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(54) Title: METABOLIC DISORDER-ASSOCIATED TARGET GENE IRNA COMPOSITIONS AND METHODS OF USE THEREOF

(57) Abstract: The present invention relates to RNAi agents, *e.g.*, double stranded RNA (dsRNA) agents, targeting a metabolic disorder-associated target gene, *e.g.*, inhibin subunit beta E (INHBE), activin A receptor type 1C (ACVR1C), perilipin-1 (PLIN1), phosphodiesterase 3B (PDE3B), or inhibin subunit beta C (INHBC) gene. The invention also relates to methods of using such RNAi agents to inhibit expression of a metabolic disorder-associated target gene gene and to methods of preventing and beating a metabolic disorder, *e.g.*, metabolic syndrome.

METABOLIC DISORDER-ASSOCIATED TARGET GENE IRNA COMPOSITIONS AND METHODS OF USE THEREOF

RELATED APPLICATIONS

This application claims the benefit of prioity to U.S. Provisional Application No. 63/223,995, filed on July 21, 2021, U.S. Provisional Application No. 63/278,126, filed on November 11, 2021, U.S. Provisional Application No. 63/285,143, filed on December 2, 2021, U.S. Provisional Application No. 63/287,578, filed on December 9, 2021, U.S. Provisional Application No. 63/321,799, filed on March 21, 2022, and U.S. Provisional Application No. 63/323,543, filed on March 25, 2022. The entire contents of each of the foregoing applications are incorporated herein by reference.

BACKGROUND OF THE INVENTION

With the successful conquest of many infectious diseases in most of the world, non-communicable diseases, metabolic disorders in particular, have become a major health hazard of the modern world. The increase in consumption of high calorie-low fiber fast food and the decrease in physical activity due to mechanized transportations and sedentary lifestyle have resulted in the spread of metabolic disorders such as metabolic syndrome, type 2 diabetes, hypertension, cardiovascular diseases, stroke, and other disabilities. Indeed, the occurences of subjects with a metabolic disorder, such as, metabolic syndrome, who have a number of health conditions placing them at higher risk for heart disease, diabetes, stroke, and other diseases have increased in the recent years.

Current treatments for disorders of metabolic disorders include lifestyle changes, dieting, exercise and treatment with agents, such as lipid lowering agents, *e.g.,* statins, and other drugs. However, these therapies and treatments are often limited by compliance, are not always effective, result in side effects, and result in drug-drug interactions. Accordingly, there is a need in the art for alternative treatments for subjects having metabolic disorders, such as metablic syndrome and related diseases, *e.g.*, diabetes, hypertension, and cardiovascular disease, such as an agent that can selectively and efficiently silence a metabolic disorder-associated target gene, *i.e.,* inhibin subunit beta E (INHBE), activin A receptor type 1C (ACVR1C), perilipin-1 (PLIN1), phosphodiesterase 3B (PDE3B), or inhibin subunit beta C (INHBC), using the cell's own RNAi machinery that has both high biological activity and *in vivo* stability, and that can effectively inhibit expression of the metabolic disorder-assocaited target INHBE gene.

SUMMARY OF THE INVENTION

The present invention provides iRNA compositions which effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of a gene encoding a metabolic disorder-associated target gene selected from the group consisting of inhibin subunit beta E (INHBE), activin A receptor type 1C (ACVR1C), perilipin-1 (PLIN1), phosphodiesterase 3B (PDE3B), and inhibin subunit beta C (INHBC). The target gene may be within a cell, *e.g.,* a cell within a subject, such as a

human subject. The present invention also provides methods of using the iRNA compositions of the invention for inhibiting the expression of a metabolic disorder-associated target gene selected from the group consisting of inhibin subunit beta E (INHBE), activin A receptor type 1C (ACVR1C), perilipin-1 (PLIN1), phosphodiesterase 3B (PDE3B), and inhibin subunit beta C (INHBC), and/or for treating a subject who would benefit from inhibiting or reducing the expression of a metabolic disorder-associated target gene selected from the group consisting of inhibin subunit beta E (INHBE), activin A receptor type 1C (ACVR1C), perilipin-1 (PLIN1), phosphodiesterase 3B (PDE3B), and inhibin subunit beta C (INHBC), *e.g.*, a subject suffering or prone to suffering from a metabolic disorder, *e.g.*, metabolic syndrome, and/or cardiovascular disease.

Accordingly, in an aspect, the invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of a metabolic disorder-associated target gene selected from the group consisting of inhibin subunit beta E (INHBE), activin A receptor type 1C (ACVR1C), perilipin-1 (PLIN1), phosphodiesterase 3B (PDE3B), and inhibin subunit beta C (INHBC) in a cell, such as an adipocyte and/or a liver cell, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15, *e.g.,* 15, 16, 17, 18, 19, 20, or 21, contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from the nucleotide sequence of any one of SEQ ID NOs:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, or 55, and the antisense strand comprises at least 15, *e.g.,* 15, 16, 17, 18, 19, 20, 21, 22, or 23, contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from the corresponding portion of the nucleotide sequence of any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, or 56.

In another aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of a metabolic disorder-associated target gene selected from the group consisting of inhibin subunit beta E (INHBE), activin A receptor type 1C (ACVR1C), perilipin-1 (PLIN1), phosphodiesterase 3B (PDE3B), and inhibin subunit beta C (INHBC) in a cell, such as an adipocyte and/or a liver cell, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a region of complementarity to an mRNA encoding the target gene, and wherein the region of complementarity comprises at least 15, *e.g.,* 15, 16, 17, 18, 19, 20, 21, 22, or 23, contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from any one of the antisense nucleotide sequences in any one of Tables 2-17, 19 and 20.

In yet another aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of a metabolic disorder-associated target gene selected from the group consisting of inhibin subunit beta E (INHBE), activin A receptor type 1C (ACVR1C), perilipin-1 (PLIN1), phosphodiesterase 3B (PDE3B), and inhibin subunit beta C (INHBC) in a cell, such as an adipocyte and/or a liver cell, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15, *e.g.,* 15, 16, 17, 18, 19, 20, or 21, contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from any one of the sense nucleotide sequences in any one of Tables 2-17, 19 and 20 and

the antisense strand comprises at least 15, *e.g.,* 15, 16, 17, 18, 19, 20, 21, 22, or 23, contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from any one of the antisense nucleotide sequences in any one of Tables 2-17, 19 and 20. In some embodiments, these dsRNA agents further comprise one or more C22 hydrocarbon chains conjugated to one or more positions, *e.g.*, internal positions, on at least one strand of the dsRNA agent.

In another aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of a metabolic disorder-associated target gene selected from the group consisting of inhibin subunit beta E (INHBE), activin A receptor type 1C (ACVR1C), perilipin-1 (PLIN1), phosphodiesterase 3B (PDE3B), and inhibin subunit beta C (INHBC) in a cell, such as an adipocyte and/or a liver cell, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15, *e.g.,* 15, 16, 17, 18, 19, 20, or 21, contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from any one of the sense nucleotide sequences in any one of Tables 2-17, 19 and 20 and the antisense strand comprises at least 15, *e.g.,* 15, 16, 17, 18, 19, 20, 21, 22, or 23, contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from any one of the antisense nucleotide sequences in any one of Tables 2-17, 19 and 20. In some embodiments, these dsRNA agents further comprise one or more GalNAcligands conjugated to at least one strand of the dsRNA agent, *e.g.,* through a bivalent or trivalent branched linker.

In one embodiment, the dsRNA agent comprises a sense strand comprising a contiguous nucleotide sequence which has at least 85%, e.g., 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, nucleotide sequence identity over its entire length to any one of the nucleotide sequences of the sense strands in any one of Tables 2-17, 19 and 20 and an antisense strand comprising a contiguous nucleotide sequence which has at least 85%, e.g., 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, nucleotide sequence identity over its entire length to any one of the nucleotide sequences of the antisense strands in any one of Tables 2-17, 19 and 20.

In one embodiment, the dsRNA agent comprises a sense strand comprising at least 15, e.g., 15, 16, 17, 18, 19, 20, or 21, contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequences of the sense strands in any one of Tables 2-17, 19 and 20 and an antisense strand comprising at least 15, e.g., 15, 16, 17, 18, 19, 20, 21, 22, or 23 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequences of the antisense strands in any one of Tables 2-17, 19 and 20.

In one embodiment, the dsRNA agent comprises a sense strand comprising at least 15, e.g., 15, 16, 17, 18, 19, 20, or 21, contiguous nucleotides differing by no more than two nucleotides from any one of the nucleotide sequences of the sense strands in any one of Tables 2-17, 19 and 20 and an antisense strand comprising at least 15, e.g., 15, 16, 17, 18, 19, 20, 21, or 23 contiguous nucleotides differing by no more than two nucleotides from any one of the nucleotide sequences of the antisense strands in any one of Tables 2-17, 19 and 20.

In one embodiment, the dsRNA agent comprises a sense strand comprising at least 15, e.g., 15, 16, 17, 18, 19, 20, or 21, contiguous nucleotides differing by no more than one nucleotide from

any one of the nucleotide sequences of the sense strands in any one of Tables 2-17, 19 and 20 and an antisense strand comprising at least 15, e.g., 15, 16, 17, 18, 19, 20, 21, 22, or 23 contiguous nucleotides differing by no more than one nucleotide from any one of the nucleotide sequences of the antisense strands in any one of Tables 2-17, 19 and 20.

In one embodiment, the dsRNA agent comprises a sense strand comprising or consisting of a nucleotide sequence selected from the group consisting of any one of the nucleotide sequences of the sense strands in any one of Tables 2-17, 19 and 20 and an antisense strand comprising or consisting of a nucleotide sequence selected from the group consisting of any one of the nucleotide sequences of the antisense strands in any one of Tables 2-17, 19 and 20.

In one embodiment, the target gene is INHBE.

In one embodiment, the target gene is ACVR1C.

In one embodiment, the target gene is PLIN1.

In one embodiment, the target gene is PDE3B.

In one embodiment, the target gene is INHBC.

In one aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of inhibin subunit beta E (INHBE) in a cell, such as an adipocyte and/or a liver cell, wherein said dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15, *e.g.*, 15, 16, 17, 18, 19, 20, or 21, contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from any one of the nucleotide sequences of nucleotides 400-422, 410-432, 518-540, 519-541, 640-662, 1430-1452, 1863-1885, or 1864-1886 of SEQ ID NO: 1, and the antisense strand comprises at least 15, *e.g.,* 15, 16, 17, 18, 19, 20, 21, 22, or 23, differing by no more than 0, 1, 2, or 3 nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2.

In one aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of inhibin subunit beta E (INHBE) in a cell, such as an adipocyte and/or a liver cell, wherein said dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15, *e.g.*, 15, 16, 17, 18, 19, 20, or 21, contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from any one of the nucleotide sequence of nucleotides 400-422, 410-432, 518-540, 519-541, 640-662, 1430-1452, 1863-1885, or 1864-1886 of SEQ ID NO: 1, and the antisense strand comprises at least 15, *e.g.,* 15, 16, 17, 18, 19, 20, 21, 22, or 23, contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2. In some embodiments, these dsRNA agents further comprise one or more C22 hydrocarbon chains conjugated to one or more positions, *e.g.*, internal positions, on at least one strand of the dsRNA agent.

In one aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of inhibin subunit beta E (INHBE) in a cell, such as an adipocyte and/or a liver cell, wherein said dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15, *e.g.*, 15, 16, 17, 18, 19, 20, or 21, contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from any one

of the nucleotide sequence of nucleotides 400-422, 410-432, 518-540, 519-541, 640-662, 1430-1452, 1863-1885, or 1864-1886 of SEQ ID NO: 1, and the antisense strand comprises at least 15, *e.g.,* 15, 16, 17, 18, 19, 20, 21, 22, or 23, contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2. In some embodiments, these dsRNA agents further comprise one or more GalNAcligands conjugated to at least one strand of the dsRNA agent, *e.g.,* through a bivalent or trivalent branched linker.

In some embodiments, the antisense strand comprises at least 15, e.g., 15, 16, 17, 18, 19, 20, 21, 22, or 23, contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-1706583, AD-1711744, AD-1706593, AD-1708473, AD-1706662, AD-1706761, AD-1707306, AD-1707639, AD-1707640.

In some embodiments, the sense and the antisense strand comprise at least 15, e.g., 15, 16, 17, 18, 19, 20, 21, 22, or 23, contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from any one of the sense and the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-1706583, AD-1711744, AD-1706593, AD-1708473, AD-1706662, AD-1706761, AD-1707306, AD-1707639, AD-1707640.

In some embodiments, the antisense strand comprises at least 15, e.g., 15, 16, 17, 18, 19, 20, 21, 22, or 23, contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from any one of the antisense strand nucleotide sequences selected from the group consisting of

(a) 5'- AGUUAUTCUGGGACGACUGGUCA -3';

(b) 5'- AGUUAUTCUGGGACGACUGGUCU -3';

(c) 5'- ATGGAGGAUGAGUUAUUCUGGGA -3';

(d) 5'- AUGAAGTGGAGUCUGUGACAGUA -3';

(e) 5'- ACUGAAGUGGAGUCUGUGACAGU -3';

(f) 5'- ACGGAAGAUCCTCAAGCAAAGAG -3';

(g) 5'- ACAGACAAGAAAGUGCCCAUUUG -3';

(h) 5'- AAGAAAGUAUAAAUGCUUGUCUC -3'; and

(i) 5'- AAAGAAAGUAUAAAUGCUUGUCU -3'.

In some embodiments, the sense strand comprises at least 15, e.g., 15, 16, 17, 18, 19, 20, or 21, contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides and the antisense strand comprises at least 15, e.g., 15, 16, 17, 18, 19, 20, 21, 22, or 23, contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from any one of the sense and antisense strand nucleotide sequences selected from the group consisting of

(a) 5'- ACCAGUCGUCCCAGAAUAACU -3' and

5'-AGUUAUTCUGGGACGACUGGUCA -3';

(b) 5'- ACCAGUCGUCCCAGAAUAACU -3' and

5'-AGUUAUTCUGGGACGACUGGUCU -3';

(c) 5'- CCAGAAUAACUCAUCCUCCAU -3' and

5'-ATGGAGGAUGAGUUAUUCUGGGA -3';

(d) 5'- CUGUCACAGACUCCACUUCAU -3' and

5'-AUGAAGTGGAGUCUGUGACAGUA -3';

(e) 5'- UGUCACAGACUCCACUUCAGU -3' and

5'-ACUGAAGUGGAGUCUGUGACAGU -3';

(f) 5'- CUUUGCUUGAGGAUCUUCCGU -3' and

5'-ACGGAAGAUCCTCAAGCAAAGAG -3';

(g) 5'- AAUGGGCACUUUCUUGUCUGU -3' and

5'-ACAGACAAGAAAGUGCCCAUUUG -3';

(h) 5'- GACAAGCAUUUAUACUUUCUU -3' and

5'-AAGAAAGUAUAAAUGCUUGUCUC -3'; and

(i) 5'- ACAAGCAUUUAUACUUUCUUU -3' and

5'-AAAGAAAGUAUAAAUGCUUGUCU -3'.

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

In one embodiment, substantially all of the nucleotides of the sense strand are modified nucleotides; substantially all of the nucleotides of the antisense strand are modified nucleotides; or substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand are modified nucleotides.

In one embodiment, all of the nucleotides of the sense strand are modified nucleotides; all of the nucleotides of the antisense strand are modified nucleotides; or all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand are modified nucleotides.

In one embodiment, 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, 2'-hydroxly-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 thermally destabilizing nucleotide, a glycol modified nucleotide (GNA), a nucleotide comprising a 2' phosphate, and a 2-O-(N-methylacetamide) modified nucleotide; and combinations thereof.

In one embodiment, at least one of the modified nucleotides is selected from the group consisting of LNA, HNA, CeNA, 2′-methoxyethyl, 2′-O-alkyl, 2′-O-allyl, 2′-C- allyl, 2′-fluoro, 2′-deoxy, 2'-hydroxyl, and glycol; and combinations thereof.

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, a nucleotide comprising a phosphorothioate group, and a vinyl-phosphonate nucleotide; and combinations thereof.

In another embodiment, at least one of the modified nucleotides is a nucleotide with a thermally destabilizing nucleotide modification.

In one embodiment, the thermally destabilizing nucleotide modification is selected from the group consisting of an abasic modification; a mismatch with the opposing nucleotide in the duplex; a destabilizing sugar modification, a 2'-deoxy modification, an acyclic nucleotide, an unlocked nucleic acid (UNA), and a glycerol nucleic acid (GNA).

In some embodiments, the modified nucleotide comprises a short sequence of 3'-terminal deoxythimidine nucleotides (dT).

In some embodiments, the dsRNA agents further comprise a phosphate or phosphate mimic at the 5'-end of the antisense strand.

In some embodiments, phosphate mimic is a 5'-vinyl phosphonate (VP).

In some embodiments, the 5'-end of the antisense strand of the dsRNA agent does not contain a 5'-vinyl phosphonate (VP).

In some embodiments, the dsRNA agent further comprises at least one terminal, chiral phosphorus atom.

A site specific, chiral modification to the internucleotide linkage may occur at the 5' end, 3' end, or both the 5' end and 3' end of a strand. This is being referred to herein as a "terminal" chiral modification. The terminal modification may occur at a 3' or 5' terminal position in a terminal region, *e.g.*, at a position on a terminal nucleotide or within the last 2, 3, 4, 5, 6, 7, 8, 9 or 10 nucleotides of a strand. A chiral modification may occur on the sense strand, antisense strand, or both the sense strand and antisense strand. Each of the chiral pure phosphorus atoms may be in either Rp configuration or Sp configuration, and combination thereof. More details regarding chiral modifications and chirally-modified dsRNA agents can be found in PCT/US18/67103, entitled "Chirally-Modified Double-Stranded RNA Agents," filed December 21, 2018, which is incorporated herein by reference in its entirety.

In some embodiments, the dsRNA agent further comprises a terminal, chiral modification occuring 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 occuring 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 occuring 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 one embodiment, the dsRNA agent further comprises a terminal, chiral modification occuring 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 occuring 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 occuring 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 one embodiment, the dsRNA agent further comprises a terminal, chiral modification occuring 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 occuring 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 occuring 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 one embodiment, the dsRNA agent further comprises a terminal, chiral modification occuring 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 occuring 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 occuring 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 occuring 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 one embodiment, the dsRNA agent further comprises a terminal, chiral modification occuring 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 occuring 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 occuring 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 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 one embodiment, the dsRNA agent further comprises at least one phosphorothioate or methylphosphonate internucleotide linkage.

In one embodiment, the phosphorothioate or methylphosphonate internucleotide linkage is at the 3'-terminus of one strand, *e.g.,* the antisense strand or the sense strand.

In another embodiment, the phosphorothioate or methylphosphonate internucleotide linkage is at the 5'-terminus of one strand, *e.g.,* the antisense strand or the sense strand.

In one embodiment, the phosphorothioate or methylphosphonate internucleotide linkage is at the both the 5'- and 3'-terminus of one strand. In one embodiment, the strand is the antisense strand.

In one embodiment, the base pair at the 1 position of the 5′-end of the antisense strand of the duplex is an AU base pair.

The double stranded region may be 19-30 nucleotide pairs in length;19-25 nucleotide pairs in length;19-23 nucleotide pairs in length; 23-27 nucleotide pairs in length; or 21-23 nucleotide pairs in length.

In one embodiment, each strand is independently no more than 30 nucleotides in length.

In one embodiment, the sense strand is 21 nucleotides in length and the antisense strand is 23 nucleotides in length.

The region of complementarity may be at least 17 nucleotides in length; between 19 and 23 nucleotides in length; or 19 nucleotides in length.

In one embodiment, at least one strand comprises a 3' overhang of at least 1 nucleotide. In another embodiment, at least one strand comprises a 3' overhang of at least 2 nucleotides.

In some embodiments, one or more C22 hydrocarbon chains is conjugated to one or more internal positions on at least one strand of the dsRNA agent.

In some embodiments, the lipophilicity of the one or more C_{22} hydrocarbon chain, measured by octanol-water partition coefficient, $\log K_{ow}$, exceeds 0. The lipophilic moiety may possess a $\log K_{ow}$ exceeding 1, exceeding 1.5, exceeding 2, exceeding 3, exceeding 4, exceeding 5, or exceeding 10.

In some embodiments, the hydrophobicity of the dsRNA agent, measured by the unbound fraction in the plasma protein binding assay of the dsRNA agent, exceeds 0.2. In one embodiment, the plasma protein binding assay determined is an electrophoretic mobility shift assay (EMSA) using human serum albumin protein. The hydrophobicity of the dsRNA agent, measured by fraction of unbound dsRNA 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 dsRNA/

The C_{22} hydrocarbon chain may be saturated or unsaturated.

The C_{22} hydrocarbon chain may be linear or branched

In some embodiments, the internal positions include all positions except the three terminal 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 exclude positions 9-12 or positions 11-13, counting from the 5'-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 exclude positions 12-14, counting from the 5'-end of the antisense strand.

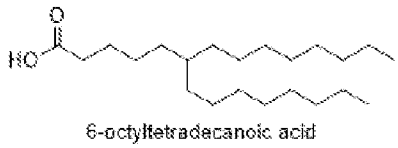
In some embodiments, the one or more C_{22} hydrocarbon chains are conjugated to one or more of the following internal positions: positions 4-8 and 13-18 on the sense strand, and positions 6-10 and 15-18 on the antisense strand, counting from the 5'end of each strand.

In some embodiments, the one or more C_{22} hydrocarbon chains are conjugated to one or more of the following internal positions: 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 one or more C_{22} hydrocarbon chains are conjugated to position 6 on the sense strand, counting from the 5'-end of the sense strand.

In some embodiments, the one or more C_{22} hydrocarbon chains is an aliphatic, alicyclic, or polyalicyclic compound, *e.g.,* the one or more C_{22} hydrocarbon chains contains a functional group selected from the group consisting of hydroxyl, amine, carboxylic acid, sulfonate, phosphate, thiol, azide, and alkyne.

In some embodiments, the one or more C_{22} hydrocarbon chains is a C22 acid, *e.g.* the C22 acid is selected from the group consisting of docosanoic acid, 6-octyltetradecanoic acid, 10-hexylhexadecanoic acid, all-cis-7,10,13,16,19-docosapentaenoic acid, all-cis-4,7,10,13,16,19-docosahexaenoic acid, all-cis-13,16-docosadienoic acid, all-cis-7,10,13,16-docosatetraenoic acid, all-cis-4,7,10,13,16-docosapentaenoic acid, and cis-13-docosenoic acid.

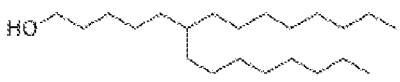


6-octyltetradecanoic acid



10-hexylhexadecanoic acid

In some embodiments, the one or more C_{22} hydrocarbon chains is a C22 alcohol, *e.g.,* the C22 alcohol is selected from the group consisting of 1-docosanol, 6-octyltetradecan-1-ol, 10-hexylhexadecan-1-ol, cis-13-docosen-1-ol, docosan-9-ol, docosan-2-ol, docosan-10-ol, docosan-11-ol, and cis-4,7,10,13,16,19-docosahexanol.



6-octyltetradecan-1-ol

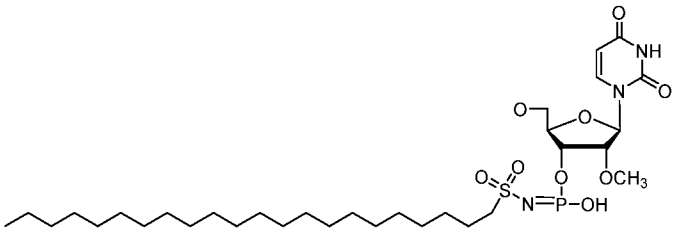


10-hexylhexadecan-1-ol

In some embodiments, the one or more C_{22} hydrocarbon chains is a C22 amide, *e.g.,* the C22 amide is selected from the group consisting of (E)-Docos-4-enamide, (E)-Docos-5-enamide, (Z)-

Docos-9-enamide, (E)-Docos-11-enamide,12-Docosenamide, (Z)-Docos-13-enamide, (Z)-N-Hydroxy-13-docoseneamide, (E)-Docos-14-enamide, 6-cis-Docosenamide, 14-Docosenamide Docos-11-enamide, (4E,13E)-Docosa-4,13-dienamide, and (5E,13E)-Docosa-5,13-dienamide.

The one or more C_{22} hydrocarbon chains may be conjugated to the dsRNA agent via a direct attachment to the ribosugar of the dsRNA agent. Alternatively, the the one or more C_{22} hydrocarbon chains may be conjugated to the dsRNA agent via a linker or a carrier. In some embodiments, the one or more C_{22} hydrocarbon chains may be conjugated to the dsRNA agent via internucleotide phosphate linkage.



In certain embodiments, the one or more C_{22} hydrocarbon chains is conjugated to the dsRNA agent via one or more linkers (tethers), *e.g.,* a carrier that replaces one or more nucleotide(s) in the internal position(s).

In some embodiments, the one or more C_{22} hydrocarbon chains is conjugated to the dsRNA 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 some embodiments, at least one of the linkers (tethers) is a redox cleavable linker (such as a reductively cleavable linker; *e.g.*, a disulfide group), an acid cleavable linker (*e.g.*, a hydrazone group, an ester group, an acetal group, or a ketal group), an esterase cleavable linker (*e.g.*, an ester group), a phosphatase cleavable linker (*e.g.*, a phosphate group), or a peptidase cleavable linker (*e.g.*, a peptide bond).

In other embodiments, at least one of the linkers (tethers) is a bio-clevable 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 certain embodiments, the one or more C_{22} hydrocarbon chains is conjugated to the dsRNA agent via a carrier that replaces one or more nucleotide(s). The carrier can be a cyclic group or an acyclic group. In one embodiment, the cyclic group is selected from the group consisting of pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, [1,3]dioxolane, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl, tetrahydrofuryl, and decalin. In one embodiment, the acyclic group is a moiety based on a serinol backbone or a diethanolamine backbone.

In some embodiments, the carrier replaces one or more nucleotide(s) in the internal position(s) of the dsRNA agent.

In some embodiments, the dsRNA agent further comprises a targeting ligand that targets a receptor which mediates delivery to adipose tissue. In one embodiment, the targeting ligand is selected from the group consisting of Angiopep-2, lipoprotein receptor related protein (LRP) ligand, bEnd.3 cell binding ligand, transferrin receptor (TfR) ligand, manose receptor ligand, glucose transporter protein, LDL receptor ligand, trans-retinol, RGD peptide, LDL receptor ligand, CD63 ligand, and carbohydrate based ligand.

In some embodiments, the dsRNA agent further comprises a targeting ligand that targets a liver tissue.

