-1784454.1	33.2	9.2	22.5	3.3	33.8	11.6
AD-1784372.1	22.8	3.7	29.4	6.7	24.2	3.2
AD-1784380.1	53.5	18.4	80.5	9.8	70.8	13.8

AD-1784387.1	28.5	5.4	53.4	27.4	51	1.9
AD-1784394.1	34	5.9	92.8	24.5	70.6	8.4
AD-1784402.1	43.7	6.3	65.4	16.2	42.8	14.7
AD-1784410.1	77.9	12.3	106.6	26.1	82.8	7.8
AD-1784417.1	25.2	6.8	45.4	7.9	53.3	12.4
AD-1784425.1	30.4	9	40.5	12	39.3	8.8
AD-1784432.1	63	17.4	64	19.8	70.6	13.2
AD-1784439.1	37.6	9.1	46.9	15.2	44.7	12.9
AD-1784447.1	32.4	8.1	50.5	19.1	44.2	2.2
AD-1784455.1	42.7	11.6	60.9	3.1	75.9	12.2
AD-1784373.1	15.7	5.9	37.1	13.7	40.8	4.7
AD-1784381.1	47.1	12.1	106.9	9.6	71.4	9.2
AD-1784388.1	32.2	5.6	38.4	8.6	27.9	8.8
AD-1784395.1	31	8.3	69.2	8.8	32.7	9.5
AD-1784403.1	27.2	10.8	88	15.5	40.6	6.6
AD-1784411.1	27.8	3.2	47.3	3.6	48.6	7.1
AD-1784418.1	22.6	0.5	62.9	8.9	68.7	23.1
AD-1784426.1	26.2	8	37.5	9.8	33.7	9.7
AD-1784433.1	70.9	22.4	76.7	28.8	55	13.4
AD-1784440.1	29.5	8.3	36.7	11.7	43.7	12.9
AD-1784448.1	47.4	15	43.2	16.8	62.6	21.7
AD-1784456.1	15	0.8	35.8	6.5	25	7
AD-1784382.1	26	7.1	57.6	27	45.1	11.4
AD-1784389.1	29.6	8.3	64.5	11.1	55.9	2.4
AD-1784396.1	33.6	8.3	73.3	13.1	46.8	7.8
AD-1784404.1	28.3	5.6	45.7	10.2	58.1	10.2
AD-1784412.1	46.9	16.2	97.1	12.2	79.9	16.7
AD-1784419.1	20.5	5.4	58	6.9	36.9	7.6
AD-1784427.1	55.7	13.1	56.5	5.6	67.5	11.8
AD-1784434.1	37.8	0	41	13.1	45.1	8.4
AD-1784441.1	64.6	22	106.3	18.5	79.5	23.7
AD-1784449.1	18.9	3.4	55.5	5.4	35.6	4
AD-1784457.1	24.8	10.7	39.5	16.5	54.1	10.8
AD-1784375.1	23.4	10.5	32	1.7	45.8	11.2
AD-1784383.1	23.3	5.7	42.7	18.5	54	12.9
AD-1784390.1	30.9	6.4	72.2	22.6	50	16.2
AD-1784397.1	25.4	4.2	33.6	9.5	30.1	6.1
AD-1784405.1	65.2	19	143.6	50.9	110.5	38.4
AD-1784420.1	22.4	3.6	29.8	6.2	52.2	11.2
AD-1784428.1	22.1	2.2	55.9	15.1	54.5	2.3
AD-1784435.1	26.4	11.1	81.9	10.3	43.4	0.5
AD-1784442.1	23.9	7.1	46.6	13.4	40.5	13.5
AD-1784450.1	20	0.8	46.5	12	47.3	14.6

CA2 Sequences

SEQ ID NO:1

>NM_000067.3 Homo sapiens carbonic anhydrase 2 (CA2), transcript variant 1, mRNA

ACACAGTGCAGGCGCCCAAGCCGCCGCCGCCAGATCGGTGCCGATTCCTGCCCTGCCCCGACCGCCAGCGCGACCAT
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GTTCAGAGCATACTGTGGATAAAAAGAAATATGCTGCAGAACTTCACTTGGTTCACTGGAACACCAAATATGGGGAT
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SEQ ID NO:2
>Reverse complement of SEQ ID NO:1
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TCGATGTCAACAGGGGACTGGCGCTCTCCCTTGGCAATGGGGAAGTCCTTATGCCAGTGCTCAGGTCCGTTGTGTTT
GCCGTACCCCCAGTGATGGGACATGGTCGCGCTGGCGGTCGGGGCAGGGCAGGAATCGGCACCGATCTGGCGGCGGC
GGCTTGGGCGCCTGCACTGTGT

WE CLAIM:

1. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of Carbonic anhydrase 2 (CA2), wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, from one of the antisense sequences listed in any one of Tables 3-10, and wherein the sense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, from a sense sequence listed in any one of Tables 3-10 that corresponds to the antisense sequence and wherein the dsRNA agent comprises at least one modified nucleotide.

2. The dsRNA agent of claim 1, wherein at least one of the sense strand and the antisense strand is conjugated to one or more lipophilic moieties.

3. The dsRNA agent of claim 2, wherein the lipophilic moiety is conjugated via a linker or carrier.

4. The dsRNA agent of claim 2 or 3, wherein one or more lipophilic moieties are conjugated to one or more internal positions on at least one strand.

5. The dsRNA agent of claim 4, wherein the one or more lipophilic moieties are conjugated to one or more internal positions on at least one strand via a linker or carrier.