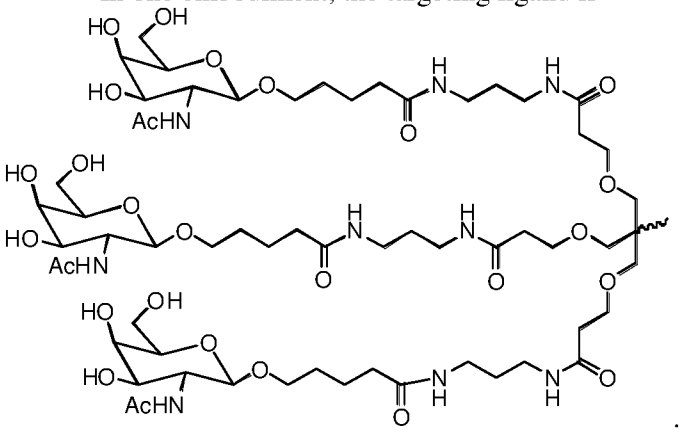
In one embodiment, the targeting ligand is conjugated to the 3' end of the sense strand of the dsRNA agent.

In some embodiments, the targeting ligand is a carbohydrate-based ligand.

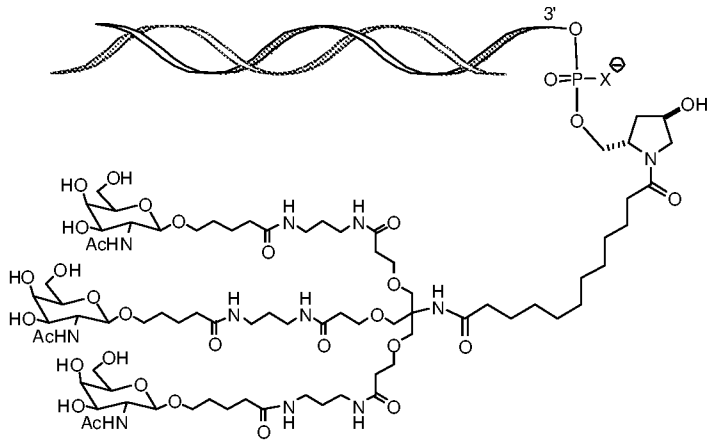
In one embodiment, the targeting ligand is an N-acetylgalactosamine (GalNAc) derivative.

In one embodiment, the targeting ligand is one or more GalNAc derivatives attached through a monovalent, bivalent, or trivalent branched linker.

In one embodiment, the targeting ligand is



In one embodiment, the dsRNA agent is conjugated to the targeting ligand as shown in the following schematic



and, wherein X is O or S.

In one embodiment, the X is O.

In som embodiments, the one or more C22 hydrocarbon chains or targeting ligand is conjugated via a bio-clevable linker selected from the group consisting of DNA, RNA, disulfide, amide, funtionalized monosaccharides or oligosaccharides of galactosamine, glucosamine, glucose, galactose, mannose, and combinations thereof.

In one aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of inhibin subunit beta E (INHBE), wherein said dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15, *e.g.*, 15, 16, 17, 18, 19, 20, or 21, contiguous nucleotides differing by no more than 0, 1, 2, 3, or 4 nucleotides from the nucleotide sequence ascscagucgUfCfCfcagaauaacu (SEQ ID NO:), wherein the antisense strand comprises at least 15, *e.g.*, 15, 16, 17, 18, 19, 20, 21, 22, or 23, contiguous nucleotides differenting by no more than 0, 1, 2, 3, or 4 nucleotides from the nucleotide sequence asdGsuudAudTcuggdGaCfgacugguscsa (SEQ ID NO:), wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U; Af, Gf, Cf, and Uf are 2'-fluoro A, G, C and U; dA, dG, dC and dT are 2`-deoxy A, G, C and T; s is a phosphorothioate linkage; and wherein the dsRNA comprises one or more C22 hydrocarbon chains conjugated to one or more internal positions on at least one strand of the dsRNA agent.

In one aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of inhibin subunit beta E (INHBE), wherein said dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15, *e.g.*, 15, 16, 17, 18, 19, 20, or 21, contiguous nucleotides differing by no more than 0, 1, 2, 3, or 4 nucleotides from the nucleotide sequence ascscagucgUfCfCfcagaauaacu (SEQ ID NO:), wherein the antisense strand comprises at least 15, *e.g.*, 15, 16, 17, 18, 19, 20, 21, 22, or 23, contiguous nucleotides differenting by no more than 0, 1, 2, 3, or 4 nucleotides from the nucleotide sequence asdGsuudAudTcuggdGaCfgacugguscsu (SEQ ID NO:), wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U; Af, Gf, Cf, and Uf are 2'-fluoro A, G, C and U; dA, dG, dC and dT are 2`-deoxy A, G, C and T; s is a phosphorothioate linkage; and wherein the dsRNA comprises one or more C22 hydrocarbon chains conjugated to one or more internal positions on at least one strand of the dsRNA agent.

In one aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of inhibin subunit beta E (INHBE), wherein said dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15, *e.g.*, 15, 16, 17, 18, 19, 20, or 21, contiguous nucleotides differing by no more than 0, 1, 2, 3, or 4 nucleotides from the nucleotide sequence cscsagaauaAfCfCfUfcauccuccau (SEQ ID NO:), wherein the antisense strand comprises at least 15, *e.g.*, 15, 16, 17, 18, 19, 20, 21, 22, or 23, contiguous nucleotides differenting by no more than 0, 1, 2, 3, or 4 nucleotides from the nucleotide sequence asdTsggdAgdGaugadGuUfauucuggsgsa (SEQ ID NO:), wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U; Af, Gf, Cf, and Uf are 2'-fluoro A, G, C and U; dA, dG, dC and dT are 2`-deoxy A, G, C and T; s is a phosphorothioate linkage; and wherein the dsRNA

comprises one or more C22 hydrocarbon chains conjugated to one or more internal positions on at least one strand of the dsRNA agent.

In one aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of inhibin subunit beta E (INHBE), wherein said dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15, *e.g.*, 15, 16, 17, 18, 19, 20, or 21, contiguous nucleotides differing by no more than 0, 1, 2, 3, or 4 nucleotides from the nucleotide sequence csusgucaCfaGfAfCfuccacuucau (SEQ ID NO:), wherein the antisense strand comprises at least 15, *e.g.*, 15, 16, 17, 18, 19, 20, 21, 22, or 23, contiguous nucleotides differenting by no more than 0, 1, 2, 3, or 4 nucleotides from the nucleotide sequence asUfsgadAg(Tgn)ggagucUfgUfgacagsusa (SEQ ID NO:), wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U; Af, Gf, Cf, and Uf are 2'-fluoro A, G, C and U; dA, dG, dC and dT are 2`-deoxy A, G, C and T; Tgn is thymidine-glycol nucleic acid (GNA) S-isomer; s is a phosphorothioate linkage; and wherein the dsRNA comprises one or more C22 hydrocarbon chains conjugated to one or more internal positions on at least one strand of the dsRNA agent.

In one aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of inhibin subunit beta E (INHBE), wherein said dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15, *e.g.*, 15, 16, 17, 18, 19, 20, or 21, contiguous nucleotides differing by no more than 0, 1, 2, 3, or 4 nucleotides from the nucleotide sequence usgsucacagAfCfUfccacuucagu (SEQ ID NO:), wherein the antisense strand comprises at least 15, *e.g.*, 15, 16, 17, 18, 19, 20, 21, 22, or 23, contiguous nucleotides differenting by no more than 0, 1, 2, 3, or 4 nucleotides from the nucleotide sequence asdCsugdAadGuggadGuCfugugacasgsu (SEQ ID NO:), wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U; Af, Gf, Cf, and Uf are 2'-fluoro A, G, C and U; dA, dG, dC and dT are 2`-deoxy A, G, C and T; s is a phosphorothioate linkage; and wherein the dsRNA comprises one or more C22 hydrocarbon chains conjugated to one or more internal positions on at least one strand of the dsRNA agent.

In one aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of inhibin subunit beta E (INHBE), wherein said dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15, *e.g.*, 15, 16, 17, 18, 19, 20, or 21, contiguous nucleotides differing by no more than 0, 1, 2, 3, or 4 nucleotides from the nucleotide sequence csusuugcuuGfAfGfgaucuuccgu (SEQ ID NO:), wherein the antisense strand comprises at least 15, *e.g.*, 15, 16, 17, 18, 19, 20, 21, 22, or 23, contiguous nucleotides differenting by no more than 0, 1, 2, 3, or 4 nucleotides from the nucleotide sequence asdCsggdAadGauccdTcAfagcaaagsasg (SEQ ID NO:), wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U; Af, Gf, Cf, and Uf are 2'-fluoro A, G, C and U; dA, dG, dC and dT are 2`-deoxy A, G, C and T; s is a phosphorothioate linkage; and wherein the dsRNA comprises one or more C22 hydrocarbon chains conjugated to one or more internal positions on at least one strand of the dsRNA agent.

In one aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of inhibin subunit beta E (INHBE), wherein said dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15, *e.g.*, 15, 16, 17, 18, 19, 20, or 21, contiguous nucleotides differing by no more than 0, 1, 2, 3, or 4 nucleotides from the nucleotide sequence asasugggcaCfUfUfucuugucugu (SEQ ID NO:), wherein the antisense strand comprises at least 15, *e.g.*, 15, 16, 17, 18, 19, 20, 21, 22, or 23, contiguous nucleotides differenting by no more than 0, 1, 2, 3, or 4 nucleotides from the nucleotide sequence asdCsagdAcdAagaadAgUfgcccauususg (SEQ ID NO:), wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U; Af, Gf, Cf, and Uf are 2'-fluoro A, G, C and U; dA, dG, dC and dT are 2`-deoxy A, G, C and T; s is a phosphorothioate linkage; and wherein the dsRNA comprises one or more C22 hydrocarbon chains conjugated to one or more internal positions on at least one strand of the dsRNA agent.

In one aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of inhibin subunit beta E (INHBE), wherein said dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15, *e.g.*, 15, 16, 17, 18, 19, 20, or 21, contiguous nucleotides differing by no more than 0, 1, 2, 3, or 4 nucleotides from the nucleotide sequence gsascaagcaUfUfUfauacuuucuu (SEQ ID NO:), wherein the antisense strand comprises at least 15, *e.g.*, 15, 16, 17, 18, 19, 20, 21, 22, or 23, contiguous nucleotides differenting by no more than 0, 1, 2, 3, or 4 nucleotides from the nucleotide sequence asdAsgadAadGuauadAaUfgcuugucsusc (SEQ ID NO:), wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U; Af, Gf, Cf, and Uf are 2'-fluoro A, G, C and U; dA, dG, dC and dT are 2`-deoxy A, G, C and T; s is a phosphorothioate linkage; and wherein the dsRNA comprises one or more C22 hydrocarbon chains conjugated to one or more positions on at least one strand of the dsRNA agent.

In one aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of inhibin subunit beta E (INHBE), wherein said dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15, *e.g.*, 15, 16, 17, 18, 19, 20, or 21, contiguous nucleotides differing by no more than 0, 1, 2, 3, or 4 nucleotides from the nucleotide sequence ascsaagcauUfUfAfuacuuucuuu (SEQ ID NO:), wherein the antisense strand comprises at least 15, *e.g.*, 15, 16, 17, 18, 19, 20, 21, 22, or 23, contiguous nucleotides differenting by no more than 0, 1, 2, 3, or 4 nucleotides from the nucleotide sequence asdAsagdAadAguaudAaAfugcuuguscsu (SEQ ID NO:), wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U; Af, Gf, Cf, and Uf are 2'-fluoro A, G, C and U; dA, dG, dC and dT are 2`-deoxy A, G, C and T; s is a phosphorothioate linkage; and wherein the dsRNA comprises one or more C22 hydrocarbon chains conjugated to one or more internal positions on at least one strand of the dsRNA agent.

In some embodiments, the lipophilicity of the one or more C_{22} hydrocarbon chain, measured by octanol-water partition coefficient, $\log K_{ow}$, exceeds 0. The lipophilic moiety may possess a $\log K_{ow}$ exceeding 1, exceeding 1.5, exceeding 2, exceeding 3, exceeding 4, exceeding 5, or exceeding 10.

In some embodiments, the hydrophobicity of the dsRNA agent, measured by the unbound fraction in the plasma protein binding assay of the dsRNA agent, exceeds 0.2. In one embodiment, the plasma protein binding assay determined is an electrophoretic mobility shift assay (EMSA) using human serum albumin protein. The hydrophobicity of the dsRNA agent, measured by fraction of unbound dsRNA 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 dsRNA/

The C_{22} hydrocarbon chain may be saturated or unsaturated.

The C_{22} hydrocarbon chain may be linear or branched

In some embodiments, the internal positions include all positions except the three terminal 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 exclude positions 9-12 or positions 11-13, counting from the 5'-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 exclude positions 12-14, counting from the 5'-end of the antisense strand.

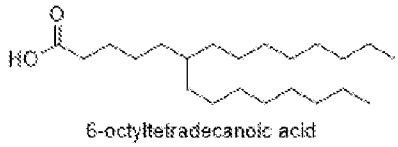
In some embodiments, the one or more C_{22} hydrocarbon chains are conjugated to one or more of the following internal positions: positions 4-8 and 13-18 on the sense strand, and positions 6-10 and 15-18 on the antisense strand, counting from the 5'end of each strand.

In some embodiments, the one or more C_{22} hydrocarbon chains are conjugated to one or more of the following internal positions: 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.

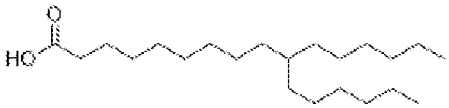
In some embodiments, the one or more C_{22} hydrocarbon chains are conjugated to position 6 on the sense strand, counting from the 5'-end of the sense strand.

In some embodiments, the one or more C_{22} hydrocarbon chains is an aliphatic, alicyclic, or polyalicyclic compound, *e.g.,* the one or more C_{22} hydrocarbon chains contains a functional group selected from the group consisting of hydroxyl, amine, carboxylic acid, sulfonate, phosphate, thiol, azide, and alkyne.

In some embodiments, the one or more C_{22} hydrocarbon chains is a C22 acid, *e.g.* the C22 acid is selected from the group consisting of docosanoic acid, 6-octyltetradecanoic acid, 10-hexylhexadecanoic acid, all-cis-7,10,13,16,19-docosapentaenoic acid, all-cis-4,7,10,13,16,19-docosahexaenoic acid, all-cis-13,16-docosadienoic acid, all-cis-7,10,13,16-docosatetraenoic acid, all-cis-4,7,10,13,16-docosapentaenoic acid, and cis-13-docosenoic acid.

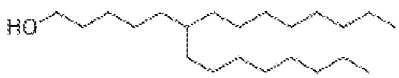


6-octyltetradecanoic acid



10-hexylhexadecanoic acid

In some embodiments, the one or more C_{22} hydrocarbon chains is a C22 alcohol, *e.g.,* the C22 alcohol is selected from the group consisting of 1-docosanol, 6-octyltetradecan-1-ol, 10-hexylhexadecan-1-ol, cis-13-docosen-1-ol, docosan-9-ol, docosan-2-ol, docosan-10-ol, docosan-11-ol, and cis-4,7,10,13,16,19-docosahexanol.



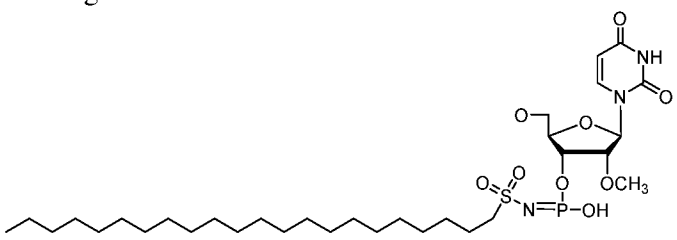
6-octyltetradecan-1-ol



10-hexylhexadecan-1-ol

In some embodiments, the one or more C_{22} hydrocarbon chains is a C22 amide, *e.g.,* the C22 amide is selected from the group consisting of (E)-Docos-4-enamide, (E)-Docos-5-enamide, (Z)-Docos-9-enamide, (E)-Docos-11-enamide,12-Docosenamide, (Z)-Docos-13-enamide, (Z)-N-Hydroxy-13-docoseneamide, (E)-Docos-14-enamide, 6-cis-Docosenamide, 14-Docosenamide Docos-11-enamide, (4E,13E)-Docosa-4,13-dienamide, and (5E,13E)-Docosa-5,13-dienamide.

The one or more C_{22} hydrocarbon chains may be conjugated to the dsRNA agent via a direct attachment to the ribosugar of the dsRNA agent. Alternatively, the the one or more C_{22} hydrocarbon chains may be conjugated to the dsRNA agent via a linker or a carrier. In some embodiments, the one or more C_{22} hydrocarbon chains may be conjugated to the dsRNA agent via internucleotide phosphate linkage.



In certain embodiments, the one or more C_{22} hydrocarbon chains is conjugated to the dsRNA agent via one or more linkers (tethers), *e.g.,* a carrier that replaces one or more nucleotide(s) in the internal position(s).

In some embodiments, the one or more C_{22} hydrocarbon chains is conjugated to the dsRNA 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 some embodiments, at least one of the linkers (tethers) is a redox cleavable linker (such as a reductively cleavable linker; *e.g.*, a disulfide group), an acid cleavable linker (*e.g.*, a hydrazone group, an ester group, an acetal group, or a ketal group), an esterase cleavable linker (*e.g.*, an ester group), a phosphatase cleavable linker (*e.g.*, a phosphate group), or a peptidase cleavable linker (*e.g.*, a peptide bond).

In other embodiments, at least one of the linkers (tethers) is a bio-clevable 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 certain embodiments, the one or more C_{22} hydrocarbon chains is conjugated to the dsRNA agent via a carrier that replaces one or more nucleotide(s). The carrier can be a cyclic group or an acyclic group. In one embodiment, the cyclic group is selected from the group consisting of pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, [1,3]dioxolane, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl, tetrahydrofuryl, and decalin. In one embodiment, the acyclic group is a moiety based on a serinol backbone or a diethanolamine backbone.

In some embodiments, the carrier replaces one or more nucleotide(s) in the internal position(s) of the dsRNA agent.

In some embodiments, the dsRNA agent further comprises a targeting ligand that targets a receptor which mediates delivery to adipose tissue. In one embodiment, the targeting ligand is selected from the group consisting of Angiopep-2, lipoprotein receptor related protein (LRP) ligand, bEnd.3 cell binding ligand, transferrin receptor (TfR) ligand, manose receptor ligand, glucose transporter protein, LDL receptor ligand, trans-retinol, RGD peptide, LDL receptor ligand, CD63 ligand, and carbohydrate based ligand.

In some embodiments, the dsRNA agent further comprises a targeting ligand that targets a liver tissue.

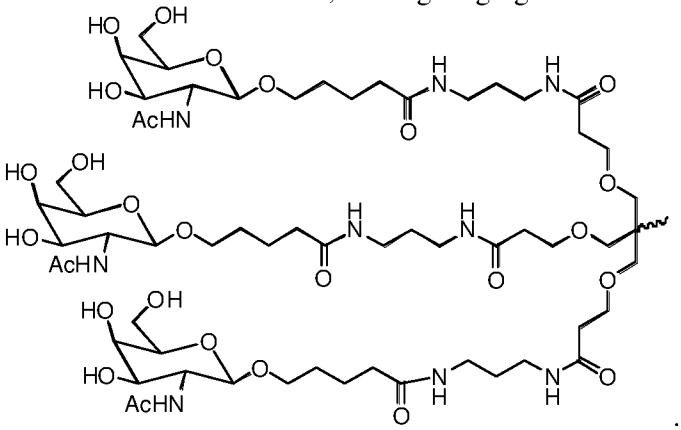
In one embodiment, the targeting ligand is conjugated to the 3' end of the sense strand of the dsRNA agent.

In some embodiments, the targeting ligand is a carbohydrate-based ligand.

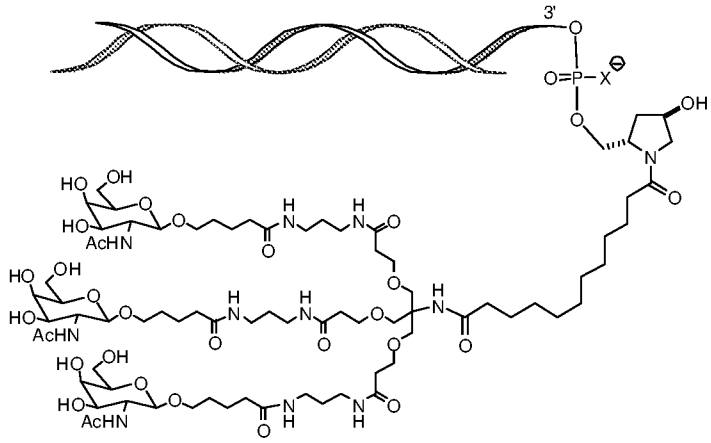
In one embodiment, the targeting ligand is an N-acetylgalactosamine (GalNAc) derivative.

In one embodiment, the targeting ligand is one or more GalNAc derivatives attached through a monovalent, bivalent, or trivalent branched linker.

In one embodiment, the targeting ligand is



In one embodiment, the dsRNA agent is conjugated to the targeting ligand as shown in the following schematic



and, wherein X is O or S.

In one embodiment, the X is O.

In som embodiments, the one or more C22 hydrocarbon chains or targeting ligand is conjugated via a bio-clevable linker selected from the group consisting of DNA, RNA, disulfide, amide, funtionalized monosaccharides or oligosaccharides of galactosamine, glucosamine, glucose, galactose, mannose, and combinations thereof.

The present invention also provides cells containing any of the dsRNA agents of the invention and pharmaceutical compositions comprising any of the dsRNA agents of the invention.

The pharmaceutical composition of the invention may include dsRNA agent in an unbuffered solution, *e.g.,* saline or water, or the pharmaceutical composition of the invention may include the dsRNA agent is in a buffer solution, *e.g.,* a buffer solution comprising acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof; or phosphate buffered saline (PBS).

In one aspect, the present invention provides a method of inhibiting expression of a metabolic disorder-associated target gene selected from the group consisting of inhibin subunit beta E (INHBE), activin A receptor type 1C (ACVR1C), perilipin-1 (PLIN1), phosphodiesterase 3B (PDE3B), and inhibin subunit beta C (INHBC) in a cell, such as an adipocyte and/or a liver cell. The method includes contacting the cell with any of the dsRNAs of the invention or any of the

pharmaceutical compositions of the invention, thereby inhibiting expression of the the target gene in the cell.

In one embodiment, the target gene is INHBE.

In one embodiment, the target gene is ACVR1C.

In one embodiment, the target gene is PLIN1.

In one embodiment, the target gene is PDE3B.

In one embodiment, the target gene is INHBC.

In one embodiment, the cell is within a subject, *e.g.,* a human subject, *e.g.,* a subject having a metabolic disorder, such as diabetes, metabolic syndrome, cardiovascular disease, or hypertension.

In one embodiment, the cell is an adipocyte.

In one embodiment, the cell is a hepatocyte.

In certain embodiments, the target gene expression is inhibited by at least about 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 95%. In one embodiment, inhibiting expression of the target gene decreases target gene protein level in serum of the subject by at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 95%.

In one aspect, the present invention provides a method of treating a metabolic disorder. The method includes administering to the subject a therapeutically effective amount of any of the dsRNAs of the invention or any of the pharmaceutical compositions of the invention, thereby treating the subject having the metabolic disorder.

In another aspect, the present invention provides a method of preventing at least one symptom in a subject having a metabolic disorder. The method includes administering to the subject a prophylactically effective amount of any of the dsRNAs of the invention or any of the pharmaceutical compositions of the invention, thereby preventing at least one symptom in the subject having the metabolic disorder.

In one embodiment, the target gene is INHBE.

In one embodiment, the target gene is ACVR1C.

In one embodiment, the target gene is PLIN1.

In one embodiment, the target gene is PDE3B.

In one embodiment, the target gene is INHBC.

In one embodiment, administration of a therapeutically or prophylactically effective amount descreases the waist-to-hip ratio adjusted for body mass index in the subject.

The metabolic disorder may be, *e.g.* metabolic syndrome, a disorder of carbohydrates, *e.g.*, type II diabetes, pre-diabetes, a lipid metabolism disorder, *e.g.*, a hyperlipidemia, hypertension, lipodystrophy; a kidney disease; a cardiovascular disease, a disorder of body weight.

In some embodiments, the metabolic disorder is metabolic syndrome.

In some embodiments, the metabolic disorder is type 2 diabetes.

In some embodiments, the metabolic disorder is obesity.

In some embodiments, the metabolic disorder is elevated triglyceride level.

In some embodiments, the metabolic disorder is lipodystrophy.

In some embodiments, the metabolic disorder liver inflammation.

In some embodiments, the metabolic disorder is fatty liver disease.

In some embodiments, the metabolic disorder is hypercholesterolemia.

In some embodiments, the metabolic disorder is elevated liver enzyme.

In some embodiments, the metabolic disorder is nonalcoholic steatohepatitis (NASH).

In some embodiments, the metabolic disorder is cardiovascular disease.

In some embodiments, the metabolic disorder is hypertension.

In some embodiments, the metabolic disorder is cardiomyopathy.

In some embodiments, the metabolic disorder is heart failure.

In some embodiments, the metabolic disorder is kidney disease.

In certain embodiments, administration of the dsRNA to the subject causes a decrease target gene protein accumulation in the subject.

In a further aspect, the present invention also provides methods of inhibiting the expression of a metabolic disorder-associated target gene selected from the group consisting of inhibin subunit beta E (INHBE), activin A receptor type 1C (ACVR1C), perilipin-1 (PLIN1), phosphodiesterase 3B (PDE3B), and inhibin subunit beta C (INHBC) in a subject. The methods include administering to the subject a therapeutically effective amount of any of the dsRNAs provided herein, thereby inhibiting the expression of the target gene in the subject.

In one embodiment, the subject is human.

In one embodiment, the dsRNA agent is administered to the subject at a dose of about 0.01 mg/kg to about 50 mg/kg.

In one embodiment, the dsRNA agent is administered to the subject subcutaneously.

In one embodiment, the methods of the invention include further determining the level of the target gene in a sample(s) from the subject.

In one embodiment, the level of the target gene in the subject sample(s) is a target gene protein level in a blood or serum or liver tissue sample(s).

In certain embodiments, the methods of the invention further comprise administering to the subject an additional therapeutic agent.

In certain embodiments, the additional therapeutic agent is selected from the group consisting of insulin, a glucagon-like peptide 1 agonist, a sulfonylurea, a seglitinide, a biguanide, a thiazolidinedione, an alpha-glucosidase inhibitor, an SGLT2 inhibitor, a DPP-4 inhibitor, an HMG-CoA reductase inhibitor, a statin, and a combination of any of the foregoing.

The present invention also provides kits comprising any of the dsRNAs of the invention or any of the pharmaceutical compositions of the invention, and optionally, instructions for use. In one embodiment, the invention provides a kit for performing a method of inhibiting expression of a metabolic disorder-associated target gene selected from the group consisting of inhibin subunit beta E (INHBE), activin A receptor type 1C (ACVR1C), perilipin-1 (PLIN1), phosphodiesterase 3B (PDE3B), and inhibin subunit beta C (INHBC) in a cell by contacting a cell with a double stranded RNAi agent of the invention in an amount effective to inhibit expression of the target gene in the cell.

The kit comprises an RNAi agent and instructions for use and, optionally, means for administering the RNAi agent to a subject.

The present invention further provides an RNA-induced silencing complex (RISC) comprising an antisense strand of any of the dsRNA agents of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a schematic of the study design to determine the pharmacodynamic activity of duplexes of interest targeting INHBE in non-human primates (NHP).

Figure 2A is a graph depicting the level of INHBE mRNA in the liver of non-human primates subcutaneously administered a single 3 mg/kg dose of the indicated duplexes at Day 28 post-dose.

Figure 2B is a graph depicting the level of INHBC mRNA in the liver of non-human primates subcutaneously administered a single 3 mg/kg dose of the indicated duplexes at Day 28 post-dose.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides iRNA compositions which effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of a metabolic disorder-associated target gene selected from the group consisting of inhibin subunit beta E (INHBE), activin A receptor type 1C (ACVR1C), perilipin-1 (PLIN1), phosphodiesterase 3B (PDE3B), and inhibin subunit beta C (INHBC). The gene may be within a cell, such as an adipocyte and/or a liver cell, *e.g.*, a cell within a subject, such as a human. The use of these iRNAs enables the targeted degradation of mRNAs of the corresponding gene (INHBE, ACVR1C, PLIN1, PDE3B, or INHBC) in mammals.

The iRNAs of the invention have been designed to target a metabolic disorder-associated target gene selected from the group consisting of inhibin subunit beta E (INHBE), activin A receptor type 1C (ACVR1C), perilipin-1 (PLIN1), phosphodiesterase 3B (PDE3B), and inhibin subunit beta C (INHBC), including portions of the gene that are conserved in orthologs of other mammalian species. Without intending to be limited by theory, it is believed that a combination or sub-combination of the foregoing properties and the specific target sites or the specific modifications in these iRNAs confer to the iRNAs of the invention improved efficacy, stability, potency, durability, and safety.

Accordingly, the present invention provides methods for treating and preventing a metabolic disorder, *e.g.* metabolic syndrome, a disorder of carbohydrates, *e.g.*, type II diabetes, pre-diabetes, a lipid metabolism disorder, *e.g.*, a hyperlipidemia, hypertension, lipodystrophy; a kidney disease; a cardiovascular disease, a disorder of body weight, using iRNA compositions which effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of a metabolic disorder-associated target gene selected from the group consisting of inhibin subunit beta E (INHBE), activin A receptor type 1C (ACVR1C), perilipin-1 (PLIN1), phosphodiesterase 3B (PDE3B), and inhibin subunit beta C (INHBC).

The iRNAs of the invention include an RNA strand (the antisense strand) having a region which is up to about 30 nucleotides or less in length, *e.g.*, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24,20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 nucleotides in length, which region is substantially complementary to at least part of an mRNA transcript of a metabolic disorder-associated target gene.

In certain embodiments, one or both of the strands of the double stranded RNAi agents of the invention is up to 66 nucleotides in length, *e.g.*, 36-66, 26-36, 25-36, 31-60, 22-43, 27-53 nucleotides in length, with a region of at least 19 contiguous nucleotides that is substantially complementary to at least a part of an mRNA transcript of a metabolic disorder-associated target gene. In some embodiments, such iRNA agents having longer length antisense strands may, for example, include a second RNA strand (the sense strand) of 20-60 nucleotides in length wherein the sense and antisense strands form a duplex of 18-30 contiguous nucleotides.

The use of iRNAs of the invention enables the targeted degradation of mRNAs of the corresponding gene (INHBE, ACVR1C, PLIN1, PDE3B, or INHBC gene) in mammals. Using *in vitro* assays, the present inventors have demonstrated that iRNAs targeting the gene can potently mediate RNAi, resulting in significant inhibition of expression of the target gene. Thus, methods and compositions including these iRNAs are useful for treating a subject having a metabolic disorder, *e.g.* metabolic syndrome, a disorder of carbohydrates, *e.g.*, type II diabetes, pre-diabetes, a lipid metabolism disorder, *e.g.*, a hyperlipidemia, hypertension, lipodystrophy; a kidney disease; a cardiovascular disease, a disorder of body weight.

Accordingly, the present invention provides methods and combination therapies for treating a subject having a metabolic disorder that would benefit from inhibiting or reducing the expression of a metabolic disorder-associated target gene selected from the group consisting of inhibin subunit beta E (INHBE), activin A receptor type 1C (ACVR1C), perilipin-1 (PLIN1), phosphodiesterase 3B (PDE3B), and inhibin subunit beta C (INHBC), *e.g.,* metabolic syndrome, a disorder of carbohydrates, *e.g.*, type II diabetes, pre-diabetes, a lipid metabolism disorder, *e.g.*, a hyperlipidemia, hypertension, lipodystrophy; a kidney disease; a cardiovascular disease, a disorder of body weight, using iRNA compositions which effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of INHBE, ACVR1C, PLIN1, PDE3B, or INHBC.

The present invention also provides methods for preventing at least one symptom in a subject having a disorder that would benefit from inhibiting or reducing the expression of a metabolic disorder-associated target gene selected from the group consisting of inhibin subunit beta E (INHBE), activin A receptor type 1C (ACVR1C), perilipin-1 (PLIN1), phosphodiesterase 3B (PDE3B), and inhibin subunit beta C (INHBC), *e.g.*, metabolic syndrome, a disorder of carbohydrates, *e.g.*, type II diabetes, pre-diabetes, a lipid metabolism disorder, *e.g.*, a hyperlipidemia, hypertension, lipodystrophy; a kidney disease; a cardiovascular disease, a disorder of body weight.

The following detailed description discloses how to make and use compositions containing iRNAs to inhibit the expression of a metabolic disorder-associated target gene selected from the group

consisting of inhibin subunit beta E (INHBE), activin A receptor type 1C (ACVR1C), perilipin-1 (PLIN1), phosphodiesterase 3B (PDE3B), and inhibin subunit beta C (INHBC), as well as compositions, uses, and methods for treating subjects that would benefit from inhibition and/or reduction of the expression of a metabolic disorder-associated target gene selected from the group consisting of inhibin subunit beta E (INHBE), activin A receptor type 1C (ACVR1C), perilipin-1 (PLIN1), phosphodiesterase 3B (PDE3B), and inhibin subunit beta C (INHBC), *e.g.*, subjects susceptible to or diagnosed with a metabolic disorder.

I. Definitions

In order that the present invention may be more readily understood, certain terms are first defined. In addition, it should be noted that whenever a value or range of values of a parameter are recited, it is intended that values and ranges intermediate to the recited values are also intended to be part of this invention.

The articles "a" and "an" are used herein to refer to one or to more than one (*i.e.*, to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element, *e.g.*, a plurality of elements.

The term "including" is used herein to mean, and is used interchangeably with, the phrase "including but not limited to".

The term "or" is used herein to mean, and is used interchangeably with, the term "and/or," unless context clearly indicates otherwise. For example, "sense strand or antisense strand" is understood as "sense strand or antisense strand or sense strand and antisense strand."

The term "about" is used herein to mean within the typical ranges of tolerances in the art. For example, "about" can be understood as about 2 standard deviations from the mean. In certain embodiments, about means ±10%. In certain embodiments, about means ±5%. When about is present before a series of numbers or a range, it is understood that "about" can modify each of the numbers in the series or range.

The term "at least", "no less than", or "or more" 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 19 nucleotides of a 21 nucleotide nucleic acid molecule" means that 19, 20, or 21 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 an overhang of "no more than 2 nucleotides" has a 2, 1, or 0 nucleotide overhang. 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, ranges include both the upper and lower limit.

As used herein, methods of detection can include determination that the amount of analyte present is below the level of detection of the method.

In the event of a conflict between an indicated target site and the nucleotide sequence for a sense or antisense strand, the indicated sequence takes precedence.

In the event of a conflict between a sequence and its indicated site on a transcript or other sequence, the nucleotide sequence recited in the specification takes precedence.

As used herein, the term "a metabolic disorder-associated target gene" or "target gene" refers to a gene encoding "inhibin subunit beta E" ("INHBE"), "activin A receptor type 1C" ("ACVR1C"), "perilipin-1" ("PLIN1"), "phosphodiesterase 3B" ("PDE3B"), or "inhibin subunit beta C" ("INHBC").

In one embodiment, a metabolic disorder-associated target gene is inhibin subunit beta E (INHBE).

As used herein, "inhibin subunit beta E," used interchangeably with the terms "INHBE," refers to a growth factor that belongs to the transforming growth factor-β (TGF-β) family. INHBE mRNA is predominantly expressed in the liver (Fang J. *et al. Biochemical & Biophysical Res. Comm.* 1997; 231(3):655-61), and INHBE is involved in the regulation of liver cell growth and differentiation (Chabicovsky M. et al. Endocrinology. 2003; 144(8):3497-504). INHBE is also known as inhibin beta E chain, activin E , inhibin beta E subunit, inhibin beta E, and MGC4638. More specifically, INHBE is a hepatokine which has been shown to positively correlate with insulin resistance and body mass index in humans. Quantitative real time-PCR analysis also showed an increase in INHBE gene expression in liver samples from insulin-resistant human subjects. In addition, Inhbe gene expression was shown to be increased in the livers of an art-recognized animal model of a metabolic disorder, *i.e.*, type 2 diabetes, the *db/db* mouse model. Inhibition of Inhbe expression in *db/db* mice was demonstrated to suppress body weight gain which was attributable to diminished fat rather than lean mass.

The sequence of a human INHBE mRNA transcript can be found at, for example, GenBank Accession No. GI: 1877089956 (NM_031479.5; SEQ ID NO:1; reverse complement, SEQ ID NO: 2). The sequence of mouse INHBE mRNA can be found at, for example, GenBank Accession No. GI: 1061899809 (NM_008382.3; SEQ ID NO:3; reverse complement, SEQ ID NO:4). The sequence of rat INHBE mRNA can be found at, for example, GenBank Accession No. GI: 148747589 (NM_031815.2; SEQ ID NO:5; reverse complement, SEQ ID NO: 6). The predicted sequence of Macaca mulatta INHBE mRNA can be found at, for example, GenBank Accession No. GI: 1622845604 (XM_001115958.3; SEQ ID NO:7; reverse complement, SEQ ID NO:8).

Additional examples of INHBE mRNA sequences are readily available through publicly available databases, e.g., GenBank, UniProt, OMIM, and the Macaca genome project web site.

Further information on INHBE can be found, for example, at www.ncbi.nlm.nih.gov/gene/?term=INHBE.

The entire contents of each of the foregoing GenBank Accession numbers and the Gene database numbers are incorporated herein by reference as of the date of filing this application.

The term INHBE, as used herein, also refers to variations of the INHBE gene including variants provided in the SNP database. Numerous seuqnce variations within the INHBE gene have been identified and may be found at, for example, NCBI dbSNP and UniProt (see, e.g., www.ncbi.nlm.nih.gov/snp/?term=INHBE, the entire contents of which is incorporated herein by reference as of the date of filing this application.

In one embodiment, a metabolic disorder-associated target gene is activin A receptor type 1C (ACVR1C).

As used herein, "activin A receptor type 1C," used interchangeably with the terms "ACVR1C," refers to a type I receptor for the TGF-β family of signaling molecule. ACVR1C has intrinsic serine/threonine kinase activities in its cytoplasmic domains, inducing phosphorylation and activation of the SMAD2/3/4 complex, which translocates into the nucleus where it binds SMAD-binding elements (SBE) to activate gene transcription. Expression levels of ACVR1C varies greatly among tissues, but white and brown adipose tissues have the highest level of expression. In addition to full length protein, variants of ACVR1C are also expressed in adipose tissues, brain and ovary (Murakami M *et al.Biochem Genet*. 2013; 51(3-4): 202-210). ACVR1C is also known as "activin receptor-like kinase 7" (ALK-7). A polymorphism in ACVR1C has been found to be associated with increased risk of metabolic syndrome in Chinese females and may be involved in cardiovascular remodeling in patients with metabolic syndrome (Zhang, W *et al. Arq Bras Cardiol.* 2013: 101(2):134-140). Additionally, variants predicted to lead to loss of ACVR1C gene function are thought to influence body fat distribution and protect against type 2 diabetes (Emdin CA *et al. Diabetes.* 2019: 68(1):226-234). A study conducted in adipocytes of an obese mouse strain demonstrated that ACVR1C dysfunction (due to a nonsense mutation) caused increased lipolysis in adipocytes and led to decreased fat accumulation, and conversely, ACVR1C activation inhibited lipolysis by suppressing the expression of adipose lipases. Furthermore, ACVR1C-deficient mice with lower body weight exhibited enhanced glucose tolerance and insulin sensitivity, and measurement of metabolic rates in these mice revealed increased O_2 consumption, decreased respiratory quotients, and increased energy expenditure (Yogosawa, S *et al. Diabetes* 2013: 62(1):115-123).

The sequence of a human ACVR1C mRNA transcript can be found at, for example, GenBank Accession No. GI: 1519315475 (NM_145259.3, SEQ ID NO:9; reverse complement, SEQ ID NO:10), GI: 1890343165 (NM_001111031.2, SEQ ID NO:11; reverse complement, SEQ ID NO:12), GI: 1676439980 (NM_001111032.2, SEQ ID NO:13, reverse complement SEQ ID NO:14), and GI: 1676318472 (NM_001111033.2, SEQ ID NO:15, reverse complement, SEQ ID NO:16). The sequence of mouse ACVR1C mRNA can be found at, for example, GenBank Accession No. GI: 161333830 (NM_001111030.1, SEQ ID NO:17; reverse complement, SEQ ID NO:18) or GI: 161333829 (NM_001033369.3, SEQ ID NO:19; reverse complement, SEQ ID NO:20). The sequence of rat ACVR1C mRNA can be found at, for example, GenBank Accession No. GI: 1937875934 (NM_139090.2; SEQ ID NO:21; reverse complement, SEQ ID NO:22). The sequence of Macaca mulatta ACVR1C mRNA can be found at, for example, GenBank Accession No. GI: 388454445 (NM_001266690.1; SEQ ID NO:23; reverse complement, SEQ ID NO:24).

Additional examples of ACVR1C mRNA sequences are readily available through publicly available databases, e.g., GenBank, UniProt, OMIM, and the Macaca genome project web site.

Further information on ACVR1C can be found, for example, at www.ncbi.nlm.nih.gov/gene/?term= ACVR1C.

The term ACVR1C, as used herein, also refers to variations of the ACVR1C gene including variants provided in the SNP database. Numerous sequence variations within the ACVR1C gene have been identified and may be found at, for example, NCBI dbSNP and UniProt (see, e.g., www.ncbi.nlm.nih.gov/snp/?term= ACVR1C, the entire contents of which is incorporated herein by reference as of the date of filing this application).

The entire contents of each of the foregoing GenBank Accession numbers and the Gene database numbers are incorporated herein by reference as of the date of filing this application.

In one embodiment, a metabolic disorder-associated target gene is perilipin-1 (PLIN1).

As used herein, "perilipin-1," used interchangeably with the terms "PLIN1," refers to a protein which coats lipid storage droplets in adipocytes, thereby protecting them until they can be broken down by hormone-sensitive lipase. PLIN1 expresses predominantly in adipose tissues. PLIN1 is also known as perilipin, lipid droplet-associated protein, PERI, PLIN and FPLD4.

Constitutive overexpression of PLIN1 in cultured adipocytes has been shown to block the ability of TNF-α to increase lipolysis. In animals, separate laboratories have independently generated lines of PLIN1-null mice and observed that the mice were lean and developed systemic insulin resistance as they got older. Studies comparing lipolysis in PLIN1-null and wild-type mice revealed that PLIN1-null adipocytes had increased rates of constitutive (unstimulated) lipolysis and reduced catecholamine-stimulated lipolysis. Several studies have found that polymorphisms in the PLIN1 gene influence body weight and the risk of metabolic disease. Interestingly, one PLIN1 polymorphism was found to be associated with reduced PLIN1 expression and increased rates of basal and stimulated adipocyte lipolysis; humans with this polymorphism tend to have reduced body weight and body fat mass (Greenberg, AS *et al. J Clin Invest.* 2011:121(6):2102–2110). Heterozygous frameshift variants in PLIN1 have also been implicated in familial partial lipodystrophy, a rare disease characterized by a limited capacity of peripheral fat to store triglycerides, which results in metabolic abnormalities including insulin resistance, hypertriglyceridemia, abd liver steatosis (Gandotra S, Le Dour C, Bottomley W, *et al. N Engl J Med* 2011;364:740–748).

The sequence of a human PLIN1 mRNA transcript can be found at, for example, GenBank Accession No. GI: 1519242647 (NM_002666.5; SEQ ID NO:25; reverse complement, SEQ ID NO:26) and GI: 1675042447 (NM_001145311.2, SEQ ID NO:27; reverse complement, SEQ ID NO:28). The sequence of mouse PLIN1 mRNA can be found at, for example, GenBank Accession No. GI: 164698407 (NM_175640.2; SEQ ID NO:29; reverse complement, SEQ ID NO:30) and GI: 164698412 (NM_001113471.1, SEQ ID NO:31; reverse complement, SEQ ID NO:32). The sequence of rat PLIN1 mRNA can be found at, for example, GenBank Accession No. GI: 815890869 (NM_001308145.1; SEQ ID NO:33; reverse complement, SEQ ID NO:34). The predicted sequence

of Macaca mulatta PLIN1 mRNA can be found at, for example, GenBank Accession No. GI: 1622954660 (XM_028851317.1; SEQ ID NO:35; reverse complement, SEQ ID NO:36).

Additional examples of PLIN1 mRNA sequences are readily available through publicly available databases, e.g., GenBank, UniProt, OMIM, and the Macaca genome project web site.

Further information on PLIN1 can be found, for example, at www.ncbi.nlm.nih.gov/gene/?term= PLIN1.

The entire contents of each of the foregoing GenBank Accession numbers and the Gene database numbers are incorporated herein by reference as of the date of filing this application.

The term PLIN1, as used herein, also refers to variations of the PLIN1 gene including variants provided in the SNP database. Numerous seuqnce variations within the PLIN1 gene have been identified and may be found at, for example, NCBI dbSNP and UniProt (see, e.g., www.ncbi.nlm.nih.gov/snp/?term= PLIN1, the entire contents of which is incorporated herein by reference as of the date of filing this application).

In one embodiment, a metabolic disorder-associated target gene is phosphodiesterase 3B (PDE3B).

As used herein, "phosphodiesterase 3B," used interchangeably with the terms "PDE3B," refers to a phosphodiesterase which hydrolyzes cAMP and cGMP and is expressed in cells of importance for regulation of energy homeostasis, including adipocytes, hepatocytes, hypothalamic cells and β cells. PDE3B is also known as CGMP-inhibited 3',5'-cyclic phosphodiesterase B, cyclic GMP-inhibited phosphodiesterase B, CGIPDE1, CGIP1 and cyclic nucleotide phosphodiesterase.

PDE3B proteins are phosphorylated and activated in hepatocytes and adipocytes in response to stimulation by insulin and/or agents that increase cAMP. Activation of PDE3B leads to increased hydrolysis of cAMP and, thereby, inhibition of catecholamine-induced lipolysis. Mice that specifically over-express PDE3B in β cells show a decrease in glucose-induced insulin secretion. PDE3B knock-out (KO) mice demonstrate a number of alterations in the regulation of energy homeostasis, including reduced fat mass, smaller adipocytes, and reduced weight gain than control mice when maintained on a high fat diet (Degerman, E. *et al. CurrOpin Pharmaco.* 2011:11(6):676-682).

The sequence of a human PDE3B mRNA transcript can be found at, for example, GenBank Accession No. GI: 1889438535 (NM_001363570.2; SEQ ID NO:37; reverse complement, SEQ ID NO:38), GI: 1519241942 (NM_000922.4, SEQ ID NO:39; reverse complement, SEQ ID NO:40) and GI: 1889636835 (NM_001363569.2, SEQ ID NO:41; reverse complement, SEQ ID NO:42). The sequence of mouse PDE3B mRNA can be found at, for example, GenBank Accession No. GI: 112983647 (NM_011055.2; SEQ ID NO:43; reverse complement, SEQ ID NO:44). The sequence of rat PDE3B mRNA can be found at, for example, GenBank Accession No. GI: 1939401976 (NM_017229.2; SEQ ID NO:45; reverse complement, SEQ ID NO:46). The predicted sequence of Macaca mulatta PDE3B mRNA can be found at, for example, GenBank Accession No. GI: 1622864110 (XM_015114810.2; SEQ ID NO:47; reverse complement, SEQ ID NO:48).

Additional examples of PDE3B mRNA sequences are readily available through publicly available databases, e.g., GenBank, UniProt, OMIM, and the Macaca genome project web site.

Further information on PDE3B can be found, for example, at www.ncbi.nlm.nih.gov/gene/?term=PDE3B.

The entire contents of each of the foregoing GenBank Accession numbers and the Gene database numbers are incorporated herein by reference as of the date of filing this application.

The term PDE3B, as used herein, also refers to variations of the PDE3B gene including variants provided in the SNP database. Numerous seuqnce variations within the PDE3B gene have been identified and may be found at, for example, NCBI dbSNP and UniProt (see, e.g., www.ncbi.nlm.nih.gov/snp/?term=PDE3B, the entire contents of which is incorporated herein by reference as of the date of filing this application.

In one embodiment, a metabolic disorder-associated target gene is inhibin subunit beta C (INHBC).

As used herein, "inhibin subunit beta C," used interchangeably with the terms "INHBC," refers to the beta C chain of inhibin, a member of the TGF-β superfamily. INHBC mRNA is predominantly expressed in the liver, and INHBC is involved in the regulation of liver cell growth and differentiation (Chabicovsky M. et al. Endocrinology. 2003; 144(8):3497-504). INHBC is also known as inhibin beta C chain, inhibin beta C subunit, inhibin beta C, activin C, activin beta-C chain, and IHBC. In mice, overexpression of INHBC increased total liver weight as a percentage of body weight and increased both hepatocyte proliferation and apoptosis. INHBC has been demonstrated to be significantly upregulated in obese insulin-resistant subjects (Choi, *et al. Front Physiol.* 2019; 10: 379). SNPs at the INHBC locus were identified as having genome-wide significance with serum urate levels, and also associated with an increase risk of gout (Yang Q, et al. 2010, *Circ. Cardiovasc. Genet.,* 3:523–530). In addition, the INHBC locus also colocalizes with GWAS signals for estimated glomerular filtration rate (eGFR), a marker of renal function (Gudjonsson A. *et al.*,2022, *Nature Communication,* 13: 480).

The sequence of a human INHBC mRNA transcript can be found at, for example, GenBank Accession No. GI: 1519246544 (NM_005538.4; SEQ ID NO:49; reverse complement, SEQ ID NO:50). The sequence of mouse INHBC mRNA can be found at, for example, GenBank Accession No. GI: 1049480142 (NM_010565.4; SEQ ID NO:51; reverse complement, SEQ ID NO:52). The sequence of rat INHBC mRNA can be found at, for example, GenBank Accession No. GI: 59709462 (NM_022614.2; SEQ ID NO:53; reverse complement, SEQ ID NO:54). The predicted sequence of Macaca mulatta INHBC mRNA can be found at, for example, GenBank Accession No. GI: 1622845603 (XM_001115940.4; SEQ ID NO:55; reverse complement, SEQ ID NO:56).

Additional examples of INHBC mRNA sequences are readily available through publicly available databases, e.g., GenBank, UniProt, OMIM, and the Macaca genome project web site.

Further information on INHBC can be found, for example, at www.ncbi.nlm.nih.gov/gene/?term=INHBC.

The entire contents of each of the foregoing GenBank Accession numbers and the Gene database numbers are incorporated herein by reference as of the date of filing this application.

The term INHBC, as used herein, also refers to variations of the INHBC gene including variants provided in the SNP database. Numerous seuqnce variations within the INHBC gene have been identified and may be found at, for example, NCBI dbSNP and UniProt (see, e.g., www.ncbi.nlm.nih.gov/snp/?term=INHBC, the entire contents of which is incorporated herein by reference as of the date of filing this application).

As used herein, "target sequence" or "target nucleic acid" refers to a contiguous portion of the nucleotide sequence of an mRNA molecule formed during the transcription of a target gene, including mRNA that is a product of RNA processing of a primary transcription product. In one embodment, the target portion of the sequence will be at least long enough to serve as a substrate for RNAi-directed cleavage at or near that portion of the nucleotide sequence of an mRNA molecule formed during the transcription of a target gene. In one embodiment, the target sequence is within the protein coding region of the target gene. In another embodiment, the target sequence is within the 3' UTR of the target gene. The target nucleic acid can be a cellular gene (or mRNA transcribed from the gene) whose expression is associated with a particular disorder or disease state.

The target sequence may be from about 19-36 nucleotides in length, *e.g.*, about 19-30 nucleotides in length. For example, the target sequence can be about 19-30 nucleotides, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24, 20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 nucleotides in length. In certain embodiments, the target sequence is 19-23 nucleotides in length, optionally 21-23 nucleotides in length. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the disclosure.

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.

"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 term "ribonucleotide" or "nucleotide" can also refer to a modified nucleotide, as further detailed below, or a surrogate replacement moiety (see, *e.g.,* Table 1). The skilled person is well aware that guanine, cytosine, adenine, and uracil can 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 can base pair with nucleotides containing adenine, cytosine, or uracil. Hence, nucleotides containing uracil, guanine, or adenine can be replaced in the nucleotide sequences of dsRNA featured in the invention 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 invention.

The terms "iRNA", "RNAi agent," "iRNA agent,", "RNA interference agent" as used interchangeably herein, refer to an agent that contains RNA as that term is defined herein, and which mediates the targeted cleavage of an RNA transcript *via* an RNA-induced silencing complex (RISC) pathway. iRNA directs the sequence-specific degradation of mRNA through a process known as RNA interference (RNAi). The iRNA modulates, *e.g.,* inhibits, the expression of a INHBE, ACVR1C, PLIN1, PDE3B, or INHBC gene in a cell, *e.g.,* a liver cell and/or adipocyte, within a subject, such as a mammalian subject.