6. The dsRNA agent of any one of claims 2-5, wherein the lipophilic moiety is an aliphatic, alicyclic, or polyalicyclic compound.

7. The dsRNA agent of claim 6, wherein the lipophilic moiety contains a saturated or unsaturated C16 hydrocarbon chain.

8. The dsRNA agent of any one of claims 2-7, wherein the lipophilic moiety is conjugated via a carrier that replaces one or more nucleotide(s) in the internal position(s) or the double stranded region.

9. The dsRNA agent of any one of claims 2-7, wherein the lipophilic moiety is conjugated to the double-stranded iRNA agent via a linker containing an ether, thioether, urea, carbonate, amine, amide, maleimide-thioether, disulfide, phosphodiester, sulfonamide linkage, a product of a click reaction, or carbamate.

10. The double-stranded iRNA agent of any one of claims 2-8, wherein the lipophilic moiety is conjugated to a nucleobase, sugar moiety, or internucleosidic linkage.

11. The dsRNA agent of any of the preceding claims, wherein no more than five of the sense strand nucleotides and not more than five of the nucleotides of the antisense strand are unmodified nucleotides.

12. The dsRNA agent of any of the preceding claims, wherein all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand comprise a modification.

13. The dsRNA agent of any of the preceding claims, wherein at least one of the modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 3'-terminal deoxythimidine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5'-phosphate, a nucleotide comprising a 5'-

phosphate mimic, a glycol modified nucleotide, and a 2-O-(N-methylacetamide) modified nucleotide; and combinations thereof.

14. The dsRNA agent of any of the preceding claims, wherein at least one strand comprises a 3' overhang of at least 2 nucleotides.

15. The dsRNA agent of any of the preceding claims, wherein the double stranded region is 15-30 nucleotide pairs in length.

16. The dsRNA agent of claim 15, wherein the double stranded region is 17-23 nucleotide pairs in length.

17. The dsRNA agent of any of the preceding claims, wherein each strand has 19-30 nucleotides.

18. The dsRNA agent of any of the preceding claims, wherein the agent comprises at least one phosphorothioate or methylphosphonate internucleotide linkage.

19. The dsRNA agent of any one of claims 2-18, further comprising a targeting ligand, e.g., a ligand that targets an ocular tissue.

20. The dsRNA agent of claim 19, wherein the ocular tissue is ciliary epithelium, an optic nerve, a trabecular meshwork, a juxtacanalicular tissue, a ganglion (e.g., including a retinal ganglion), episcleral veins or a Schlemm's canal (e.g., including an endothelial cell).

21. The dsRNA agent of any one of the preceding claims, further comprising a phosphate or phosphate mimic at the 5'-end of the antisense strand.

22. The dsRNA agent of claim 21, wherein the phosphate mimic is a 5'-vinyl phosphonate (VP).

23. The dsRNA of any one of claims 1-22 wherein the dsRNA agent targets a hotspot region of an mRNA encoding CA2.

24. A dsRNA agent that targets a hotspot region of a Carbonic anhydrase 2 (CA2) mRNA.

25. A cell containing the dsRNA agent of any one of claims 1-24.

26. A pharmaceutical composition for inhibiting expression of a CA2, comprising the dsRNA agent of any one of claims 1-24 and a pharmaceutically acceptable buffer.

27. A method of inhibiting expression of CA2 in a cell, the method comprising:

a. contacting the cell with the dsRNA agent of any one of claims 1-24, or a pharmaceutical composition of claim 26; and

b. maintaining the cell produced in step (a) for a time sufficient to reduce levels of CA2 mRNA, CA2 protein, or both of CA2 mRNA and protein, thereby inhibiting expression of CA2 in the cell.

28. The method of claim 27, wherein the cell is within a subject.

29. The method of claim 28, wherein the subject is a human.

30. The method of claim 29, wherein the subject has been diagnosed with a CA2-associated disorder.

31. A method of treating a subject diagnosed with a CA2-associated disorder comprising administering to the subject a therapeutically effective amount of the dsRNA agent of any one of claims 1-24 or a pharmaceutical composition of claim 26, thereby treating the disorder.

32. The method of claim 31, wherein the CA2-associated disorder is glaucoma.

33. The method of claim 31 or 32, wherein treating comprises amelioration of at least one sign or symptom of the disorder.

34. The method of any one of claims 31-33, wherein the treating comprises one or more of (a) inhibiting or reducing intraocular pressure; (b) inhibiting or reducing the expression or activity of CA2; (c) decreasing the amount of aqueous humor; (d) inhibiting or reducing optic nerve damage; (e) inhibiting or reducing retinal ganglion cell death; (f) medication to reduce intraocular pressure; (g) laser treatment; (h) surgery; (i) or trabeculectomy.

35. The method of any one of claims 24-34, wherein the dsRNA agent is administered to the subject intraocularly, intravenously, or topically.

36. The method of claim 35, wherein the intraocular administration comprises intravitreal administration (e.g., intravitreal injection), transscleral administration (e.g., transscleral injection), subconjunctival administration (e.g., subconjunctival injection), retrobulbar administration (e.g., retrobulbar injection), intracameral administration (e.g., intracameral injection), or subretinal administration (e.g., subretinal injection).

37. The method of any one of claims 24-36, further comprising administering to the subject an additional agent or therapy comprising one or more of a prostaglandin analog, a beta blocker, an alpha-adrenergic agonist, a carbonic anhydrase inhibitor, or an anti-CA2 agent suitable for treatment or prevention of a CA2-associated disorder.