In one embodiment, an RNAi agent of the invention includes a single stranded RNA that interacts with a target RNA sequence, *e.g.,* a metabolic disorder-associated target mRNA sequence, to direct the cleavage of the target RNA. Without wishing to be bound by theory it is believed that long double stranded RNA introduced into cells is broken down into siRNA by a Type III endonuclease known as Dicer (Sharp *et al.* (2001) *Genes Dev.* 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 cleave the target to induce silencing (Elbashir, *et al.*, (2001) *Genes Dev.* 15:188). Thus, in one aspect the invention relates to a single stranded RNA (siRNA) generated within a cell and which promotes the formation of a RISC complex to effect silencing of the target gene, *i.e.,* a metabolic disorder-associated target gene selected from the group consisting of inhibin subunit beta E (INHBE), activin A receptor type 1C (ACVR1C), perilipin-1 (PLIN1), phosphodiesterase 3B (PDE3B), and inhibin subunit beta C (INHBC). Accordingly, the term "siRNA" is also used herein to refer to an iRNA as described above.

In certain embodiments, the RNAi agent may be a single-stranded siRNA (ssRNAi) that is introduced into a cell or organism to inhibit a target mRNA. Single-stranded RNAi agents bind to the RISC endonuclease, Argonaute 2, which then cleaves the target mRNA. The single-stranded siRNAs are generally 15-30 nucleotides and are 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 may be used as a single-stranded siRNA as described herein or as chemically modified by the methods described in Lima *et al.*, (2012) *Cell* 150:883-894.

In certain embodiments, an "iRNA" for use in the compositions, uses, and methods of the invention is a double stranded RNA and is referred to herein as a "double stranded RNA agent," "double stranded RNA (dsRNA) molecule," "dsRNA agent," or "dsRNA". The term "dsRNA", refers to a complex of ribonucleic acid molecules, having a duplex structure comprising two anti-parallel and substantially complementary nucleic acid strands, referred to as having "sense" and "antisense" orientations with respect to a target RNA, *i.e.,* a metabolic disorder-associated target gene selected from the group consisting of inhibin subunit beta E (INHBE), activin A receptor type 1C (ACVR1C),

perilipin-1 (PLIN1), phosphodiesterase 3B (PDE3B), and inhibin subunit beta C (INHBC). In some embodiments of the invention, a double stranded RNA (dsRNA) triggers the degradation of a target RNA, *e.g.,* an mRNA, through a post-transcriptional gene-silencing mechanism referred to herein as RNA interference or RNAi.

In general, the majority of nucleotides of each strand of a dsRNA molecule are ribonucleotides, but as described in detail herein, each or both strands can also include one or more non-ribonucleotides, *e.g.*, a deoxyribonucleotide or a modified nucleotide. In addition, as used in this specification, an "iRNA" may include ribonucleotides with chemical modifications; an iRNA may include substantial modifications at multiple nucleotides. As used herein, the term "modified nucleotide" refers to a nucleotide having, independently, a modified sugar moiety, a modified internucleotide linkage, or modified nucleobase, or any combination thereof. Thus, the term modified nucleotide encompasses substitutions, additions or removal of, *e.g.,* a functional group or atom, to internucleoside linkages, sugar moieties, or nucleobases. The modifications suitable for use in the agents of the invention include all types of modifications disclosed herein or known in the art. Any such modifications, as used in a siRNA type molecule, are encompassed by "iRNA" or "RNAi agent" for the purposes of this specification and claims.

In certain embodiments of the instant disclosure, inclusion of a deoxy-nucleotide if present within an RNAi agent can be considered to constitute a modified nucleotide.

The duplex region may be of any length that permits specific degradation of a desired target RNA through a RISC pathway, and may range from about 19 to 36 base pairs in length, *e.g.*, about 19-30 base pairs in length, for example, about 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 base pairs in length, such as about 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24,20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 base pairs in length. In certain embodiments, the duplex region is 19-21 base pairs in length, *e.g.*, 21 base pairs in length. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the disclosure.

The two strands forming the duplex structure may be different portions of one larger RNA molecule, or they may be separate RNA molecules. Where the two strands are part of one larger molecule, and therefore are connected by an uninterrupted chain of nucleotides between the 3'-end of one strand and the 5'-end of the respective other strand forming the duplex structure, the connecting RNA chain is referred to as a "hairpin loop." A hairpin loop can comprise at least one unpaired nucleotide. In some embodiments, the hairpin loop can comprise at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 23 or more unpaired nucleotides. In some embodiments, the hairpin loop can be 10 or fewer nucleotides. In some embodiments, the hairpin loop can be 8 or fewer unpaired nucleotides. In some embodiments, the hairpin loop can be 4-10 unpaired nucleotides. In some embodiments, the hairpin loop can be 4-8 nucleotides.

In certain embodiment, the two strands of double-stranded oligomeric compound can be linked together. The two strands can be linked to each other at both ends, or at one end only. By

linking at one end is meant that 5'-end of first strand is linked to the 3'-end of the second strand or 3'-end of first strand is linked to 5'-end of the second strand. When the two strands are linked to each other at both ends, 5'-end of first strand is linked to 3'-end of second strand and 3'-end of first strand is linked to 5'-end of second strand. The two strands can be linked together by an oligonucleotide linker including, but not limited to, (N)n; wherein N is independently a modified or unmodified nucleotide and n is 3-23. In some embodiemtns, n is 3-10, *e.g.*, 3, 4, 5, 6, 7, 8, 9, or 10. In some embodiments, the oligonucleotide linker is selected from the group consisting of GNRA, (G)4, (U)4, and (dT)4, wherein N is a modified or unmodified nucleotide and R is a modified or unmodified purine nucleotide. Some of the nucleotides in the linker can be involved in base-pair interactions with other nucleotides in the linker. The two strands can also be linked together by a non-nucleosidic linker, *e.g.* a linker described herein. It will be appreciated by one of skill in the art that any oligonucleotide chemical modifications or variations describe herein can be used in the oligonucleotide linker.

Hairpin and dumbbell type oligomeric compounds will have a duplex region equal to or at least 14, 15, 15, 16, 17, 18, 19, 29, 21, 22, 23, 24, or 25 nucleotide pairs. The duplex region can be equal to or less than 200, 100, or 50, in length. In some embodiments, ranges for the duplex region are 15-30, 17 to 23, 19 to 23, and 19 to 21 nucleotides pairs in length.

The hairpin oligomeric compounds can have a single strand overhang or terminal unpaired region, in some embodiments at the 3', and in some embodiments on the antisense side of the hairpin. In some embodiments, the overhangs are 1-4, more generally 2-3 nucleotides in length. The hairpin oligomeric compounds that can induce RNA interference are also referred to as "shRNA" herein.

Where the two substantially complementary strands of a dsRNA are comprised by separate RNA molecules, those molecules need not be, but can be covalently connected. Where the two strands are connected covalently by means other than an uninterrupted chain of nucleotides between the 3'-end of one strand and the 5'-end of the respective other strand forming the duplex structure, the connecting structure is referred to as a "linker." The RNA strands may have the same or a different number of nucleotides. The maximum number of base pairs is the number of nucleotides in the shortest strand of the dsRNA minus any overhangs that are present in the duplex. In addition to the duplex structure, an RNAi may comprise one or more nucleotide overhangs. In one embodiment of the RNAi agent, at least one strand comprises a 3' overhang of at least 1 nucleotide. In another embodiment, at least one strand comprises a 3' overhang of at least 2 nucleotides, *e.g.*, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 14, or 15 nucleotides. In other embodiments, at least one strand of the RNAi agent comprises a 5' overhang of at least 1 nucleotide. In certain embodiments, at least one strand comprises a 5' overhang of at least 2 nucleotides, *e.g.*, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 14, or 15 nucleotides. In still other embodiments, both the 3' and the 5' end of one strand of the RNAi agent comprise an overhang of at least 1 nucleotide.

In certain embodiments, an iRNA agent of the invention is a dsRNA, each strand of which comprises 19-23 nucleotides, that interacts with a target RNA sequence, *e.g.*, a metabolic disorder-associated target gene sequence, to direct cleavage of the target RNA.

In some embodiments, an iRNA of the invention is a dsRNA of 24-30 nucleotides that interacts with a target RNA sequence, *e.g.*, a metabolic disorder-associated target gene mRNA sequence, to direct the cleavage of the target RNA.

As used herein, the term "nucleotide overhang" refers to at least one unpaired nucleotide that protrudes from the duplex structure of a double stranded iRNA. 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, 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) can 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 one embodiment, the antisense strand of a dsRNA has a 1-10 nucleotide, *e.g.,* a 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotide, overhang at the 3'-end or the 5'-end. In one embodiment, the sense strand of a dsRNA has a 1-10 nucleotide, *e.g.,* a 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotide, overhang at the 3'-end or the 5'-end. In another embodiment, one or more of the nucleotides in the overhang is replaced with a nucleoside thiophosphate.

In certain embodiments, the antisense strand of a dsRNA has a 1-10 nucleotide, *e.g.*, 0-3, 1-3, 2-4, 2-5, 4-10, 5-10, *e.g.*, a 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotide, overhang at the 3'-end or the 5'-end. In one embodiment, the sense strand of a dsRNA has a 1-10 nucleotide, *e.g.*, a 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotide, overhang at the 3'-end or the 5'-end. In another embodiment, one or more of the nucleotides in the overhang is replaced with a nucleoside thiophosphate.

In certain embodiments, the antisense strand of a dsRNA has a 1-10 nucleotides, *e.g.,* a 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotide, overhang at the 3'-end or the 5'-end. In certain embodiments, the overhang on the sense strand or the antisense strand, or both, can include extended lengths longer than 10 nucleotides, *e.g.*, 1-30 nucleotides, 2-30 nucleotides, 10-30 nucleotides, 10-25 nucleotides, 10-20 nucleotides, or 10-15 nucleotides in length. In certain embodiments, an extended overhang is on the sense strand of the duplex. In certain embodiments, an extended overhang is present on the 3' end of the sense strand of the duplex. In certain embodiments, an extended overhang is present on the 5' end of the sense strand of the duplex. In certain embodiments, an extended overhang is on the antisense strand of the duplex. In certain embodiments, an extended overhang is present on the 3'end of the antisense strand of the duplex. In certain embodiments, an extended overhang is present on the 5'end of the antisense strand of the duplex. In certain embodiments, one or more of the nucleotides in the extended overhang is replaced with a nucleoside thiophosphate. In certain embodiments, the overhang includes a self-complementary portion such that the overhang is capable of forming a hairpin structure that is stable under physiological conditions.

"Blunt" or "blunt end" means that there are no unpaired nucleotides at that end of the double stranded RNA agent, *i.e.*, no nucleotide overhang. A "blunt ended" double stranded RNA agent is double stranded over its entire length, *i.e.*, no nucleotide overhang at either end of the molecule. The

RNAi agents of the invention include RNAi agents with no nucleotide overhang at one end (*i.e.*, agents with one overhang and one blunt end) or with no nucleotide overhangs at either end. Most often such a molecule will be double-stranded over its entire length.

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, *e.g.*, a metabolic disorder-associated target gene mRNA.

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, *e.g.*, an INHBE 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 molecule. Generally, the most tolerated mismatches are in the terminal regions, *e.g.*, within 5, 4, or 3 nucleotides of the 5'- or 3'-end of the iRNA. In some embodiments, a double stranded RNA agent of the invention includes a nucleotide mismatch in the antisense strand. In some embodiments, the antisense strand of the double stranded RNA agent of the invention includes no more than 4 mismatches with the target mRNA, *e.g.*, the antisense strand includes 4, 3, 2, 1, or 0 mismatches with the target mRNA. In some embodiments, the antisense strand double stranded RNA agent of the invention includes no more than 4 mismatches with the sense strand, *e.g.*, the antisense strand includes 4, 3, 2, 1, or 0 mismatches with the sense strand. In some embodiments, a double stranded RNA agent of the invention includes a nucleotide mismatch in the sense strand. In some embodiments, the sense strand of the double stranded RNA agent of the invention includes no more than 4 mismatches with the antisense strand, *e.g.*, the sense strand includes 4, 3, 2, 1, or 0 mismatches with the antisense strand. In some embodiments, the nucleotide mismatch is, for example, within 5, 4, 3 nucleotides from the 3'-end of the iRNA. In another embodiment, the nucleotide mismatch is, for example, in the 3'-terminal nucleotide of the iRNA agent. In some embodiments, the mismatch(s) is not in the seed region.

Thus, an RNAi agent as described herein can contain one or more mismatches to the target sequence. In one embodiment, an RNAi agent as described herein contains no more than 3 mismatches (*i.e.*, 3, 2, 1, or 0 mismatches). In one embodiment, an RNAi agent as described herein contains no more than 2 mismatches. In one embodiment, an RNAi agent as described herein contains no more than 1 mismatch. In one embodiment, an RNAi agent as described herein contains 0 mismatches. In certain embodiments, if the antisense strand of the RNAi agent contains mismatches to the target sequence, the mismatch can optionally be restricted to be within the last 5 nucleotides from either the 5'- or 3'-end of the region of complementarity. For example, in such embodiments, for a 23 nucleotide RNAi agent, the strand which is complementary to a region of a metabolic disorder-associated target gene, 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 RNAi agent containing a mismatch to a target sequence is effective in inhibiting the expression of a target gene. Consideration of the efficacy of RNAi agents with mismatches in inhibiting expression of an INHBE, ACVR1C, PLIN1, PDE3B, or INHBC target gene is important, especially if the particular

region of complementarity in the target gene is known to have polymorphic sequence variation within the population.

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.

As used herein, "substantially all of the nucleotides are modified" are largely but not wholly modified and can include not more than 5, 4, 3, 2, or 1 unmodified nucleotides.

As used herein, the term "cleavage region" refers to a region that is located immediately adjacent to the cleavage site. The cleavage site is the site on the target at which cleavage occurs. In some embodiments, the cleavage region comprises three bases on either end of, and immediately adjacent to, the cleavage site. In some embodiments, the cleavage region comprises two bases on either end of, and immediately adjacent to, the cleavage site. In some embodiments, the cleavage site specifically occurs at the site bound by nucleotides 10 and 11 of the antisense strand, and the cleavage region comprises nucleotides 11, 12 and 13.

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, for example, be stringent conditions, where stringent conditions can include: 400 mM NaCl, 40 mM PIPES pH 6.4, 1 mM EDTA, 50°C or 70°C for 12-16 hours followed by washing (see, *e.g.*, "Molecular Cloning: A Laboratory Manual, Sambrook, *et al.* (1989) Cold Spring Harbor Laboratory Press). Other conditions, such as physiologically relevant conditions as can 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 can 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, while retaining the ability to hybridize under the conditions most relevant to their ultimate application, *e.g.*, inhibition of gene expression, *in vitro* or *in vivo*. 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, can yet be referred to as "fully complementary" for the purposes described herein.

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

The terms "complementary," "fully complementary" and "substantially complementary" herein can be used with respect to the base matching between the sense strand and the antisense strand of a dsRNA, or between two oligonucletoides or polynucleotides, such as the antisense strand of a double stranded RNA 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 metabolic disorder-associated target gene). For example, a polynucleotide is complementary to at least a part of a metabolic disorder-associated target gene mRNA if the sequence is substantially complementary to a non-interrupted portion of an mRNA encoding a metabolic disorder-associated target gene.

Accordingly, in some embodiments, the antisense strand polynucleotides disclosed herein are fully complementary to the target gene sequence.

In some embodiments, the antisense strand polynucleotides disclosed herein are substantially complementary to the target gene sequence and comprise a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to the equivalent region of the nucleotide sequence of SEQ ID NOs: 1, 3, 5, or 7 for INHBE, or a fragment of SEQ ID NOs: 1, 3, 5, or 7, such as about 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or about 99% complementary.

In some embodiments, the antisense polynucleotides disclosed herein are substantially complementary to a fragment of a target INHBE sequence and comprise a contiguous nucleotide sequence which is at least 80% complementary over its entire length to a fragment of SEQ ID NO: 1 selected from the group of nucleotides 400-422, 410-432, 518-540, 519-541, 640-662, 1430-1452, 1863-1885, or1864-1886 of SEQ ID NO: 1, 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.

In other embodiments, the antisense polynucleotides disclosed herein are substantially complementary to the target INHBE sequence and comprise a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to any one of the sense strand nucleotide sequences in any one of Tables 2-3, or a fragment of any one of the sense strand nucleotide sequences in any one of Tables 2-3, such as about 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or about 99% complementary.

In one embodiment, an RNAi agent of the disclosure includes a sense strand that is substantially complementary to an antisense polynucleotide which, in turn, is the same as a target INHBE sequence, and wherein the sense strand polynucleotide comprises a contiguous nucleotide

sequence which is at least about 80% complementary over its entire length to the equivalent region of the nucleotide sequence of SEQ ID NOs: 2, 4, 6, or 8, or a fragment of any one of SEQ ID NOs: 2, 4, 6, or 8, such as about 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or about 99% complementary.

In some embodiments, an iRNA of the invention includes a sense strand that is substantially complementary to an antisense polynucleotide which, in turn, is complementary to a target INHBE sequence, and wherein the sense strand polynucleotide comprises a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to any one of the antisense strand nucleotide sequences in any one of any one of Tables 2-3, or a fragment of any one of the antisense strand nucleotide sequences in any one of Tables 2-3, such as about 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or about 99% complementary.

In some embodiments, the sense and antisense strands are selected from any one of duplexes AD-1706583, AD-1711744, AD-1706593, AD-1708473, AD-1706662, AD-1706761, AD-1707306, AD-1707639, and AD-1707640.

In some embodiments, the sense and antisense strands are selected from duplex AD-1706583.

In some embodiments, the sense and antisense strands are selected from duplex AD-1711744.

In some embodiments, the sense and antisense strands are selected from duplex AD-1706593.

In some embodiments, the sense and antisense strands are selected from duplex AD-1708473.

In some embodiments, the sense and antisense strands are selected from duplex AD-1706662.

In some embodiments, the sense and antisense strands are selected from duplex AD-1706761.

In some embodiments, the sense and antisense strands are selected from duplex AD-1707306.

In some embodiments, the sense and antisense strands are selected from duplex AD-1707639.

In some embodiments, the sense and antisense strands are selected from duplex AD-1707640.

In other embodiments, the antisense strand polynucleotides disclosed herein are substantially complementary to the target gene sequence and comprise a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to the equivalent region of the nucleotide sequence of SEQ ID NOs: 9, 11, 13, 15, 17, 19, 21, or 23 for ACVR1C, or a fragment of SEQ ID NOs: 9, 11, 13, 15, 17, 19, 21, or 23, such as about 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or about 99% complementary.

In other embodiments, the antisense polynucleotides disclosed herein are substantially complementary to the target ACVR1C sequence and comprise a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to any one of the sense strand nucleotide sequences in any one of Tables 4-7, or a fragment of any one of the sense strand nucleotide sequences in any one of Tables 4-7, such as about 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or about 99% complementary.

In one embodiment, an RNAi agent of the disclosure includes a sense strand that is substantially complementary to an antisense polynucleotide which, in turn, is the same as a target ACVR1C sequence, and wherein the sense strand polynucleotide comprises a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to the equivalent region of

the nucleotide sequence of SEQ ID NOs: 10, 12, 14, 16, 18, 20, 22, or 24, or a fragment of any one of SEQ ID NOs: 10, 12, 14, 16, 18, 20, 22, or 24, such as about 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or about 99% complementary.

In some embodiments, an iRNA of the invention includes a sense strand that is substantially complementary to an antisense polynucleotide which, in turn, is complementary to a target ACVR1C sequence, and wherein the sense strand polynucleotide comprises a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to any one of the antisense strand nucleotide sequences in any one of any one of Tables 4-7, or a fragment of any one of the antisense strand nucleotide sequences in any one of Tables 4-7, such as about 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or about 99% complementary.

In other embodiments, the antisense strand polynucleotides disclosed herein are substantially complementary to the target gene sequence and comprise a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to the equivalent region of the nucleotide sequence of SEQ ID NOs:25, 27, 29, 31, 33, or 35 for PLIN1, or a fragment of SEQ ID NOs: 25, 27, 29, 31, 33, or 35, such as about 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or about 99% complementary.

In other embodiments, the antisense polynucleotides disclosed herein are substantially complementary to the target PLIN1 sequence and comprise a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to any one of the sense strand nucleotide sequences in any one of Tables 8-11, or a fragment of any one of the sense strand nucleotide sequences in any one of Tables 8-11, such as about 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or about 99% complementary.

In one embodiment, an RNAi agent of the disclosure includes a sense strand that is substantially complementary to an antisense polynucleotide which, in turn, is the same as a target PLIN1 sequence, and wherein the sense strand polynucleotide comprises a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to the equivalent region of the nucleotide sequence of SEQ ID NOs: 26, 28, 30, 32, 34, or 36, or a fragment of any one of SEQ ID NOs: 26, 28, 30, 32, 34, or 36, such as about 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or about 99% complementary.

In some embodiments, an iRNA of the invention includes a sense strand that is substantially complementary to an antisense polynucleotide which, in turn, is complementary to a target PLIN1 sequence, and wherein the sense strand polynucleotide comprises a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to any one of the antisense strand nucleotide sequences in any one of any one of Tables 8-11, or a fragment of any one of the antisense strand nucleotide sequences in any one of Tables 8-11, such as about 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or about 99% complementary.

In other embodiments, the antisense strand polynucleotides disclosed herein are substantially complementary to the target gene sequence and comprise a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to the equivalent region of the nucleotide

sequence of SEQ ID NOs:37, 39, 41, 43, 45, or 47 for PDE3B, or a fragment of SEQ ID NOs: 37, 39, 41, 43, 45, or 47, such as about 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or about 99% complementary.

In other embodiments, the antisense polynucleotides disclosed herein are substantially complementary to the target PDE3B sequence and comprise a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to any one of the sense strand nucleotide sequences in any one of Tables 12-15, or a fragment of any one of the sense strand nucleotide sequences in any one of Tables 12-15, such as about 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or about 99% complementary.

In one embodiment, an RNAi agent of the disclosure includes a sense strand that is substantially complementary to an antisense polynucleotide which, in turn, is the same as a target PDE3B sequence, and wherein the sense strand polynucleotide comprises a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to the equivalent region of the nucleotide sequence of SEQ ID NOs: 38, 40, 42, 44, 46, or 48, or a fragment of any one of SEQ ID NOs: 38, 40, 42, 44, 46, or 48, such as about 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or about 99% complementary.

In some embodiments, an iRNA of the invention includes a sense strand that is substantially complementary to an antisense polynucleotide which, in turn, is complementary to a target PDE3B sequence, and wherein the sense strand polynucleotide comprises a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to any one of the antisense strand nucleotide sequences in any one of any one of Tables 12-15, or a fragment of any one of the antisense strand nucleotide sequences in any one of Tables 12-15, such as about 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or about 99% complementary.

In other embodiments, the antisense strand polynucleotides disclosed herein are substantially complementary to the target gene sequence and comprise a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to the equivalent region of the nucleotide sequence of SEQ ID NOs:49, 51, 53, or 55 for INHBC, or a fragment of SEQ ID NOs: 49, 51, 53, or 55, such as about 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or about 99% complementary.

In other embodiments, the antisense polynucleotides disclosed herein are substantially complementary to the target INHBC sequence and comprise a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to any one of the sense strand nucleotide sequences in any one of Tables 16-17, or a fragment of any one of the sense strand nucleotide sequences in any one of Tables 16-17, such as about 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or about 99% complementary.

In one embodiment, an RNAi agent of the disclosure includes a sense strand that is substantially complementary to an antisense polynucleotide which, in turn, is the same as a target INHBC sequence, and wherein the sense strand polynucleotide comprises a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to the equivalent region of

the nucleotide sequence of SEQ ID NOs: 50, 52, 54, or 56, or a fragment of any one of SEQ ID NOs: 50, 52, 54, or 56, such as about 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or about 99% complementary.

In some embodiments, an iRNA of the invention includes a sense strand that is substantially complementary to an antisense polynucleotide which, in turn, is complementary to a target INHBC sequence, and wherein the sense strand polynucleotide comprises a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to any one of the antisense strand nucleotide sequences in any one of any one of Tables 16-17, or a fragment of any one of the antisense strand nucleotide sequences in any one of Tables 16-17, such as about 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or about 99% complementary.

In some embodiments, the double-stranded region of a double-stranded iRNA agent is equal to or at least, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 23, 24, 25, 26, 27, 28, 29, 30 or more nucleotide pairs in length.

In some embodiments, the antisense strand of a double-stranded iRNA agent is equal to or at least 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length.

In some embodiments, the sense strand of a double-stranded iRNA agent is equal to or at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length.

In one embodiment, the sense and antisense strands of the double-stranded iRNA agent are each independently 15 to 30 nucleotides in length.

In one embodiment, the sense and antisense strands of the double-stranded iRNA agent are each independently 19 to 25 nucleotides in length.

In one embodiment, the sense and antisense strands of the double-stranded iRNA agent are each independently 21 to 23 nucleotides in length.

In one embodiment, the sense strand of the iRNA agent is 21-nucleotides in length, and the antisense strand is 23-nucleotides in length, wherein the strands form a double-stranded region of 21 consecutive base pairs having a 2-nucleotide long single stranded overhangs at the 3'-end.

In general, an "iRNA" includes ribonucleotides with chemical modifications. Such modifications may include all types of modifications disclosed herein or known in the art. Any such modifications, as used in a dsRNA molecule, are encompassed by "iRNA" for the purposes of this specification and claims.

In certain embodiments of the instant disclosure, inclusion of a deoxy-nucleotide if present within an RNAi agent can be considered to constitute a modified nucleotide.

In an aspect of the invention, an agent for use in the methods and compositions of the invention is a single-stranded antisense oligonucleotide molecule that inhibits a target mRNA *via* an antisense inhibition mechanism. The single-stranded antisense oligonucleotide molecule is complementary to a sequence within the target mRNA. The single-stranded antisense oligonucleotides can inhibit translation in a stoichiometric manner by base pairing to the mRNA and physically obstructing the translation machinery, see Dias, N. *et al.*, (2002) *Mol Cancer Ther* 1:347-

355. The single-stranded antisense oligonucleotide molecule may be about 14 to about 30 nucleotides in length and have a sequence that is complementary to a target sequence. For example, the single-stranded antisense oligonucleotide molecule may comprise a sequence that is at least about 14, 15, 16, 17, 18, 19, 20, or more contiguous nucleotides from any one of the antisense sequences described herein.

The phrase "contacting a cell with an iRNA," such as a dsRNA, as used herein, includes contacting a cell by any possible means. Contacting a cell with an iRNA includes contacting a cell *in vitro* with the iRNA or contacting a cell *in vivo* with the iRNA. The contacting may be done directly or indirectly. Thus, for example, the iRNA may be put into physical contact with the cell by the individual performing the method, or alternatively, the iRNA 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 iRNA. Contacting a cell *in vivo* may be done, for example, by injecting the iRNA into or near the tissue where the cell is located, or by injecting the iRNA into another area, *e.g.*, the bloodstream or the subcutaneous space, such that the agent will subsequently reach the tissue where the cell to be contacted is located. For example, the iRNA may contain or be coupled to a targeting ligand, *e.g.*, GalNAc, that directs the iRNA to a site of interest, *e.g.*, the liver. In other embodiments, the RNAi agent may contain or be coupled to one or more C22 hydrocarbon chains and one or more GalNAc derivatives. In other embodiments, the RNAi agent contains or is coupled to one or more C22 hydrocarbon chains and does not contain or is not coupled to one or more GalNAc derivatives. 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.

In certain embodiments, contacting a cell with an iRNA includes "introducing" or "delivering the iRNA into the cell" by facilitating or effecting uptake or absorption into the cell. Absorption or uptake of an iRNA can occur through unaided diffusion or active cellular processes, or by auxiliary agents or devices. Introducing an iRNA into a cell may be *in vitro* or *in vivo*. For example, for *in vivo* introduction, iRNA can be injected into a tissue site or administered systemically. *In vitro* introduction into a cell includes methods known in the art such as electroporation and lipofection. Further approaches are described herein below or are known in the art.

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.*, an iRNA or a plasmid from which an iRNA 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, a "subject" is an animal, such as a mammal, including a primate (such as a human, a non-human primate, *e.g.*, a monkey, and a chimpanzee), a non-primate (such as a cow, a pig, a horse, a goat, a rabbit, a sheep, a hamster, a guinea pig, a cat, a dog, a rat, or a mouse), or a bird that expresses the target gene, either endogenously or heterologously. In an embodiment, the subject is a human, such as a human being treated or assessed for a disease or disorder that would benefit

from reduction in metabolic disorder-associated target gene expression; a human at risk for a disease or disorder that would benefit from reduction in metabolic disorder-associated target gene expression; a human having a disease or disorder that would benefit from reduction in metabolic disorder-associated target gene expression; or human being treated for a disease or disorder that would benefit from reduction in metabolic disorder-associated target gene expression as described herein. In some embodiments, the subject is a female human. In other embodiments, the subject is a male human. In one embodiment, the subject is an adult subject. In another embodiment, the subject is a pediatric subject.

As used herein, the terms "treating" or "treatment" refer to a beneficial or desired result, such as reducing at least one sign or symptom of a metabolic disorder in a subject. Treatment also includes a reduction of one or more sign or symptoms associated with unwanted metabolic disorder-associated target gene expression; diminishing the extent of unwanted metabolic disorder-associated target gene activation or stabilization; amelioration or palliation of unwanted metabolic disorder-associated target gene activation or stabilization. "Treatment" can also mean prolonging survival as compared to expected survival in the absence of treatment.

The term "lower" in the context of the level a metabolic disorder-associated target gene in a subject or a disease marker or symptom refers to a statistically significant decrease in such level. The decrease can be, for example, at least 10%, 15%, 20%, 25%, 30%, %, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more. In certain embodiments, a decrease is at least 20%. In certain embodiments, the decrease is at least 50% in a disease marker, *e.g.*, protein or gene expression level. "Lower" in the context of the level of a metabolic disorder-associated target gene in a subject is a decrease to a level accepted as within the range of normal for an individual without such disorder. In certain embodiments, "lower" is the decrease in the difference between the level of a marker or symptom for a subject suffering from a disease and a level accepted within the range of normal for an individual. The term "lower" can also be used in association with normalizing a symptom of a disease or condition, *i.e.* decreasing the difference between a level in a subject suffering from a metabolic disorder towards or to a level in a normal subject not suffering from an metabolic disorder. As used herein, if a disease is associated with an elevated value for a symptom, "normal" is considered to be the upper limit of normal. If a disease is associated with a decreased value for a symptom, "normal" is considered to be the lower limit of normal.

As used herein, "prevention" or "preventing," when used in reference to a disease, disorder or condition thereof, may be treated or ameliorated by a reduction in expression of a metabolic disorder-associated target gene, refers to a reduction in the likelihood that a subject will develop a symptom associated with such a disease, disorder, or condition, *e.g.,* a symptom of a metabolic disorder, *e.g.*, diabetes. The failure to develop a disease, disorder or condition, or the reduction in the development of a symptom associated with such a disease, disorder or condition (*e.g.*, by at least about 10% on a clinically accepted scale for that disease or disorder), or the exhibition of delayed symptoms delayed (*e.g.*, by days, weeks, months or years) is considered effective prevention.

The treatment and prophylactic methods of the invention are useful for treating any disease or disorder that is caused by, or associated with INHBE, ACVR1C, PLIN1, PDE3B, and/or INHBC gene expression or INHBE, ACVR1C, PLIN1, PDE3B, and/or INHBC protein production and includes a disease, disorder or condition that would benefit from a decrease in INHBE, ACVR1C, PLIN1, PDE3B, and/or INHBC gene expression, replication, or protein activity such as a metabolic disorder. In some embodiments, the metabolic disorder is metabolic syndrome.

A "metabolic disorder" is a disorder that disrupts normal metabolism, the process of converting food to energy on a cellular level. Metabolic diseases affect the ability of the cell to perform critical biochemical reactions that involve the processing or transport of proteins (amino acids), carbohydrates (sugars and starches), or lipids (fatty acids).

For example, metabolic disorders may be associated with a body fat distribution characterized by higher accumulation of fat around the waist (such as greater abdominal fat or larger waist circumference) and/or lower accumulation of fat around the hips (such as lower gluteofemoral fat or smaller hip circumference), resulting in a greater waist-to-hip ratio (WHR), and higher cardio-metabolic risk independent of body mass index (BMI).

Non-limiting examples of metabolic diseases include disorders of carbohydrates, *e.g.*, diabetes, type I diabetes, type II diabetes, galactosemia, hereditary fructose intolerance, fructose 1,6-diphosphatase deficiency, glycogen storage disorders, congenital disorders of glycosylation, insulin resistance, insulin insufficiency, hyperinsulinemia, impaired glucose tolerance (IGT), abnormal glycogen metabolism; disorders of amino acid metabolism, *e.g.*, maple syrup urine disease (MSUD), or homocystinuria; disorder of organic acid metabolism, *e.g.*,methylmalonic aciduria, 3-methylglutaconic aciduria -Barth syndrome, glutaric aciduria or 2-hydroxyglutaric aciduria – D and L forms; disorders of fatty acid beta-oxidation, *e.g.*, medium-chain acyl-CoA dehydrogenase deficiency (MCAD), long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHAD), very-long-chain acyl-CoA dehydrogenase deficiency (VLCAD); disorders of lipid metabolism, *e.g.*, GM1 Gangliosidosis, Tay-Sachs Disease, Sandhoff Disease, Fabry Disease, Gaucher Disease, Niemann-Pick Disease, Krabbe Disease, Mucolipidoses, or Mucopolysaccharidoses; disorders of lipid distribution and/or storage, *e.g.*, lipodystrophy, mitochondrial disorders, *e.g.*, mitochondrial cardiomyopathies; Leigh disease; mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS); myoclonic epilepsy with ragged-red fibers (MERRF); neuropathy, ataxia, and retinitis pigmentosa (NARP); Barth syndrome; peroxisomal disorders, *e.g.*, Zellweger Syndrome (cerebrohepatorenal syndrome), X-Linked Adrenoleukodystrophy or Refsum Disease.

In certain embodiment, metabolic disorders are associated with body fat distribution and include, but are not limited to metabolic syndrome, type 2 diabetes, hyperlipidemia or dyslipidemia (high or altered circulating levels of low-density lipoprotein cholesterol (LDL-C), triglycerides, very low-density lipoprotein cholesterol (VLDL-C), apolipoprotein B or other lipid fractions), obesity (particularly abdominal obesity), lipodystrophy (such as an inability to deposit fat in adipose depots regionally (partial lipodystrophy) or in the whole body (lipoatrophy)), insulin resistance or higher or altered insulin levels at fasting or during a metabolic challenge, liver fat deposition or fatty liver

disease and their complications (such as, for example, cirrhosis, fibrosis, or inflammation of the liver), nonalcoholic steatohepatitis, other types of liver inflammation, higher or elevated or altered liver enzyme levels or other markers of liver damage, inflammation or fat deposition in the liver, higher blood pressure and/or hypertension, higher blood sugar or glucose or hyperglycemia, metabolic syndrome, coronary artery disease, and other atherosclerotic conditions, and the complications of each of the aforementioned conditions.

In one embodiment, a metabolic disorder is metabolic syndrome. The term "metabolic syndrome," as used herein, is disorder that includes a clustering of components that reflect overnutrition, sedentary lifestyles, genetic factors, increasing age, and resultant excess adiposity. Metabolic syndrome includes the clustering of abdominal obesity, insulin resistance, dyslipidemia, and elevated blood pressure and is associated with other comorbidities including the prothrombotic state, proinflammatory state, nonalcoholic fatty liver disease, and reproductive disorders. The prevalence of the metabolic syndrome has increased to epidemic proportions not only in the United States and the remainder of the urbanized world but also in developing nations. Metabolic syndrome is associated with an approximate doubling of cardiovascular disease risk and a 5-fold increased risk for incident type 2 diabetes mellitus.

Abdominal adiposity (*e.g.,* a large waist circumference (high waist-to-hip ratio)), high blood pressure, insulin resistance and dislipidemia are central to metabolic syndrome and its individual components (*e.g.*, central obesity, fasting blood glucose (FBG)/pre-diabetes/diabetes, hypercholesterolemia, hypertriglyceridemia, and hypertension).

In one embodiment, a metabolic disorder is a disorder of carbohydrates. In one embodiment, the disorder of carbohydrates is diabetes.

As used herein, the term "diabetes" refers to a group of metabolic disorders characterized by high blood sugar (glucose) levels which result from defects in insulin secretion or action, or both. There are two most common types of diabetes, namely type 1 diabetes and type 2 diabetes, which both result from the body's inability to regulate insulin. Insulin is a hormone released by the pancreas in response to increased levels of blood sugar (glucose) in the blood.

The term "type I diabetes," as used herein, refers to a chronic disease that occurs when the pancreas produces too little insulin to regulate blood sugar levels appropriately. Type I diabetes is also referred to as insulin-dependent diabetes mellitus, IDDM, and juvenile onset diabetes. People with type I diabetes (insulin-dependent diabetes) produce little or no insulin at all. Although about 6 percent of the United States population has some form of diabetes, only about 10 percent of all diabetics have type I disorder. Most people who have type I diabetes developed the disorder before age 30. Type 1 diabetes represents the result of a progressive autoimmune destruction of the pancreatic β-cells with subsequent insulin deficiency. More than 90 percent of the insulin-producing cells (beta cells) of the pancreas are permanently destroyed. The resulting insulin deficiency is severe, and to survive, a person with type I diabetes must regularly inject insulin.

In type II diabetes (also referred to as noninsulin-dependent diabetes mellitus, NDDM), the pancreas continues to manufacture insulin, sometimes even at higher than normal levels. However,

the body develops resistance to its effects, resulting in a relative insulin deficiency. Type II diabetes may occur in children and adolescents but usually begins after age 30 and becomes progressively more common with age: about 15 percent of people over age 70 have type II diabetes. Obesity is a risk factor for type II diabetes, and 80 to 90 percent of the people with this disorder are obese.

In some embodiments, diabetes includes pre-diabetes. "Pre-diabetes" refers to one or more early diabetic conditions including impaired glucose utilization, abnormal or impaired fasting glucose levels, impaired glucose tolerance, impaired insulin sensitivity and insulin resistance. Prediabetes is a major risk factor for the development of type 2 diabetes mellitus, cardiovascular disease and mortality. Much focus has been given to developing therapeutic interventions that prevent the development of type 2 diabetes by effectively treating prediabetes.

Diabetes can be diagnosed by the administration of a glucose tolerance test. Clinically, diabetes is often divided into several basic categories. Primary examples of these categories include, autoimmune diabetes mellitus, non-insulin-dependent diabetes mellitus (type 1 NDDM), insulin-dependent diabetes mellitus (type 2 IDDM), non-autoimmune diabetes mellitus, non-insulin-dependent diabetes mellitus (type 2 NIDDM), and maturity-onset diabetes of the young (MODY). A further category, often referred to as secondary, refers to diabetes brought about by some identifiable condition which causes or allows a diabetic syndrome to develop. Examples of secondary categories include, diabetes caused by pancreatic disease, hormonal abnormalities, drug- or chemical-induced diabetes, diabetes caused by insulin receptor abnormalities, diabetes associated with genetic syndromes, and diabetes of other causes. (see *e.g.*, Harrison's (1996) 14th ed., New York, McGraw-Hill).

In one embodiment, a metabolic disorder is a lipid metabolism disorder. As used herein, a "lipid metabolism disorder" or "disorder of lipid metabolism" refers to any disorder associated with or caused by a disturbance in lipid metabolism. This term also includes any disorder, disease or condition that can lead to hyperlipidemia, or condition characterized by abnormal elevation of levels of any or all lipids and/or lipoproteins in the blood. This term refers to an inherited disorder, such as familial hypertriglyceridemia, familial partial lipodystrophy type 1 (FPLD1), or an induced or acquired disorder, such as a disorder induced or acquired as a result of a disease, disorder or condition (*e.g.*, renal failure), a diet, or intake of certain drugs (*e.g.*, as a result of highly active antiretroviral therapy (HAART) used for treating, *e.g.*, AIDS or HIV). This term also refers to a disorder of fat distribution/storage, *e.g.*, lipodystrophy.

Additional examples of disorders of lipid metabolism include, but are not limited to, atherosclerosis, dyslipidemia, hypertriglyceridemia (including drug-induced hypertriglyceridemia, diuretic-induced hypertriglyceridemia, alcohol-induced hypertriglyceridemia, β-adrenergic blocking agent-induced hypertriglyceridemia, estrogen-induced hypertriglyceridemia, glucocorticoid-induced hypertriglyceridemia, retinoid-induced hypertriglyceridemia, cimetidine-induced hypertriglyceridemia, and familial hypertriglyceridemia), acute pancreatitis associated with hypertriglyceridemia, chylomicron syndrom, familial chylomicronemia, Apo-E deficiency or resistance, LPL deficiency or hypoactivity, hyperlipidemia (including familial combined

hyperlipidemia), hypercholesterolemia, lipodystrophy, gout associated with hypercholesterolemia, xanthomatosis (subcutaneous cholesterol deposits), hyperlipidemia with heterogeneous LPL deficiency, hyperlipidemia with high LDL and heterogeneous LPL deficiency, fatty liver disease, or non-alcoholic stetohepatitis (NASH).

Cardiovascular diseases are also considered "metabolic disorders", as defined herein. These diseases may include coronary artery disease (also called ischemic heart disease), hypertension, inflammation associated with coronary artery disease, restenosis, peripheral vascular diseases, and stroke.

Kidney diseases are also considered "metabolic disorders", as defined herein. Such diseases may include chronic kidney disease, diabetic nephrophathy, diabetic kidney disease, or gout.

Disorders related to body weight are also considered "metabolic disorders", as defined herein. Such disorders may include obesity, hypo-metabolic states, hypothyroidism, uremia, and other conditions associated with weight gain (including rapid weight gain), weight loss, maintenance of weight loss, or risk of weight regain following weight loss.

Blood sugar disorders are further considered "metabolic disorders", as defined herein. Such disorders may include diabetes, hypertension, and polycystic ovarian syndrome related to insulin resistance. Other exemplary disorders of metabolic disorders may also include renal transplantation, nephrotic syndrome, Cushing's syndrome, acromegaly, systemic lupus erythematosus, dysglobulinemia, lipodystrophy, glycogenosis type I, and Addison's disease.

In one embodiment, a metabolic disorder is primary hypertension. "Primary hypertension" is a result of environmental or genetic causes (*e.g.*, a result of no obvious underlying medical cause).

In one embodiment, a metabolic disorder disorder is secondary hypertension. "Secondary hypertension" has an identifiable underlying disorder which can be of multiple etiologies, including renal, vascular, and endocrine causes, *e.g.*, renal parenchymal disease (*e.g.*, polycystic kidneys, glomerular or interstitial disease), renal vascular disease (*e.g.*, renal artery stenosis, fibromuscular dysplasia), endocrine disorders (*e.g.*, adrenocorticosteroid or mineralocorticoid excess, pheochromocytoma, hyperthyroidism or hypothyroidism, growth hormone excess, hyperparathyroidism), coarctation of the aorta, or oral contraceptive use.

In one embodiment, a metabolic disorder is resistant hypertension. "Resistant hypertension" is blood pressure that remains above goal (*e.g.*, above 130 mm Hg systolic or above 90 diastolic) in spite of concurrent use of three antihypertensive agents of different classes, one of which is a thiazide diuretic. Subjects whose blood pressure is controlled with four or more medications are also considered to have resistant hypertension.

Additional diseases or conditions related to metabolic disorders that would be apparent to the skilled artisan and are within the scope of this disclosure.

"Therapeutically effective amount," as used herein, is intended to include the amount of an RNAi agent that, when administered to a subject having a metabolic disorder, is sufficient to effect treatment of the disease (*e.g.*, by diminishing, ameliorating, or maintaining the existing disease or one or more symptoms of disease). The "therapeutically effective amount" may vary depending on the

RNAi agent, how the agent is administered, the disease and its severity and the history, age, weight, family history, genetic makeup, the types of preceding or concomitant treatments, if any, and other individual characteristics of the subject to be treated.

"Prophylactically effective amount," as used herein, is intended to include the amount of an RNAi agent that, when administered to a subject having a metabolic disorder, is sufficient to prevent or ameliorate the disease or one or more symptoms of the disease. Ameliorating the disease includes slowing the course of the disease or reducing the severity of later-developing disease. The "prophylactically effective amount" may vary depending on the RNAi agent, how the agent is administered, the degree of risk of disease, and the history, age, weight, family history, genetic makeup, the types of preceding or concomitant treatments, if any, and other individual characteristics of the patient to be treated.

A "therapeutically-effective amount" or "prophylactically effective amount" also includes an amount of an RNAi agent that produces some desired effect at a reasonable benefit/risk ratio applicable to any treatment. The iRNA employed in the methods of the present invention may be administered in a sufficient amount to produce a reasonable benefit/risk ratio applicable to such treatment.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human subjects and animal subjects without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The phrase "pharmaceutically-acceptable carrier" as used herein means a pharmaceutically-acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, excipient, manufacturing aid (*e.g.*, lubricant, talc magnesium, calcium or zinc stearate, or steric acid), or solvent encapsulating material, involved in carrying or transporting the subject compound from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the subject being treated. Such carriers are known in the art. Pharmaceutically acceptable carriers include carriers for administration by injection.

The term "sample," as used herein, includes a collection of similar fluids, cells, or tissues isolated from a subject, as well as fluids, cells, or tissues present within a subject. Examples of biological fluids include blood, serum and serosal fluids, plasma, cerebrospinal fluid, ocular fluids, lymph, urine, saliva, and the like. Tissue samples may include samples from tissues, organs, or localized regions. For example, samples may be derived from particular organs, parts of organs, or fluids or cells within those organs. In certain embodiments, samples may be derived from the liver (*e.g.*, whole liver or certain segments of liver or certain types of cells in the liver, such as, *e.g.*, hepatocytes). In some embodiments, a "sample derived from a subject" refers to urine obtained from the subject. A "sample derived from a subject" can refer to blood or blood derived serum or plasma from the subject.

II. iRNAs of the Invention

The present invention provides iRNAs which inhibit the expression of a metabolic disorder-associated target gene, *e.g.,* INHBE, ACVR1C, PLIN1, PDE3B, or INHBC. In certain embodiments, the iRNA includes double stranded ribonucleic acid (dsRNA) molecules for inhibiting the expression of a metabolic disorder-associated target gene in a cell (*e.g.,* an adipocyte and/or a hepatocyte), such as a cell within a subject, *e.g.,* a mammal, such as a human susceptible to developing a metabolic disorder, *e.g.,* metabolic syndrome, a disorder of carbohydrates, *e.g.*, type II diabetes, pre-diabetes, a lipid metabolism disorder, *e.g.*, a hyperlipidemia, hypertension, lipodystrophy; a kidney disease; a cardiovascular disease, a disorder of body weight. The dsRNAi agent 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 a metabolic disorder-associated target gene. The region of complementarity is about 19-30 nucleotides in length (*e.g.,* about 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, or 19 nucleotides in length).

Upon contact with a cell expressing the target gene, the iRNA inhibits the expression of the target gene (*e.g.,* a human, a primate, a non-primate, or a rat INHBE, ACVR1C, PLIN1, PDE3B, or INHBC gene) by at least about 50% as assayed by, for example, a PCR or branched DNA (bDNA)-based method, or by a protein-based method, such as by immunofluorescence analysis, using, for example, western blotting or flow cytometric techniques. In certain embodiments, inhibition of expression is determined by the qPCR method provided in the examples herein with the siRNA at, *e.g.,* a 10 nM concentration, in an appropriate organism cell line provided therein. In certain embodiments, inhibition of expression *in vivo* is determined by knockdown of the human gene in a rodent expressing the human gene, *e.g.*, a mouse or an AAV-infected mouse expressing the human target gene, *e.g.*, when administered as single dose, *e.g.,* at 3 mg/kg at the nadir of RNA expression.

A dsRNA includes two RNA strands that are complementary and hybridize to form a duplex structure under conditions in which the dsRNA will be used. One strand of a dsRNA (the antisense strand) includes a region of complementarity that is substantially complementary, and generally fully complementary, to a target sequence. The target sequence can be derived from the sequence of an mRNA formed during the expression of an INHBE, ACVR1C, PLIN1, PDE3B, or INHBC gene. The other strand (the sense strand) 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. 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.

Generally, the duplex structure is 15 to 30 base pairs in length, *e.g.,* 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 18-30, 18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24,20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 base pairs in length. In certain embodiments, the

duplex structure is 18 to 25 base pairs in length, *e.g.*, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-25, 20-24,20-23, 20-22, 20-21, 21-25, 21-24, 21-23, 21-22, 22-25, 22-24, 22-23, 23-25, 23-24 or 24-25 base pairs in length, for example, 19-21 basepairs in length. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the disclosure.

Similarly, the region of complementarity to the target sequence is 15 to 30 nucleotides in length, *e.g.,* 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 18-30, 18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24,20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 nucleotides in length, for example 19-23 nucleotides in length or 21-23 nucleotides in length. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the disclosure.

In some embodiments, the duplex structure is 19 to 30 base pairs in length. Similarly, the region of complementarity to the target sequence is 19 to 30 nucleotides in length.

In some embodiments, the dsRNA is about 19 to about 23 nucleotides in length, or about 25 to about 30 nucleotides in length. In general, the dsRNA is long enough to serve as a substrate for the Dicer enzyme. For example, it is well-known in the art that dsRNAs longer than about 21-23 nucleotides in length may serve as substrates for Dicer. As the ordinarily skilled person will also recognize, the 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 allow it to be a substrate for RNAi-directed cleavage (*i.e.*, cleavage through a RISC pathway).

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 about 19 to about 30 base pairs, *e.g.*, about 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24,20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 base pairs. Thus, in one embodiment, 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 one embodiment, a miRNA is a dsRNA. In another embodiment, a dsRNA is not a naturally occurring miRNA. In another embodiment, an iRNA agent useful to target INHBE, ACVR1C, PLIN1, PDE3B, or INHBC gene expression is not generated in the target cell by cleavage of a larger dsRNA.

A dsRNA as described herein can further include one or more single-stranded nucleotide overhangs, *e.g.,* 1-4, 2-4, 1-3, 2-3, 1, 2, 3, or 4 nucleotides. dsRNAs having at least one nucleotide overhang can have superior inhibitory properties relative to their blunt-ended counterparts. A nucleotide overhang can comprise or consist of a nucleotide/nucleoside analog, including a deoxynucleotide/nucleoside. The overhang(s) can 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 an antisense or sense strand of a dsRNA.

A dsRNA can be synthesized by standard methods known in the art. Double stranded RNAi compounds of the invention may be prepared using a two-step procedure. First, the individual strands of the double stranded RNA molecule are prepared separately. Then, the component strands are annealed. The individual strands of the siRNA compound can be prepared using solution-phase or solid-phase organic synthesis or both. Organic synthesis offers the advantage that the oligonucleotide strands comprising unnatural or modified nucleotides can be easily prepared. Similarly, single-stranded oligonucleotides of the invention can be prepared using solution-phase or solid-phase organic synthesis or both.

In an aspect, a dsRNA of the invention includes at least two nucleotide sequences, a sense sequence and an anti-sense sequence. The sense strand is selected from the group of sequences provided in any one of Tables 2-17, 19 and 20, and the corresponding antisense strand of the sense strand is selected from the group of sequences of any one of Tables 2-17, 19 and 20. In this aspect, 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 in the expression of a-associated target gene. As such, in this aspect, a dsRNA will include two oligonucleotides, where one oligonucleotide is described as the sense strand in any one of Tables 2-17, 19 and 20, and the second oligonucleotide is described as the corresponding antisense strand of the sense strand in any one of Tables 2-17, 19 and 20.

In certain embodiments, the substantially complementary sequences of the dsRNA are contained on separate oligonucleotides. In other embodiments, the substantially complementary sequences of the dsRNA are contained on a single oligonucleotide.

In some embodiments, the sense or antisense strands are selected from the sense or antisense strand of any one of duplexes AD-1706583, AD-1711744, AD-1706593, AD-1708473, AD-1706662, AD-1706761, AD-1707306, AD-1707639, and AD-1707640.

In some embodiments, the sense or antisense strands are selected from the sense or antisense strand of duplex AD-1706583.

In some embodiments, the sense or antisense strands are selected from the sense or antisense strand of duplex AD-1711744.

In some embodiments, the sense or antisense strands are selected from the sense or antisense strand of duplex AD-1706593.

In some embodiments, the sense or antisense strands are selected from the sense or antisense strand of duplex AD-1708473.

In some embodiments, the sense or antisense strands are selected from the sense or antisense strand of duplex AD-1706662.

In some embodiments, the sense or antisense strands are selected from the sense or antisense strand of duplex AD-1706761.

In some embodiments, the sense or antisense strands are selected from the sense or antisense strand of duplex AD-1707306.

In some embodiments, the sense or antisense strands are selected from the sense or antisense strand of duplex AD-1707639.

In some embodiments, the sense or antisense strands are selected from the sense or antisense strand of duplex AD-1707640.

It will be understood that, although the sequences in, for example, Table 2, are not described as modified or conjugated sequences, the RNA of the iRNA of the invention *e.g.*, a dsRNA of the invention, may comprise any one of the sequences set forth in any one of Tables 2-17, 19 and 20 that is un-modified, un-conjugated, or modified or conjugated differently than described therein. In other words, the invention encompasses dsRNA of Tables 2-17, 19 and 20 which are un-modified, un-conjugated, modified, or conjugated, as described herein.

The skilled person is well aware that dsRNAs having a duplex structure of about 20 to 23 base pairs, *e.g.,* 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 also be effective (Chu and Rana (2007) *RNA* 14:1714-1719; Kim *et al.* (2005) *Nat Biotech* 23:222-226). In the embodiments described above, by virtue of the nature of the oligonucleotide sequences provided in any one of Tables 2-17, 19 and 20. dsRNAs described herein can include at least one strand of a length of minimally 21 nucleotides. It can be reasonably expected that shorter duplexes having any one of the sequences in any one of Tables 2-17, 19 and 20 minus only a few nucleotides on one or both ends can be similarly effective as compared to the dsRNAs described above. Hence, dsRNAs having a sequence of at least 19, 20, or more contiguous nucleotides derived from any one of the sequences of any one of Tables 2-17, 19 and 20, and differing in their ability to inhibit the expression of an INHBE gene by not more than about 5, 10, 15, 20, 25, or 30 % inhibition from a dsRNA comprising the full sequence, are contemplated to be within the scope of the present invention.

In addition, the RNAs provided in Tables 2-17, 19 and 20 identify a site(s) in a metabolic disorder-associated target gene transcript that is susceptible to RISC-mediated cleavage. As such, the present invention further features iRNAs that target within one of these sites. As used herein, an iRNA is said to target within a particular site of an RNA transcript if the iRNA promotes cleavage of the transcript anywhere within that particular site. Such an iRNA will generally include at least about 19 contiguous nucleotides from any one of the sequences provided in any one of Tables 2-17, 19 and 20 coupled to additional nucleotide sequences taken from the region contiguous to the selected sequence in a metabolic disorder-associated target gene.

III. Modifications for the RNAi Agents of the Invention

In certain embodiments, the RNA of the iRNA of the invention *e.g.*, a dsRNA, is un-modified, and does not comprise, *e.g.*, chemical modifications or conjugations known in the art and described herein. In other embodiments, the RNA of an iRNA of the invention, *e.g.*, a dsRNA, is

chemically modified to enhance stability or other beneficial characteristics. In certain embodiments of the invention, substantially all of the nucleotides of an iRNA of the invention are modified. In other embodiments of the invention, all of the nucleotides of an iRNA or substantially all of the nucleotides of an iRNA are modified, *i.e.*, not more than 5, 4, 3, 2, or 1unmodified nucleotides are present in a strand of the iRNA.

In some embodiments, the dsRNA agents of the invention comprise at least one nucleic acid modification described herein. For example, at least one modification selected from the group consisting of modified internucleoside linkage, modified nucleobase, modified sugar, and any combinations thereof. Without limitations, such a modification can be present anywhere in the dsRNA agent of the invention. For example, the modification can be present in one of the RNA molecules.

In one embodiment, the dsRNA agents of the disclosure comprise one or more C22 hydrocarbon chains conjugated to one or more internal positions on at least one strand and do not comprise additional chemical modifications known in the art and described herein, in the remaining positions of the sense and anti-sense strands.

In some embodiments, the dsRNA agents of the invention comprise one or more C22 hydrocarbon chains conjugated to one or more internal positions on at least one strand, and comprise at least one additional nucleic acid modification described herein. For example, at least one modification selected from the group consisting of modified internucleoside linkage, modified nucleobase, modified sugar, and any combinations thereof. Without limitations, such a modification can be present anywhere in the dsRNA agent of the invention. For example, the modification can be present in one of the RNA molecules.

In one embodiment, the dsRNA agents of the disclosure comprise one or more targeting ligands, *e.g.,* one or more GalNAc derivatives, and do not comprise additional chemical modifications known in the art and described herein, in the remaining positions of the sense and anti-sense strands.

In some embodiments, the dsRNA agents of the invention comprise one or more targeting ligands, *e.g.,* one or more GalNAc derivatives, and comprise at least one additional nucleic acid modification described herein. For example, at least one modification selected from the group consisting of modified internucleoside linkage, modified nucleobase, modified sugar, and any combinations thereof. Without limitations, such a modification can be present anywhere in the dsRNA agent of the invention. For example, the modification can be present in one of the RNA molecules.

Modifications include, for example, end modifications, *e.g.*, 5'-end modifications (phosphorylation, conjugation, inverted linkages) or 3'-end modifications (conjugation, DNA nucleotides, inverted linkages, etc.); 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; sugar modifications (*e.g.*, at the 2'-position or 4'-position) or replacement of the sugar; or backbone modifications, including modification or replacement of the phosphodiester linkages. Specific examples of RNAi agents useful in the embodiments described

herein 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 some embodiments, a modified RNAi agent will have a phosphorus atom in its internucleoside backbone.

A. Nucleobase Modifications

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

In addition to "unmodified" or "natural" nucleobases such as the purine nucleobases adenine (A) and guanine (G), and the pyrimidine nucleobases thymine (T), cytosine (C) and uracil (U), many modified nucleobases or nucleobase mimetics known to those skilled in the art are amenable with the compounds described herein. The unmodified or natural nucleobases can be modified or replaced to provide iRNAs having improved properties. For example, nuclease resistant oligonucleotides can be prepared with these bases or with synthetic and natural nucleobases (*e.g.*, inosine, xanthine, hypoxanthine, nubularine, isoguanisine, or tubercidine) and any one of the oligomer modifications described herein. Alternatively, substituted or modified analogs of any of the above bases and "universal bases" can be employed. When a natural base is replaced by a non-natural and/or universal base, the nucleotide is said to comprise a modified nucleobase and/or a nucleobase modification herein. Modified nucleobase and/or nucleobase modifications also include natural, non-natural and universal bases, which comprise conjugated moieties, *e.g.* a ligand described herein. Preferred conjugate moieties for conjugation with nucleobases include cationic amino groups which can be conjugated to the nucleobase via an appropriate alkyl, alkenyl or a linker with an amide linkage.

An oligomeric compound described herein can 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). Exemplary modified nucleobases include, but are not limited to, other synthetic and natural nucleobases such as inosine, xanthine, hypoxanthine, nubularine, isoguanisine, tubercidine, 2-(halo)adenine, 2-(alkyl)adenine, 2-(propyl)adenine, 2-(amino)adenine, 2-(aminoalkyll)adenine, 2-(aminopropyl)adenine, 2-(methylthio)-N^6-(isopentenyl)adenine, 6-(alkyl)adenine, 6-(methyl)adenine, 7-(deaza)adenine, 8-(alkenyl)adenine, 8-(alkyl)adenine, 8-(alkynyl)adenine, 8-(amino)adenine, 8-(halo)adenine, 8-(hydroxyl)adenine, 8-(thioalkyl)adenine, 8-

(thiol)adenine, N^6-(isopentyl)adenine, N^6-(methyl)adenine, N^6, N^6-(dimethyl)adenine, 2-(alkyl)guanine,2-(propyl)guanine, 6-(alkyl)guanine, 6-(methyl)guanine, 7-(alkyl)guanine, 7-(methyl)guanine, 7-(deaza)guanine, 8-(alkyl)guanine, 8-(alkenyl)guanine, 8-(alkynyl)guanine, 8-(amino)guanine, 8-(halo)guanine, 8-(hydroxyl)guanine, 8-(thioalkyl)guanine, 8-(thiol)guanine, N-(methyl)guanine, 2-(thio)cytosine, 3-(deaza)-5-(aza)cytosine, 3-(alkyl)cytosine, 3-(methyl)cytosine, 5-(alkyl)cytosine, 5-(alkynyl)cytosine, 5-(halo)cytosine, 5-(methyl)cytosine, 5-(propynyl)cytosine, 5-(propynyl)cytosine, 5-(trifluoromethyl)cytosine, 6-(azo)cytosine, N^4-(acetyl)cytosine, 3-(3-amino-3-carboxypropyl)uracil, 2-(thio)uracil, 5-(methyl)-2-(thio)uracil, 5-(methylaminomethyl)-2-(thio)uracil, 4-(thio)uracil, 5-(methyl)-4-(thio)uracil, 5-(methylaminomethyl)-4-(thio)uracil, 5-(methyl)-2,4-(dithio)uracil, 5-(methylaminomethyl)-2,4-(dithio)uracil, 5-(2-aminopropyl)uracil, 5-(alkyl)uracil, 5-(alkynyl)uracil, 5-(allylamino)uracil, 5-(aminoallyl)uracil, 5-(aminoalkyl)uracil, 5-(guanidiniumalkyl)uracil, 5-(1,3-diazole-1-alkyl)uracil, 5-(cyanoalkyl)uracil, 5-(dialkylaminoalkyl)uracil, 5-(dimethylaminoalkyl)uracil, 5-(halo)uracil, 5-(methoxy)uracil, uracil-5-oxyacetic acid, 5-(methoxycarbonylmethyl)-2-(thio)uracil, 5-(methoxycarbonyl-methyl)uracil, 5-(propynyl)uracil, 5-(propynyl)uracil, 5-(trifluoromethyl)uracil, 6-(azo)uracil, dihydrouracil, N^3-(methyl)uracil, 5-uracil (*i.e.,* pseudouracil), 2-(thio)pseudouracil,4-(thio)pseudouracil,2,4-(dithio)psuedouracil,5-(alkyl)pseudouracil, 5-(methyl)pseudouracil, 5-(alkyl)-2-(thio)pseudouracil, 5-(methyl)-2-(thio)pseudouracil, 5-(alkyl)-4-(thio)pseudouracil, 5-(methyl)-4-(thio)pseudouracil, 5-(alkyl)-2,4-(dithio)pseudouracil, 5-(methyl)-2,4-(dithio)pseudouracil, 1-substituted pseudouracil, 1-substituted 2(thio)-pseudouracil, 1-substituted 4-(thio)pseudouracil, 1-substituted 2,4-(dithio)pseudouracil, 1-(aminocarbonylethylenyl)-pseudouracil, 1-(aminocarbonylethylenyl)-2(thio)-pseudouracil, 1-(aminocarbonylethylenyl)-4-(thio)pseudouracil, 1-(aminocarbonylethylenyl)-2,4-(dithio)pseudouracil, 1-(aminoalkylaminocarbonylethylenyl)-pseudouracil, 1-(aminoalkylamino-carbonylethylenyl)-2(thio)-pseudouracil, 1-(aminoalkylaminocarbonylethylenyl)-4-(thio)pseudouracil, 1-(aminoalkylaminocarbonylethylenyl)-2,4-(dithio)pseudouracil, 1,3-(diaza)-2-(oxo)-phenoxazin-1-yl, 1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl, 1,3-(diaza)-2-(oxo)-phenthiazin-1-yl, 1-(aza)-2-(thio)-3-(aza)-phenthiazin-1-yl, 7-substituted 1,3-(diaza)-2-(oxo)-phenoxazin-1-yl, 7-substituted 1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl, 7-substituted 1,3-(diaza)-2-(oxo)-phenthiazin-1-yl, 7-substituted 1-(aza)-2-(thio)-3-(aza)-phenthiazin-1-yl, 7-(aminoalkylhydroxy)-1,3-(diaza)-2-(oxo)-phenoxazin-1-yl, 7-(aminoalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl, 7-(aminoalkylhydroxy)-1,3-(diaza)-2-(oxo)-phenthiazin-1-yl, 7-(aminoalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenthiazin-1-yl, 7-(guanidiniumalkylhydroxy)-1,3-(diaza)-2-(oxo)-phenoxazin-1-yl, 7-(guanidiniumalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl, 7-(guanidiniumalkyl-hydroxy)-1,3-(diaza)-2-(oxo)-phenthiazin-1-yl, 7-(guanidiniumalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenthiazin-1-yl, 1,3,5-(triaza)-2,6-(dioxa)-naphthalene, inosine, xanthine, hypoxanthine, nubularine, tubercidine, isoguanisine, inosinyl, 2-aza-inosinyl, 7-deaza-inosinyl, nitroimidazolyl, nitropyrazolyl, nitrobenzimidazolyl, nitroindazolyl, aminoindolyl, pyrrolopyrimidinyl, 3-(methyl)isocarbostyrilyl, 5-(methyl)isocarbostyrilyl, 3-(methyl)-7-(propynyl)isocarbostyrilyl, 7-(aza)indolyl, 6-(methyl)-7-(aza)indolyl, imidizopyridinyl, 9-(methyl)-imidizopyridinyl, pyrrolopyrizinyl, isocarbostyrilyl, 7-

(propynyl)isocarbostyrilyl, propynyl-7-(aza)indolyl, 2,4,5-(trimethyl)phenyl, 4-(methyl)indolyl, 4,6-(dimethyl)indolyl, phenyl, napthalenyl, anthracenyl, phenanthracenyl, pyrenyl, stilbenyl, tetracenyl, pentacenyl, difluorotolyl, 4-(fluoro)-6-(methyl)benzimidazole, 4-(methyl)benzimidazole, 6-(azo)thymine, 2-pyridinone, 5-nitroindole, 3-nitropyrrole, 6-(aza)pyrimidine, 2-(amino)purine, 2,6-(diamino)purine, 5-substituted pyrimidines, N^2-substituted purines, N^6-substituted purines, O^6-substituted purines, substituted 1,2,4-triazoles, pyrrolo-pyrimidin-2-on-3-yl, 6-phenyl-pyrrolo-pyrimidin-2-on-3-yl, *para*-substituted-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl, *ortho*-substituted-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl, bis-*ortho*-substituted-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl, *para*-(aminoalkylhydroxy)- 6-phenyl-pyrrolo-pyrimidin-2-on-3-yl, *ortho*-(aminoalkylhydroxy)- 6-phenyl-pyrrolo-pyrimidin-2-on-3-yl, bis-*ortho*--(aminoalkylhydroxy)- 6-phenyl-pyrrolo-pyrimidin-2-on-3-yl, pyridopyrimidin-3-yl, 2-oxo-7-amino-pyridopyrimidin-3-yl, 2-oxo-pyridopyrimidine-3-yl, or any O-alkylated or N-alkylated derivatives thereof. Alternatively, substituted or modified analogs of any of the above bases and "universal bases" can be employed.

As used herein, a universal nucleobase is any nucleobase that can base pair with all of the four naturally occurring nucleobases without substantially affecting the melting behavior, recognition by intracellular enzymes or activity of the iRNA duplex. Some exemplary universal nucleobases include, but are not limited to, 2,4-difluorotoluene, nitropyrrolyl, nitroindolyl, 8-aza-7-deazaadenine, 4-fluoro-6-methylbenzimidazle, 4-methylbenzimidazle, 3-methyl isocarbostyrilyl, 5- methyl isocarbostyrilyl, 3-methyl-7-propynyl isocarbostyrilyl, 7-azaindolyl, 6-methyl-7-azaindolyl, imidizopyridinyl, 9-methyl-imidizopyridinyl, pyrrolopyrizinyl, isocarbostyrilyl, 7-propynyl isocarbostyrilyl, propynyl-7-azaindolyl, 2,4,5-trimethylphenyl, 4-methylinolyl, 4,6-dimethylindolyl, phenyl, napthalenyl, anthracenyl, phenanthracenyl, pyrenyl, stilbenyl, tetracenyl, pentacenyl, and structural derivatives thereof (see for example, Loakes, 2001, *Nucleic Acids Research*, 29, 2437-2447).

Further nucleobases include those disclosed in U.S. Pat. No. 3,687,808; those disclosed in International Application No. PCT/US09/038425, filed March 26, 2009; those disclosed in the Concise Encyclopedia Of Polymer Science And Engineering, pages 858-859, Kroschwitz, J. I., ed. John Wiley & Sons, 1990; those disclosed by English *et al.*, Angewandte Chemie, International Edition, 1991, 30, 613; those disclosed in Modified Nucleosides in Biochemistry, Biotechnology and Medicine, Herdewijin, P.Ed. Wiley-VCH, 2008; and those disclosed by Sanghvi, Y.S., Chapter 15, dsRNA Research and Applications, pages 289-302, Crooke, S.T. and Lebleu, B., Eds., CRC Press, 1993. Contents of all of the above are herein incorporated by reference.

In certain embodiments, a modified nucleobase is a nucleobase that is fairly similar in structure to the parent nucleobase, such as for example a 7-deaza purine, a 5-methyl cytosine, or a G-clamp. In certain embodiments, nucleobase mimetic include more complicated structures, such as for example a tricyclic phenoxazine nucleobase mimetic. Methods for preparation of the above noted modified nucleobases are well known to those skilled in the art.

B. Sugar Modifications

DsRNA agent of the inventions provided herein can comprise one or more (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or more) monomer, including a nucleoside or nucleotide, having a modified sugar moiety. For example, the furanosyl sugar ring of a nucleoside can be modified in a number of ways including, but not limited to, addition of a substituent group, bridging of two non-geminal ring atoms to form a locked nucleic acid or bicyclic nucleic acid. In certain embodiments, oligomeric compounds comprise one or more (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or more) monomers that are LNA.

In some embodiments of a locked nucleic acid, the 2′ position of furnaosyl is connected to the 4’ position by a linker selected independently from –$[C(R1)(R2)]_n$–, –$[C(R1)(R2)]_n$–O–, –$[C(R1)(R2)]_n$-N(R1)–, –$[C(R1)(R2)]_n$-N(R1)–O-, —$[C(R1R2)]_n$-O-N(R1)—, –C(R1)=C(R2)–O–, –C(R1)=N–, –C(R1)=N–O-, —C(=NR1)-, —C(=NR1)-O-, —C(=O)—, —C(=O)O—, —C(=S)—, —C(=S)O—, —C(=S)S—, —O—, —Si(R1)2-, —$S(=O)_x$- and —N(R1)-;

wherein:

x is 0, 1, or 2;

n is 1, 2, 3, or 4;

each R1 and R2 is, independently, H, a protecting group, hydroxyl, C1-C12 alkyl, substituted C1-C12 alkyl, C2-C12 alkenyl, substituted C2-C12 alkenyl, C2-C12 alkynyl, substituted C2-C12 alkynyl, C5-C20 aryl, substituted C5-C20 aryl, heterocycle radical, substituted heterocycle radical, heteroaryl, substituted heteroaryl, C5-C7 alicyclic radical, substituted C5-C7 alicyclic radical, halogen, OJ1, NJ1J2, SJ1, N3, COOJ1, acyl (C(=O)—H), substituted acyl, CN, sulfonyl (S(=O)2-J1), or sulfoxyl (S(=O)-J1); and

each J1 and J2 is, independently, H, C1-C12 alkyl, substituted C1-C12 alkyl, C2-C12 alkenyl, substituted C2-C12 alkenyl, C2-C12 alkynyl, substituted C2-C12 alkynyl, C5-C20 aryl, substituted C5-C20 aryl, acyl (C(=O)—H), substituted acyl, a heterocycle radical, a substituted heterocycle radical, C1-C12 aminoalkyl, substituted C1-C12 aminoalkyl or a protecting group.

In some embodiments, each of the linkers of the LNA compounds is, independently, —[C(R1)(R2)]n-, —[C(R1)(R2)]n-O—, —C(R1R2)-N(R1)-O— or —C(R1R2)-O—N(R1)-. In another embodiment, each of said linkers is, independently, 4′-CH_2-2′, 4′-$(CH_2)_2$-2′, 4′-$(CH_2)_3$-2′, 4′-CH_2-O-2′, 4′-$(CH_2)_2$-O-2′, 4′-CH_2-O—N(R1)-2′ and 4′-CH_2-N(R1)-O-2′- wherein each R1 is, independently, H, a protecting group or C1-C12 alkyl.

Certain LNA's have been prepared and disclosed in the patent literature as well as in scientific literature (Singh et al., Chem. Commun., 1998, 4, 455-456; Koshkin et al., Tetrahedron, 1998, 54, 3607-3630; Wahlestedt et al., Proc. Natl. Acad. Sci. U.S.A., 2000, 97, 5633-5638; Kumar et al., Bioorg. Med. Chem. Lett., 1998, 8, 2219-2222; WO 94/14226; WO 2005/021570; Singh et al., J. Org. Chem., 1998, 63, 10035-10039; Examples of issued US patents and published applications that disclose LNA s include, for example, U.S. Pat. Nos. 7,053,207; 6,268,490; 6,770,748; 6,794,499; 7,034,133; and 6,525,191; and U.S. Pre-Grant Publication Nos. 2004-0171570; 2004-0219565; 2004-0014959; 2003-0207841; 2004-0143114; and 20030082807.

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

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

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

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

Modified sugar moieties are well known and can be used to alter, typically increase, the affinity of the antisense compound for its target and/or increase nuclease resistance. A representative list of preferred modified sugars includes but is not limited to bicyclic modified sugars, including methyleneoxy (4′-CH_2-O-2′) LNA and ethyleneoxy (4′-$(CH_2)_2$-O-2′ bridge) ENA; substituted sugars, especially 2′-substituted sugars having a 2′-F, 2′-OCH_3 or a 2′-$O(CH_2)_2$-OCH_3 substituent group; and 4′-thio modified sugars. Sugars can also be replaced with sugar mimetic groups among others. Methods for the preparations of modified sugars are well known to those skilled in the art. Some representative patents and publications that teach the preparation of such modified sugars include, but are not limited to, U.S. 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; 5,792,747; 5,700,920; 6,531,584; and 6,600,032; and WO 2005/121371.

Examples of "oxy"-2′ hydroxyl group modifications include alkoxy or aryloxy (OR, *e.g.*, R = H, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl or sugar); polyethyleneglycols (PEG), $O(CH_2CH_2O)_nCH_2CH_2OR$, n =1-50; "locked" nucleic acids (LNA) in which the furanose portion of the nucleoside includes a bridge connecting two carbon atoms on the furanose ring, thereby forming a bicyclic ring system; O-AMINE or $O-(CH_2)_nAMINE$ (n = 1-10, AMINE = NH_2; alkylamino, dialkylamino, heterocyclyl, arylamino, diaryl amino, heteroaryl amino, diheteroaryl amino, ethylene diamine or polyamino); and $O-CH_2CH_2(NCH_2CH_2NMe_2)_2$.

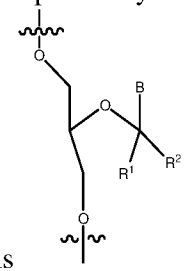
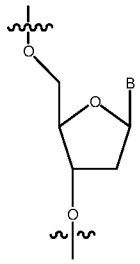
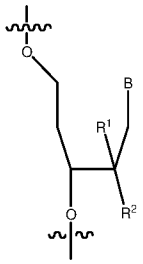
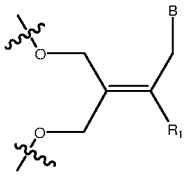
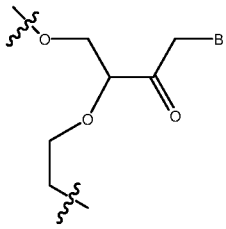
"Deoxy" modifications include hydrogen (*i.e.* deoxyribose sugars, which are of particular relevance to the single-strand overhangs); halo (*e.g.*, fluoro); amino (*e.g.* NH_2; alkylamino, dialkylamino, heterocyclyl, arylamino, diaryl amino, heteroaryl amino, diheteroaryl amino, or amino acid); $NH(CH_2CH_2NH)_nCH_2CH_2$-AMINE (AMINE = NH_2; alkylamino, dialkylamino, heterocyclyl, arylamino, diaryl amino, heteroaryl amino, or diheteroaryl amino); -NHC(O)R (R = alkyl, cycloalkyl, aryl, aralkyl, heteroaryl or sugar); cyano; mercapto; alkyl-thio-alkyl; thioalkoxy; thioalkyl; alkyl; cycloalkyl; aryl; alkenyl and alkynyl, which can be optionally substituted with *e.g.*, an amino functionality.

Other suitable 2'-modifications, *e.g.*, modified MOE, are described in U.S. Patent Application PublicationNo. 20130130378, contents of which are herein incorporated by reference.

A modification at the 2' position can be present in the arabinose configuration The term "arabinose configuration" refers to the placement of a substituent on the C2' of ribose in the same configuration as the 2'-OH is in the arabinose.

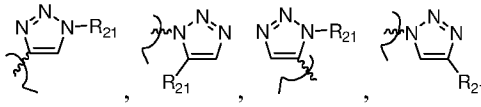
The sugar can comprise two different modifications at the same carbon in the sugar, *e.g.*, *gem* modification. The sugar group can also contain one or more carbons that possess the opposite stereochemical configuration than that of the corresponding carbon in ribose. Thus, an oligomeric compound can include one or more monomers containing *e.g.*, arabinose, as the sugar. The monomer can have an alpha linkage at the 1' position on the sugar, *e.g.*, alpha-nucleosides. The monomer can also have the opposite configuration at the 4'-position, *e.g.*, C5' and H4' or substituents replacing them are interchanged with each other. When the C5' and H4' or substituents replacing them are interchanged with each other, the sugar is said to be modified at the 4' position.

DsRNA agent of the inventions disclosed herein can also include abasic sugars, *i.e.*, a sugar which lack a nucleobase at C-1′ or has other chemical groups in place of a nucleobase at C1'. See for example U.S. Pat. No. 5,998,203, content of which is herein incorporated in its entirety. These abasic sugars can also be further containing modifications at one or more of the constituent sugar atoms. DsRNA agent of the inventions can also contain one or more sugars that are the L isomer, *e.g.* L-nucleosides. Modification to the sugar group can also include replacement of the 4'-O with a sulfur, optionally substituted nitrogen or CH_2 group. In some embodiments, linkage between C1' and nucleobase is in α configuration.

Sugar modifications can also include acyclic nucleotides, wherein a C-C bonds between ribose carbons (*e.g.*, C1'-C2', C2'-C3', C3'-C4', C4'-O4', C1'-O4') is absent and/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).

In some embodiments, sugar modifications are selected from the group consisting of 2'-H, 2'-*O*-Me (2'-*O*-methyl), 2'-*O*-MOE (2'-*O*-methoxyethyl), 2'-F, 2'-*O*-[2-(methylamino)-2-oxoethyl] (2'-*O*-NMA), 2'-*S*-methyl, 2'-O-CH_2-(4'-C) (LNA), 2'-O-CH_2CH_2-(4'-C) (ENA), 2'-O-aminopropyl (2'-O-AP), 2'-O-dimethylaminoethyl (2'-O-DMAOE), 2'-O-dimethylaminopropyl (2'-O-DMAP), 2'-O-dimethylaminoethyloxyethyl (2'-O-DMAEOE) and *gem* 2'-OMe/2'F with 2'-O-Me in the arabinose configuration.

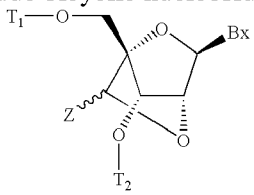
It is to be understood that when a particular nucleotide is linked through its 2'-position to the next nucleotide, the sugar modifications described herein can be placed at the 3'-position of the sugar for that particular nucleotide, *e.g.*, the nucleotide that is linked through its 2' -position. A modification at the 3' position can be present in the xylose configuration The term "xylose configuration" refers to the placement of a substituent on the C3' of ribose in the same configuration as the 3'-OH is in the xylose sugar.

The hydrogen attached to C4' and/or C1' can be replaced by a straight- or branched-optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, wherein backbone of the alkyl, alkenyl and alkynyl can contain one or more of O, S, S(O), SO_2, N(R'), C(O), N(R')C(O)O, OC(O)N(R'), CH(Z'), phosphorous containing linkage, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclic or optionally substituted cycloalkyl, where R' is hydrogen, acyl or optionally substituted aliphatic, Z' is selected from the group consisting of OR_{11}, COR_{11}, CO_2R_{11},  , $NR_{21}R_{31}$, $CONR_{21}R_{31}$, $CON(H)NR_{21}R_{31}$, $ONR_{21}R_{31}$, $CON(H)N=CR_{41}R_{51}$, $N(R_{21})C(=NR_{31})NR_{21}R_{31}$, $N(R_{21})C(O)NR_{21}R_{31}$, $N(R_{21})C(S)NR_{21}R_{31}$, $OC(O)NR_{21}R_{31}$, $SC(O)NR_{21}R_{31}$, $N(R_{21})C(S)OR_{11}$,

$N(R_{21})C(O)OR_{11}$, $N(R_{21})C(O)SR_{11}$, $N(R_{21})N=CR_{41}R_{51}$, $ON=CR_{41}R_{51}$, SO_2R_{11}, SOR_{11}, SR_{11}, and substituted or unsubstituted heterocyclic; R_{21} and R_{31} for each occurrence are independently hydrogen, acyl, unsubstituted or substituted aliphatic, aryl, heteroaryl, heterocyclic, OR_{11}, COR_{11}, CO_2R_{11}, or $NR_{11}R_{11}$'; or R_{21} and R_{31}, taken together with the atoms to which they are attached, form a heterocyclic ring; R_{41} and R_{51} for each occurrence are independently hydrogen, acyl, unsubstituted or substituted aliphatic, aryl, heteroaryl, heterocyclic, OR_{11}, COR_{11}, or CO_2R_{11}, or $NR_{11}R_{11}$'; and R_{11} and R_{11}' are independently hydrogen, aliphatic, substituted aliphatic, aryl, heteroaryl, or heterocyclic. In some embodiments, the hydrogen attached to the C4' of the 5' terminal nucleotide is replaced.

In some embodiments, C4' and C5' together form an optionally substituted heterocyclic, preferably comprising at least one -PX(Y)-, wherein X is H, OH, OM, SH, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkylthio, optionally substituted alkylamino or optionally substituted dialkylamino, where M is independently for each occurrence an alki metal or transition metal with an overall charge of +1; and Y is O, S, or NR', where R' is hydrogen, optionally substituted aliphatic. Preferably this modification is at the 5 terminal of the iRNA.

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



wherein:

Bx is a heterocyclic base moiety;

T_1 is H or a hydroxyl protecting group;

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

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

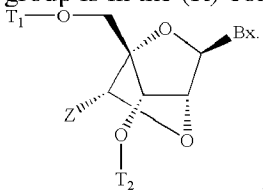
In some embodiments, each of the substituted groups, is, independently, mono or poly substituted with optionally protected substituent groups independently selected from halogen, oxo, hydroxyl, OJ1, NJ1J2, SJ1, N3, OC(=X)J1, OC(=X)NJ1J2, NJ3C(=X)NJ1J2 and CN, wherein each J1, J2 and J3 is, independently, H or C_1-C_6 alkyl, and X is O, S or NJ1.

In certain such embodiments, each of the substituted groups, is, independently, mono or poly substituted with substituent groups independently selected from halogen, oxo, hydroxyl, OJ1, NJ1J2, SJ1, N3, OC(=X)J1, and NJ3C(=X)NJ1J2, wherein each J1, J2 and J3 is, independently, H, C_1-C_6 alkyl, or substituted C_1-C_6 alkyl and X is O or NJ1.

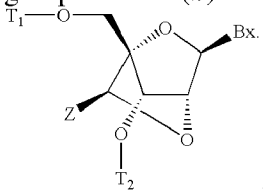
In certain embodiments, the Z group is C_1-C_6 alkyl substituted with one or more Xx, wherein each Xx is independently OJ1, NJ1J2, SJ1, N3, OC(=X)J1, OC(=X)NJ1J2, NJ3C(=X)NJ1J2 or CN; wherein each J1, J2 and J3 is, independently, H or C_1-C_6 alkyl, and X is O, S or NJ1. In another embodiment, the Z group is C_1-C_6 alkyl substituted with one or more Xx, wherein each Xx is independently halo (*e.g.*, fluoro), hydroxyl, alkoxy (*e.g.*, CH_3O—), substituted alkoxy or azido.

In certain embodiments, the Z group is —CH_2Xx, wherein Xx is OJ1, NJ1J2, SJ1, N3, OC(=X)J1, OC(=X)NJ1J2, NJ3C(=X)NJ1J2 or CN; wherein each J1, J2 and J3 is, independently, H or C_1-C_6 alkyl, and X is O, S or NJ1. In another embodiment, the Z group is —CH_2Xx, wherein Xx is halo (*e.g.*, fluoro), hydroxyl, alkoxy (*e.g.*, CH_3O—) or azido.

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



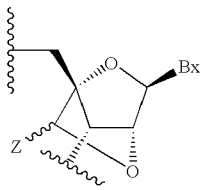
In certain such embodiments, the Z group is in the (S)-configuration:



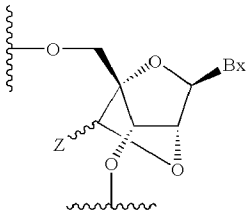
In certain embodiments, each T_1 and T_2 is a hydroxyl protecting group. A preferred list of hydroxyl protecting groups includes benzyl, benzoyl, 2,6-dichlorobenzyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, mesylate, tosylate, dimethoxytrityl (DMT), 9-phenylxanthine-9-yl (Pixyl) and 9-(p-methoxyphenyl)xanthine-9-yl (MOX). In certain embodiments, T_1 is a hydroxyl protecting group selected from acetyl, benzyl, t-butyldimethylsilyl, t-butyldiphenylsilyl and dimethoxytrityl wherein a more preferred hydroxyl protecting group is T_1 is 4,4′-dimethoxytrityl.

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

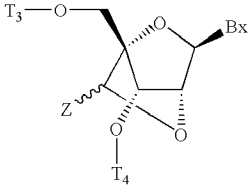
In certain embodiments, the compounds of the invention comprise at least one monomer of the formula:



or of the formula:



or of the formula:



wherein

Bx is a heterocyclic base moiety;

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

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

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

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

In some embodiments, each of the substituted groups, is, independently, mono or poly substituted with optionally protected substituent groups independently selected from halogen, oxo, hydroxyl, OJ1, NJ1J2, SJ1, N3, OC(=X)J1, OC(=X)NJ1J2, NJ3C(=X)NJ1J2 and CN, wherein each J1, J2 and J3 is, independently, H or C1-C6 alkyl, and X is O, S or NJ1.

In some embodiments, each of the substituted groups, is, independently, mono or poly substituted with substituent groups independently selected from halogen, oxo, hydroxyl, OJ1, NJ1J2, SJ1, N3, OC(=X)J1, and NJ3C(=X)NJ1J2, wherein each J1, J2 and J3 is, independently, H or C_1-C_6 alkyl, and X is O or NJ1.

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

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

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

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

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

In certain embodiments, at least one substituent group is hydroxyl (*e.g.*, at least one Z is C1-C6 alkyl substituted with one or more hydroxyl). In certain embodiments, each substituent group is, independently, hydroxyl (*e.g.*, each Z is, independently, C_1-C_6 alkyl substituted with one or more hydroxyl). In certain embodiments, at least one Z is $HOCH_2$-. In another embodiment, each Z is $HOCH_2$-.

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

In certain embodiments, at least one Z group is C_1-C_6 alkyl substituted with one or more Xx, wherein each Xx is, independently, OJ1, NJ1J2, SJ1, N3, OC(=X)J1, OC(=X)NJ1J2, NJ3C(=X)NJ1J2 or CN; wherein each J1, J2 and J3 is, independently, H or C_1-C_6 alkyl, and X is O, S or NJ1. In another embodiment, at least one Z group is C_1-C_6 alkyl substituted with one or more Xx, wherein each Xx is, independently, halo (*e.g.*, fluoro), hydroxyl, alkoxy (*e.g.*, CH_3O—) or azido.

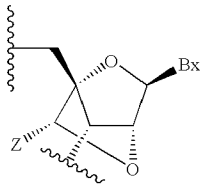
In certain embodiments, each Z group is, independently, C_1-C_6 alkyl substituted with one or more Xx, wherein each Xx is independently OJ1, NJ1J2, SJ1, N3, OC(=X)J1, OC(=X)NJ1J2, NJ3C(=X)NJ1J2 or CN; wherein each J1, J2 and J3 is, independently, H or C_1-C_6 alkyl, and X is O, S or NJ1. In another embodiment, each Z group is, independently, C_1-C_6 alkyl substituted with one or more Xx, wherein each Xx is independently halo (*e.g.*, fluoro), hydroxyl, alkoxy (*e.g.*, CH_3O—) or azido.

In certain embodiments, at least one Z group is —CH_2Xx, wherein Xx is OJ1, NJ1J2, SJ1, N3, OC(=X)J1, OC(=X)NJ1J2, NJ3C(=X)NJ1J2 or CN; wherein each J1, J2 and J3 is, independently, H or C_1-C_6 alkyl, and X is O, S or NJ1 In certain embodiments, at least one Z group is —CH_2Xx, wherein Xx is halo (*e.g.*, fluoro), hydroxyl, alkoxy (*e.g.*, CH_3O—) or azido.

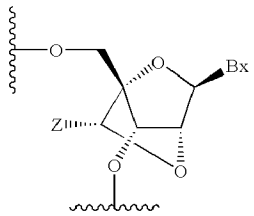
In certain embodiments, each Z group is, independently, —CH_2Xx, wherein each Xx is, independently, OJ1, NJ1J2, SJ1, N3, OC(=X)J1, OC(=X)NJ1J2, NJ3C(=X)NJ1J2 or CN; wherein each J1, J2 and J3 is, independently, H or C_1-C_6 alkyl, and X is O, S or NJ1. In another embodiment, each Z group is, independently, —CH_2Xx, wherein each Xx is, independently, halo (*e.g.*, fluoro), hydroxyl, alkoxy (*e.g.*, CH_3O—) or azido.

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

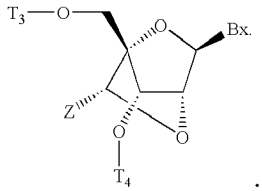
In certain embodiments, the Z group of at least one monomer is in the (R)— configuration represented by the formula:



or the formula:



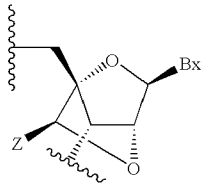
or the formula:



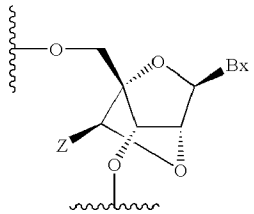
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IN certain embodiments, the Z group of each monomer of the formula is in the (R)— configuration.

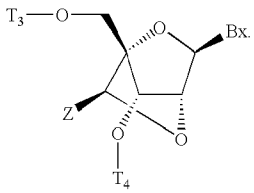
In certain embodiments, the Z group of at least one monomer is in the (S)— configuration represented by the formula:



or the formula:



or the formula:

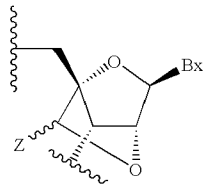


In certain embodiments, the Z group of each monomer of the formula is in the (S)— configuration.

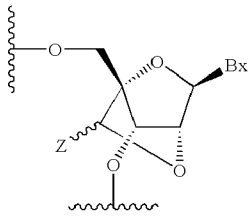
In certain embodiments, T_3 is H or a hydroxyl protecting group. In certain embodiments, T_4 is H or a hydroxyl protecting group. In a further embodiment T_3 is an internucleoside linking group attached to a nucleoside, a nucleotide or a monomeric subunit. In certain embodiments, T_4 is an internucleoside linking group attached to a nucleoside, a nucleotide or a monomeric subunit. In certain embodiments, T_3 is an internucleoside linking group attached to an oligonucleoside or an oligonucleotide. In certain embodiments, T_4 is an internucleoside linking group attached to an oligonucleoside or an oligonucleotide. In certain embodiments, T_3 is an internucleoside linking group attached to an oligomeric compound. In certain embodiments, T_4 is an internucleoside linking group

attached to an oligomeric compound. In certain embodiments, at least one of T_3 and T_4 comprises an internucleoside linking group selected from phosphodiester or phosphorothioate.

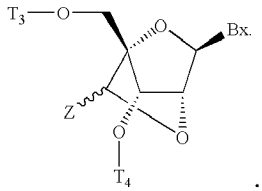
In certain embodiments, dsRNA agent of the invention comprise at least one region of at least two contiguous monomers of the formula:



or of the formula:



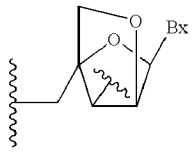
or of the formula:



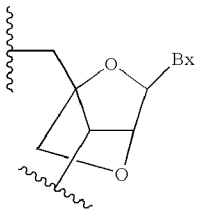
.

In certain such embodiments, LNAs include, but are not limited to, (A) α-L-Methyleneoxy (4′-CH_2-O-2′) LNA, (B) β-D-Methyleneoxy (4′-CH_2-O-2′) LNA, (C) Ethyleneoxy (4′-$(CH_2)_2$-O-2′) LNA, (D) Aminooxy (4′-CH_2-O—N(R)-2′) LNA and (E) Oxyamino (4′-CH_2-N(R)—O-2′) LNA, as depicted below:

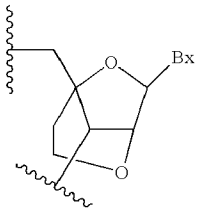
(A)



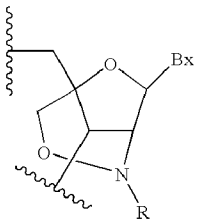
(B)



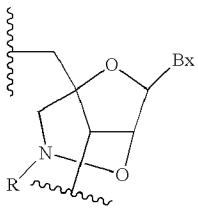
(C)



(D)

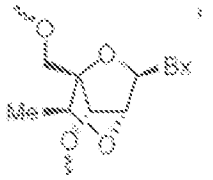


(E)



In certain embodiments, the dsRNA agent of the invention comprises at least two regions of at least two contiguous monomers of the above formula. In certain embodiments, the dsRNA agent of the invention comprises a gapped motif. In certain embodiments, the dsRNA agent of the invention comprises at least one region of from about 8 to about 14 contiguous β-D-2′-deoxyribofuranosyl nucleosides. In certain embodiments, the dsRNA agent of the invention comprises at least one region of from about 9 to about 12 contiguous β-D-2′-deoxyribofuranosyl nucleosides.

In certain embodiments, the dsRNA agent of the invention comprises at least one (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or more) comprises at least one (S)-cEt monomer of the formula:



S-cEt (C)

,

wherein Bx is heterocyclic base moiety.

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

C. Intersugar Linkage Modifications

Described herein are linking groups that link monomers (including, but not limited to, modified and unmodified nucleosides and nucleotides) together, thereby forming an oligomeric compound, *e.g.*, an oligonucleotide. Such linking groups are also referred to as intersugar linkage. The two main classes of linking groups are defined by the presence or absence of a phosphorus atom. Representative phosphorus containing linkages include, but are not limited to, phosphodiesters (P=O), phosphotriesters, methylphosphonates, phosphoramidate, and phosphorothioates (P=S). Representative non-phosphorus containing linking groups include, but are not limited to, methylenemethylimino (—CH_2-$N(CH_3)$-O—CH2-), thiodiester (—O—C(O)—S—), thionocarbamate (—O—C(O)(NH)—S—); siloxane (—O—$Si(H)_2$-O—); and N,N′-dimethylhydrazine (—CH_2-$N(CH_3)$-$N(CH_3)$-). Modified linkages, compared to natural phosphodiester linkages, can be used to alter, typically increase, nuclease resistance of the oligonucleotides. In certain embodiments, linkages having a chiral atom can be prepared as racemic mixtures, as separate enantomers. Representative chiral linkages include, but are not limited to, alkylphosphonates and phosphorothioates. Methods of preparation of phosphorous-containing and non-phosphorous-containing linkages are well known to those skilled in the art.

The phosphate group in the linking group can be modified by replacing one of the oxygens with a different substituent. One result of this modification can be increased resistance of the oligonucleotide to nucleolytic breakdown. Examples of modified phosphate groups include phosphorothioate, phosphoroselenates, borano phosphates, borano phosphate esters, hydrogen phosphonates, phosphoroamidates, alkyl or aryl phosphonates and phosphotriesters. In some

embodiments, one of the non-bridging phosphate oxygen atoms in the linkage can be replaced by any of the following: S, Se, BR_3 (R is hydrogen, alkyl, aryl), C (*i.e.* an alkyl group, an aryl group, etc…), H, NR_2 (R is hydrogen, optionally substituted alkyl, aryl), or OR (R is optionally substituted alkyl or aryl). The phosphorous atom in an unmodified phosphate group is achiral. However, replacement of one of the non-bridging oxygens with one of the above atoms or groups of atoms renders the phosphorous atom chiral; in other words a phosphorous atom in a phosphate group modified in this way is a stereogenic center. The stereogenic phosphorous atom can possess either the "R" configuration (herein Rp) or the "S" configuration (herein Sp).

Phosphorodithioates have both non-bridging oxygens replaced by sulfur. The phosphorus center in the phosphorodithioates is achiral which precludes the formation of oligonucleotides diastereomers. Thus, while not wishing to be bound by theory, modifications to both non-bridging oxygens, which eliminate the chiral center, *e.g.* phosphorodithioate formation, can be desirable in that they cannot produce diastereomer mixtures. Thus, the non-bridging oxygens can be independently any one of O, S, Se, B, C, H, N, or OR (R is alkyl or aryl).

The phosphate linker can also be modified by replacement of bridging oxygen, (*i.e.* oxygen that links the phosphate to the sugar of the monomer), with nitrogen (bridged phosphoroamidates), sulfur (bridged phosphorothioates) and carbon (bridged methylenephosphonates). The replacement can occur at the either one of the linking oxygens or at both linking oxygens. When the bridging oxygen is the 3'-oxygen of a nucleoside, replacement with carbon is preferred. When the bridging oxygen is the 5'-oxygen of a nucleoside, replacement with nitrogen is preferred.

Modified phosphate linkages where at least one of the oxygen linked to the phosphate has been replaced or the phosphate group has been replaced by a non-phosphorous group, are also referred to as "non-phosphodiester intersugar linkage" or "non-phosphodiester linker."

In certain embodiments, the phosphate group can be replaced by non-phosphorus containing connectors, *e.g.* dephospho linkers. Dephospho linkers are also referred to as non-phosphodiester linkers herein. While not wishing to be bound by theory, it is believed that since the charged phosphodiester group is the reaction center in nucleolytic degradation, its replacement with neutral structural mimics should impart enhanced nuclease stability. Again, while not wishing to be bound by theory, it can be desirable, in some embodiment, to introduce alterations in which the charged phosphate group is replaced by a neutral moiety.

Examples of moieties which can replace the phosphate group include, but are not limited to, amides (for example amide-3 (3'-CH_2-C(=O)-N(H)-5') and amide-4 (3'-CH_2-N(H)-C(=O)-5')), hydroxylamino, siloxane (dialkylsiloxxane), carboxamide, carbonate, carboxymethyl, carbamate, carboxylate ester, thioether, ethylene oxide linker, sulfide,sulfonate, sulfonamide, sulfonate ester, thioformacetal (3'-S-CH_2-O-5'), formacetal (3 '-O-CH_2-O-5'), oxime, methyleneimino, methykenecarbonylamino, methylenemethylimino (MMI, 3'-CH_2-N(CH_3)-O-5'), methylenehydrazo, methylenedimethylhydrazo, methyleneoxymethylimino, ethers (C3'-O-C5'), thioethers (C3'-S-C5'), thioacetamido (C3'-N(H)-C(=O)-CH_2-S-C5', C3'-O-P(O)-O-SS-C5', C3'-CH_2-NH-NH-C5', 3'-NHP(O)(OCH_3)-O-5' and 3'-NHP(O)(OCH_3)-O-5' and nonionic linkages containing mixed N, O, S

and CH_2 component parts. See for example, Carbohydrate Modifications in Antisense Research; Y.S. Sanghvi and P.D. Cook Eds. ACS Symposium Series 580; Chapters 3 and 4, (pp. 40-65). Preferred embodiments include methylenemethylimino (MMI),methylenecarbonylamino, amides,carbamate and ethylene oxide linker.

One skilled in the art is well aware that in certain instances replacement of a non-bridging oxygen can lead to enhanced cleavage of the intersugar linkage by the neighboring 2'-OH, thus in many instances, a modification of a non-bridging oxygen can necessitate modification of 2'-OH, *e.g.*, a modification that does not participate in cleavage of the neighboring intersugar linkage, *e.g.*, arabinose sugar, 2'-O-alkyl, 2'-F, LNA and ENA.

Preferred non-phosphodiester intersugar linkages include phosphorothioates, phosphorothioates with an at least 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80% , 90% 95% or more enantiomeric excess of Sp isomer, phosphorothioates with an at least 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80% , 90% 95% or more enantiomeric excess of Rp isomer, phosphorodithioates, phsophotriesters, aminoalkylphosphotrioesters, alkyl-phosphonaters (*e.g.*, methyl-phosphonate), selenophosphates, phosphoramidates (*e.g.*, N-alkylphosphoramidate), and boranophosphonates.

In some embodiments, the dsRNA agent of the invention comprises at least one (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or more and upto including all) modified or nonphosphodiester linkages. In some embodiments, the dsRNA agent of the invention comprises at least one (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or more and upto including all) phosphorothioate linkages.

The dsRNA agent of the inventions can also be constructed wherein the phosphate linker and the sugar are replaced by nuclease resistant nucleoside or nucleotide surrogates. While not wishing to be bound by theory, it is believed that the absence of a repetitively charged backbone diminishes binding to proteins that recognize polyanions (*e.g.* nucleases). Again, while not wishing to be bound by theory, it can be desirable in some embodiment, to introduce alterations in which the bases are tethered by a neutral surrogate backbone. Examples include the morpholino, cyclobutyl, pyrrolidine, peptide nucleic acid (PNA), aminoethylglycyl PNA (*aeg*PNA) and backnone-extended pyrrolidine PNA (*bep*PNA) nucleoside surrogates. A preferred surrogate is a PNA surrogate.

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

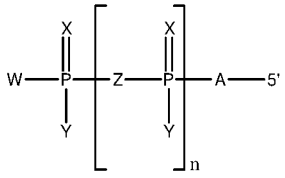
D. Terminal Modifications

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

In some embodiments, the 5'-end of the antisense strand of the dsRNA agent does not contain a 5'-vinyl phosphonate (VP).

Ends of the iRNA agent of the invention can be modified. Such modifications can be at one end or both ends. For example, the 3′ and/or 5′ ends of an iRNA can be conjugated to other functional molecular entities such as labeling moieties, *e.g.*, fluorophores (*e.g.*, pyrene, TAMRA, fluorescein, Cy3 or Cy5 dyes) or protecting groups (based *e.g.*, on sulfur, silicon, boron or ester). The functional molecular entities can be attached to the sugar through a phosphate group and/or a linker. The terminal atom of the linker can connect to or replace the linking atom of the phosphate group or the C-3′ or C-5′ O, N, S or C group of the sugar. Alternatively, the linker can connect to or replace the terminal atom of a nucleotide surrogate (*e.g.*, PNAs).

When a linker/phosphate-functional molecular entity-linker/phosphate array is interposed between two strands of a double stranded oligomeric compound, this array can substitute for a hairpin loop in a hairpin-type oligomeric compound.

Terminal modifications useful for modulating activity include modification of the 5' end of iRNAs with phosphate or phosphate analogs. In certain embodiments, the 5'end of an iRNA is phosphorylated or includes a phosphoryl analog. Exemplary 5'-phosphate modifications include those which are compatible with RISC mediated gene silencing. Modifications at the 5'-terminal end can also be useful in stimulating or inhibiting the immune system of a subject. In some embodiments, the 5'-end of the oligomeric compound comprises the modification , wherein W, X and Y are each independently selected from the group consisting of O, OR (R is hydrogen, alkyl, aryl), S, Se, BR_3 (R is hydrogen, alkyl, aryl), BH_3^-, C (*i.e.* an alkyl group, an aryl group, etc…), H, NR_2 (R is hydrogen, alkyl, aryl), or OR (R is hydrogen, alkyl or aryl); A and Z are each independently for each occurrence absent, O, S, CH_2, NR (R is hydrogen, alkyl, aryl), or optionally substituted alkylene, wherein backbone of the alkylene can comprise one or more of O, S, SS and NR (R is hydrogen, alkyl, aryl) internally and/or at the end; and n is 0-2. In some embodiments, n is 1 or 2. It is understood that A is replacing the oxygen linked to 5' carbon of sugar. When n is 0, W and Y together with the P to which they are attached can form an optionally substituted 5-8 membered heterocyclic, wherein W an Y are each independently O, S, NR' or alkylene. Preferably the heterocyclic is substituted with an aryl or heteroaryl. In some embodiments, one or both hydrogen on C5' of the 5'- terminal nucleotides are replaced with a halogen, *e.g.*, F.

Exemplary 5'-modifications include, but are not limited to, 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'-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'); 5'-alpha-thiotriphosphate; 5'-beta-thiotriphosphate; 5'-gamma-thiotriphosphate; 5'-phosphoramidates ($(HO)_2(O)P$-NH-5', $(HO)(NH_2)(O)P$-O-5'). Other 5'-modification include 5'-alkylphosphonates

(R(OH)(O)P-O-5', R=alkyl, *e.g.*, methyl, ethyl, isopropyl, propyl, etc…), 5'-alkyletherphosphonates (R(OH)(O)P-O-5', R=alkylether, *e.g.*, methoxymethyl (CH_2OMe), ethoxymethyl, etc…). Other exemplary 5'-modifications include where Z is optionally substituted alkyl at least once, *e.g.*, $((HO)_2(X)P\text{-}O[\text{-}(CH_2)_a\text{-}O\text{-}P(X)(OH)\text{-}O]_b\text{-}5'$, $((HO)_2(X)P\text{-}O[\text{-}(CH_2)_a\text{-}P(X)(OH)\text{-}O]_b\text{-}5'$, $((HO)2(X)P\text{-}[\text{-}(CH_2)_a\text{-}O\text{-}P(X)(OH)\text{-}O]_b\text{-}5'$; dialkyl terminal phosphates and phosphate mimics: $HO[\text{-}(CH_2)_a\text{-}O\text{-}P(X)(OH)\text{-}O]_b\text{-}5'$, $H_2N[\text{-}(CH_2)_a\text{-}O\text{-}P(X)(OH)\text{-}O]_b\text{-}5'$, $H[\text{-}(CH_2)_a\text{-}O\text{-}P(X)(OH)\text{-}O]_b\text{-}5'$, $Me_2N[\text{-}(CH_2)_a\text{-}O\text{-}P(X)(OH)\text{-}O]_b\text{-}5'$, $HO[\text{-}(CH_2)_a\text{-}P(X)(OH)\text{-}O]_b\text{-}5'$, $H_2N[\text{-}(CH_2)_a\text{-}P(X)(OH)\text{-}O]_b\text{-}5'$, $H[\text{-}(CH_2)_a\text{-}P(X)(OH)\text{-}O]_b\text{-}5'$, $Me_2N[\text{-}(CH_2)_a\text{-}P(X)(OH)\text{-}O]_b\text{-}5'$, wherein a and b are each independently 1-10. Other embodiments, include replacement of oxygen and/or sulfur with BH_3, BH_3^- and/or Se.

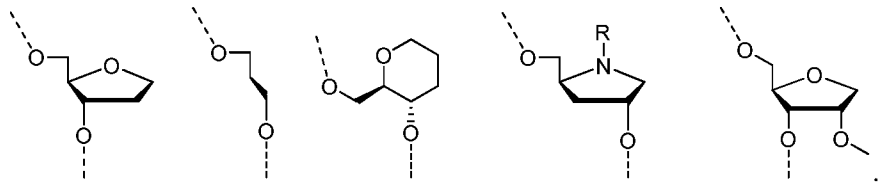
Terminal modifications can also be useful for monitoring distribution, and in such cases the preferred groups to be added include fluorophores, *e.g.*, fluorescein or an Alexa dye, *e.g.*, Alexa 488. Terminal modifications can also be useful for enhancing uptake, useful modifications for this include targeting ligands. Terminal modifications can also be useful for cross-linking an oligonucleotide to another moiety; modifications useful for this include mitomycin C, psoralen, and derivatives thereof.

E. Thermally Destabilizing Modifications

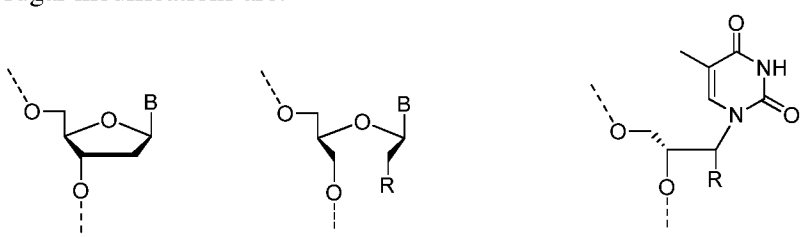
The compounds of the invention, such as iRNAs or dsRNA agents, can be optimized for RNA interference by increasing the propensity of the iRNA duplex to disassociate or melt (decreasing the free energy of duplex association) by introducing a thermally destabilizing modification in the sense strand at a site opposite to the seed region of the antisense strand (*i.e.*, at positions 2-8 of the 5'-end of the antisense strand, or at positions 2-9 of the 5'-end of the antisense strand). This modification can increase the propensity of the duplex to disassociate or melt in the seed region of the antisense strand.

The thermally destabilizing modifications can include 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 glycerol nuceltic acid (GNA).

Exemplified abasic modifications are:



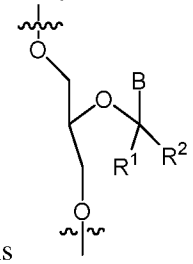
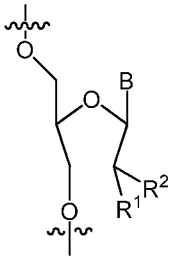
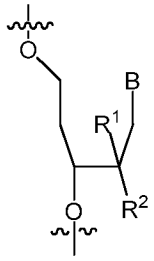
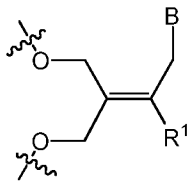
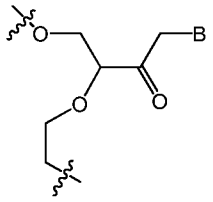
Exemplified sugar modifications are:



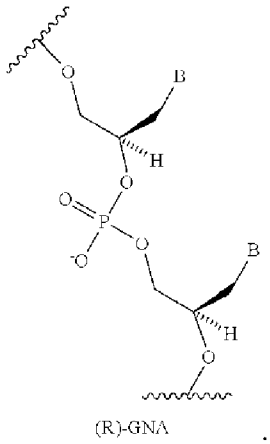
2'-deoxy

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

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

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 and/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 .

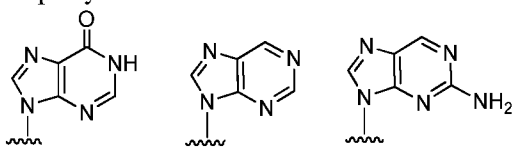
The thermally destabilizing modification can be mismatches (*i.e.*, noncomplementary base pairs) between the thermally destabilizing nucleotide and the opposing nucleotide in the opposite strand within the dsRNA duplex. Exemplary mismatch basepairs include G:G, G:A, G:U, G:T, A:A, A:C, C:C, C:U, C:T, 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 compounds of the invention, such as siRNA or iRNA agent, 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.

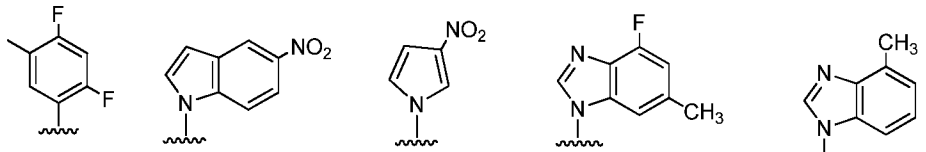
More examples of abasic nucleotide, acyclic nucleotide modifications (including UNA and GNA), and mismatch modifications have been described in detail in WO 2011/133876, which is herein incorporated by reference in its entirety.

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.

Nucleobase modifications with impaired or completely abolished capability to form hydrogen bonds with bases in the opposite strand 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:

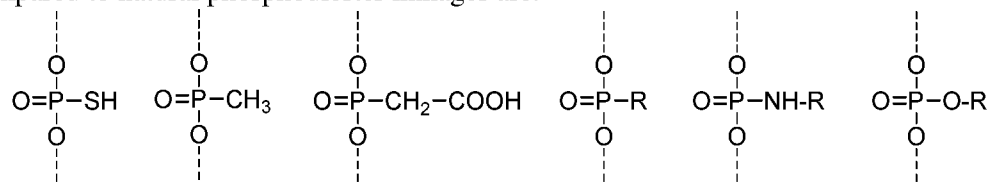


inosine nebularine 2-aminopurine



2,4-difluorotoluene 5-nitroindole 3-nitropyrrole 4-Fluoro-6-methylbenzimidazole 4-Methylbenzimidazole

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



R = alkyl

In some embodiments, compounds of the invention 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, compounds of the invention can comprise L sugars (*e.g.*, L ribose, L-arabinose with 2'-H, 2'-OH and 2'-OMe). For example, these L sugar 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 one embodimennt the iRNA agent of the invention is conjugated to a ligand via a carrier, wherein the carrier can be cyclic group or acyclic group; preferably, the cyclic group is selected from

pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, [1,3]dioxolane, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl, tetrahydrofuryl and and decalin; preferably, the acyclic group is selected from serinol backbone or diethanolamine backbone.

In some embodoments, at least one strand of the iRNA agent of the invention disclosed herein is 5' phosphorylated or includes 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)(NH2)(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 (MeOCH2-), ethoxymethyl, etc., *e.g.* RP(OH)(O)-O-5'-).

IV. Modified RNAi agents of the Invention Comprising 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 U.S. Patent Nos. 9,796,974 and 10,668,170, and U.S. Patent Publication Nos. 2014/288158, 2018/008724, 2019/038768, and 2020/353097, the entire contents of each of which are incorporated herein by reference. As shown therein and in PCT Publication No. WO 2013/074974 (the entire contents of which are incorporated by reference), one or more motifs of three identical modifications on three consecutive nucleotides may be introduced 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 modified with a (S)-glycol nucleic acid (GNA) modification, for instance on one or more residues of the antisense strand.

In one embodiment, the iRNA agent of the invention is a double ended bluntmer of 19 nt in length, wherein the sense strand contains at least one motif of three 2'-F modifications on three consecutive nucleotides at positions 7,8,9 from the 5'end. The antisense strand contains at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at positions 11,12,13 from the 5'end.

In one embodiment, the iRNA agent of the invention is a double ended bluntmer of 20 nt in length, wherein the sense strand contains at least one motif of three 2'-F modifications on three consecutive nucleotides at positions 8,9,10 from the 5'end. The antisense strand contains at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at positions 11,12,13 from the 5'end.

In one embodiment, the iRNA agent of the invention is a double ended bluntmer of 21 nt in length, wherein the sense strand contains at least one motif of three 2'-F modifications on three consecutive nucleotides at positions 9,10,11 from the 5'end. The antisense strand contains at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at positions 11,12,13 from the 5'end.

In one embodiment, the iRNA agent of the invention comprises a 21 nucleotides (nt) sense strand and a 23 nucleotides (nt) antisense, wherein the sense strand contains at least one motif of three 2'-F modifications on three consecutive nucleotides at positions 9,10,11 from the 5'end; the antisense strand contains at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at positions 11,12,13 from the 5'end, wherein one end of the iRNA is blunt, while the other end is comprises a 2 nt overhang. Preferably, the 2 nt overhang is at the 3'-end of the antisense. Optionally, the iRNA agent further comprises a ligand (*e.g.*, $GalNAc_3$).

In one embodiment, the iRNA agent of the invention comprises a sense and antisense strands, wherein: the sense strand is 25-30 nucleotide residues in length, wherein starting from the 5' terminal nucleotide (position 1) positions 1 to 23 of said first strand comprise at least 8 ribonucleotides; antisense strand is 36-66 nucleotide residues in length and, starting from the 3' terminal nucleotide, comprises at least 8 ribonucleotides in the positions paired with positions 1- 23 of sense strand to form a duplex; wherein at least the 3 ' terminal nucleotide of antisense strand is unpaired with sense strand, and up to 6 consecutive 3' terminal nucleotides are unpaired with sense strand, thereby forming a 3' single stranded overhang of 1-6 nucleotides; wherein the 5' terminus of antisense strand comprises from 10-30 consecutive nucleotides which are unpaired with sense strand, thereby forming a 10-30 nucleotide single stranded 5' overhang; wherein at least the sense strand 5' terminal and 3' terminal nucleotides are base paired with nucleotides of antisense strand when sense and antisense strands are aligned for maximum complementarity, thereby forming a substantially duplexed region between sense and antisense strands; and antisense strand is sufficiently complementary to a target RNA along at least 19 ribonucleotides of antisense strand length to reduce target gene expression when said double stranded nucleic acid is introduced into a mammalian cell; and wherein the sense strand contains at least one motif of three 2'-F modifications on three consecutive nucleotides, where at least one of the motifs occurs at or near the cleavage site. The antisense strand contains at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at or near the cleavage site.

In one embodiment, the iRNA agent of the invention comprises a sense and antisense strands, wherein said iRNA agent comprises a first strand having a length which is at least 25 and at most 29 nucleotides and a second strand having a length which is at most 30 nucleotides with at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at position 11,12,13 from

the 5' end; wherein said 3' end of said first strand and said 5' end of said second strand form a blunt end and said second strand is 1-4 nucleotides longer at its 3' end than the first strand, wherein the duplex region region which is at least 25 nucleotides in length, and said second strand is sufficiently complemenatary to a target mRNA along at least 19 nt of said second strand length to reduce target gene expression when said iRNA agent is introduced into a mammalian cell, and wherein dicer cleavage of said iRNA preferentially results in an siRNA comprising said 3' end of said second strand, thereby reducing expression of the target gene in the mammal. Optionally, the iRNA agent further comprises a ligand (*e.g.*, $GalNAc_3$).

In one embodiment, the sense strand of the iRNA agent contains at least one motif of three identical modifications on three consecutive nucleotides, where one of the motifs occurs at the cleavage site in the sense strand. For instance, the sense strand can contain at least one motif of three 2'-F modifications on three consecutive nucleotides within 7-15 positions from the 5'end.

In one embodiment, the antisense strand of the iRNA agent can also contain at least one motif of three identical modifications on three consecutive nucleotides, where one of the motifs occurs at or near the cleavage site in the antisense strand. For instance, the antisense strand can contain at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides within 9-15 positions from the 5'end.

For iRNA agent having a duplex region of 17-23 nt in length, the cleavage site of the antisense strand is typically around the 10, 11 and 12 positions from the 5'-end. Thus the motifs of three identical modifications may occur at the 9, 10, 11 positions; 10, 11, 12 positions; 11, 12, 13 positions; 12, 13, 14 positions; or 13, 14, 15 positions of the antisense strand, the count starting from the 1^{st} nucleotide from the 5'-end of the antisense strand, or, the count starting from the 1^{st} paired nucleotide within the duplex region from the 5'- end of the antisense strand. The cleavage site in the antisense strand may also change according to the length of the duplex region of the iRNA from the 5'-end.

In some embodiments, the iRNA agent comprises a sense strand and antisense strand each having 14 to 30 nucleotides, wherein the sense strand contains at least two motifs of three identical modifications on three consecutive nucleotides, where at least one of the motifs occurs at or near the cleavage site within the strand and at least one of the motifs occurs at another portion of the strand that is separated from the motif at the cleavage site by at least one nucleotide. In one embodiment, the antisense strand also contains at least one motif of three identical modifications on three consecutive nucleotides, where at least one of the motifs occurs at or near the cleavage site within the strand. The modification in the motif occurring at or near the cleavage site in the sense strand is different than the modification in the motif occurring at or near the cleavage site in the antisense strand.

In some embodiments, the iRNA agent comprises a sense strand and antisense strand each having 14 to 30 nucleotides, wherein the sense strand contains at least one motif of three 2'-F modifications on three consecutive nucleotides, where at least one of the motifs occurs at or near the cleavage site in the strand. In one embodiment, the antisense strand also contains at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at or near the cleavage site.

In some embodiments, the iRNA agent comprises a sense strand and antisense strand each having 14 to 30 nucleotides, wherein the sense strand contains at least one motif of three 2'-F modifications on three consecutive nucleotides at positions 9,10,11 from the 5'end, and wherein the antisense strand contains at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at positions 11,12,13 from the 5'end.

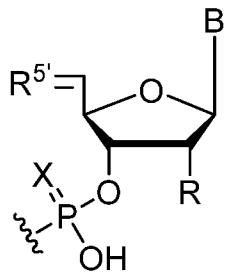
In one embodiment, the iRNA agent of the invention comprises mismatch(es) with the target, within the duplex, or combinations thereof. The mistmatch can occur in the overhang region or the duplex region. The base pair can be ranked on the basis of their propensity to promote dissociation or melting (*e.g.*, 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 one embodiment, the iRNA agent of the invention 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 one embodiment, 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.

In another embodiment, the nucleotide at the 3'-end of the sense strand is deoxythimidine (dT). In another embodiment, the nucleotide at the 3'-end of the antisense strand is deoxythimidine (dT). In one embodiment, there is a short sequence of deoxythimidine nucleotides, for example, two dT nucleotides on the 3'-end of the sense or antisense strand.

In certain embodiments, the compositions and methods of the disclosure include a vinyl phosphonate (VP) modification of an RNAi agent as described herein. In exemplary embodiments, a 5'-vinyl phosphonate modified nucleotide of the disclosure has the structure:



wherein X is O or S;

R is hydrogen, hydroxy, fluoro, or C_{1-20}alkoxy (*e.g.*, methoxy or n-hexadecyloxy);

$R^{5'}$ is =C(H)-P(O)$(OH)_2$ and the double bond between the C5' carbon and $R^{5'}$ is in the *E* or *Z* orientation (*e.g.*, *E* orientation); and

B is a nucleobase or a modified nucleobase, optionally where B is adenine, guanine, cytosine, thymine, or uracil.

A vinyl phosphonate 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.

Vinyl phosphate modifications are also contemplated for the compositions and methods of the instant disclosure. An exemplary vinyl phosphate structure includes the preceding structure, where R5' is =C(H)-OP(O)(OH)2 and the double bond between the C5' carbon and R5' is in the E or Z orientation (*e.g.*, E orientation).

In one aspect, the invention relates to a double-stranded RNA (dsRNA) agent for inhibiting the expression of a target gene having reduced off-target effects as described in U.S. Patent Nos. 10,233448, 10,612,024, and 10,612,027, and U.S. Patent Publication Nos. 2017/275626, 2019/241891, 2019/241893, and 2021/017519, the entire contents of each of which are incorporated herein by reference. As exemplified therein, a motif comprising, *e.g.,* a thermally destabilizing nucleotide, *e.g.,* i) a nucleotide that forms a mismatch pair with the opposing nucleotide in the antisense strand, ii) a nucleotide having an abasic modification, and/or iii) a nucleotide having a sugar modification, and placed at a site opposite to the seed region (positions 2-8) may be introduced into the sense strand.

In one embodiment, the dsRNA agent of the invention does not contain any 2'-F modification.

In one embodiment, the sense strand and/or antisense strand of the dsRNA agent comprises one or more blocks of phosphorothioate or methylphosphonate internucleotide linkages. In one example, the sense strand comprises one block of two phosphorothioate or methylphosphonate internucleotide linkages. In one example, the antisense strand comprises two blocks of two phosphorothioate or methylphosphonate internucleotide linkages. For example, the two blocks of phosphorothioate or methylphosphonate internucleotide linkages are separated by 16-18 phosphate internucleotide linkages.

In one embodiment, each of the sense and antisense strands of the dsRNA agent has 15-30 nucleotides. In one example, the sense strand has 19-22 nucleotides, and the antisense strand has 19-25 nucleotides. In another example, the sense strand has 21 nucleotides, and the antisense strand has 23 nucleotides.

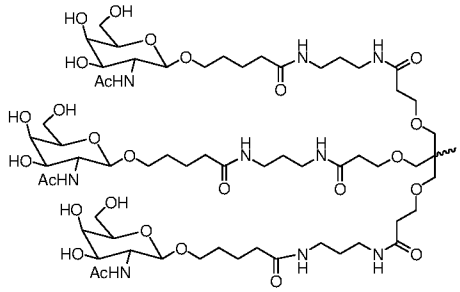
In one embodiment, the nucleotide at position 1 of the 5'-end of the antisense strand in the duplex is selected from the group consisting of A, dA, dU, U, and dT. In one embodiment, at least one of the first, second, and third base pair from the 5'-end of the antisense strand is an AU base pair.

In one embodiment, the antisense strand of the dsRNA agent of the invention is 100% complementary to a target RNA to hybridize thereto and inhibits its expression through RNA

interference. In another embodiment, the antisense strand of the dsRNA agent of the invention is at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55%, or at least 50% complementary to a target RNA.

In one aspect, the invention relates to a dsRNA agent as defined herein capable of inhibiting the expression of a target gene. The dsRNA agent comprises a sense strand and an antisense strand, each strand having 14 to 40 nucleotides. The sense strand contains at least one thermally destabilizing nucleotide, wherein at least one of said thermally destabilizing nucleotide occurs at or near the site that is opposite to the seed region of the antisense strand (*i.e.* at position 2-8 of the 5'-end of the antisense strand, or at positions 2-9 of the 5'-end of the antisense strand). Each of the embodiments and aspects described in this specification relating to the dsRNA represented by formula (I) can also apply to the dsRNA containing the thermally destabilizing nucleotide.

The thermally destabilizing nucleotide can occur, for example, between positions 14-17 of the 5'-end of the sense strand when the sense strand is 21 nucleotides in length. The antisense strand contains at least two modified nucleic acids that are smaller than a sterically demanding 2'-OMe modification. Preferably, the two modified nucleic acids that are smaller than a sterically demanding 2'-OMe are separated by 11 nucleotides in length. For example, the two modified nucleic acids are at positions 2 and 14 of the 5'end of the antisense strand.

In one embodiment, the dsRNA agent further comprises at least one ASGPR ligand. For example, the ASGPR ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker, such as:  . In one example, the ASGPR ligand is attached to the 3' end of the sense strand.

For example, the dsRNA agent as defined herein can comprise i) a phosphorus-containing group at the 5'-end of the sense strand or antisense strand; ii) with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end of the sense strand), 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 of the antisense strand); and iii) a ligand, such as a ASGPR ligand (*e.g.*, one or more GalNAc derivatives) at 5'-end or 3'-end of the sense strand or antisense strand. For instance, the ligand may be at the 3'-end of the sense strand.

In a particular embodiment, the dsRNA agents of the present invention comprise:

(a) a sense strand having:

(i) a length of 21 nucleotides;

(ii) optionally an ASGPR ligand attached to the 3'-end, wherein said ASGPR ligand comprises three GalNAc derivatives attached through a trivalent branched linker; and

(iii) 2'-F modifications at positions 1, 3, 5, 7, 9 to 11, 13, 17, 19, and 21, and 2'-OMe modifications at positions 2, 4, 6, 8, 12, 14 to 16, 18, and 20 (counting from the 5' end); and

(b) an antisense strand having:

(i) a length of 23 nucleotides;

(ii) 2'-OMe modifications at positions 1, 3, 5, 9, 11 to 13, 15, 17, 19, 21, and 23, and 2'F modifications at positions 2, 4, 6 to 8, 10, 14, 16, 18, 20, and 22 (counting from the 5' end); and

(iii) phosphorothioate internucleotide linkages between nucleotide positions 21 and 22, and between nucleotide positions 22 and 23 (counting from the 5' end);

wherein the dsRNA agents have a two nucleotide overhang at the 3'-end of the antisense strand, and a blunt end at the 5'-end of the antisense strand.

In another particular embodiment, the dsRNA agents of the present invention comprise:

(a) a sense strand having:

(i) a length of 21 nucleotides;

(ii) optionally an ASGPR ligand attached to the 3'-end, wherein said ASGPR ligand comprises three GalNAc derivatives attached through a trivalent branched linker;

(iii) 2'-F modifications at positions 1, 3, 5, 7, 9 to 11, 13, 15, 17, 19, and 21, and 2'-OMe modifications at positions 2, 4, 6, 8, 12, 14, 16, 18, and 20 (counting from the 5' end); and

(iv) phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, and between nucleotide positions 2 and 3 (counting from the 5' end);

and

(b) an antisense strand having:

(i) a length of 23 nucleotides;

(ii) 2'-OMe modifications at positions 1, 3, 5, 7, 9, 11 to 13, 15, 17, 19, and 21 to 23, and 2'F modifications at positions 2, 4, 6, 8, 10, 14, 16, 18, and 20 (counting from the 5' end); and

(iii) phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, between nucleotide positions 2 and 3, between nucleotide positions 21 and 22, and between nucleotide positions 22 and 23 (counting from the 5' end);

wherein the dsRNA agents have a two nucleotide overhang at the 3'-end of the antisense strand, and a blunt end at the 5'-end of the antisense strand.

In another particular embodiment, the dsRNA agents of the present invention comprise:

(a) a sense strand having:

(i) a length of 21 nucleotides;

(ii) optionally an ASGPR ligand attached to the 3'-end, wherein said ASGPR ligand comprises three GalNAc derivatives attached through a trivalent branched linker;

(iii) 2'-OMe modifications at positions 1 to 6, 8, 10, and 12 to 21, 2'-F modifications at positions 7, and 9, and a desoxy-nucleotide (*e.g.* dT) at position 11 (counting from the 5' end); and

(iv) phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, and between nucleotide positions 2 and 3 (counting from the 5' end);

and

(b) an antisense strand having:

(i) a length of 23 nucleotides;

(ii) 2'-OMe modifications at positions 1, 3, 7, 9, 11, 13, 15, 17, and 19 to 23, and 2'-F modifications at positions 2, 4 to 6, 8, 10, 12, 14, 16, and 18 (counting from the 5' end); and

(iii) phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, between nucleotide positions 2 and 3, between nucleotide positions 21 and 22, and between nucleotide positions 22 and 23 (counting from the 5' end);

wherein the dsRNA agents have a two nucleotide overhang at the 3'-end of the antisense strand, and a blunt end at the 5'-end of the antisense strand.

In another particular embodiment, the dsRNA agents of the present invention comprise:

(a) a sense strand having:

(i) a length of 21 nucleotides;

(ii) optionally an ASGPR ligand attached to the 3'-end, wherein said ASGPR ligand comprises three GalNAc derivatives attached through a trivalent branched linker;

(iii) 2'-OMe modifications at positions 1 to 6, 8, 10, 12, 14, and 16 to 21, and 2'-F modifications at positions 7, 9, 11, 13, and 15; and

(iv) phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, and between nucleotide positions 2 and 3 (counting from the 5' end);

and

(b) an antisense strand having:

(i) a length of 23 nucleotides;

(ii) 2'-OMe modifications at positions 1, 5, 7, 9, 11, 13, 15, 17, 19, and 21 to 23, and 2'-F modifications at positions 2 to 4, 6, 8, 10, 12, 14, 16, 18, and 20 (counting from the 5' end); and

(iii) phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, between nucleotide positions 2 and 3, between nucleotide positions 21 and 22, and between nucleotide positions 22 and 23 (counting from the 5' end);

wherein the dsRNA agents have a two nucleotide overhang at the 3'-end of the antisense strand, and a blunt end at the 5'-end of the antisense strand.

In another particular embodiment, the dsRNA agents of the present invention comprise:

(a) a sense strand having:

(i) a length of 21 nucleotides;

(ii) optionally an ASGPR ligand attached to the 3'-end, wherein said ASGPR ligand comprises three GalNAc derivatives attached through a trivalent branched linker;

(iii) 2'-OMe modifications at positions 1 to 9, and 12 to 21, and 2'-F modifications at positions 10, and 11; and

(iv) phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, and between nucleotide positions 2 and 3 (counting from the 5' end);

and

(b) an antisense strand having:

(i) a length of 23 nucleotides;

(ii) 2'-OMe modifications at positions 1, 3, 5, 7, 9, 11 to 13, 15, 17, 19, and 21 to 23, and 2'-F modifications at positions 2, 4, 6, 8, 10, 14, 16, 18, and 20 (counting from the 5' end); and

(iii) phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, between nucleotide positions 2 and 3, between nucleotide positions 21 and 22, and between nucleotide positions 22 and 23 (counting from the 5' end);

wherein the dsRNA agents have a two nucleotide overhang at the 3'-end of the antisense strand, and a blunt end at the 5'-end of the antisense strand.

In another particular embodiment, the dsRNA agents of the present invention comprise:

(a) a sense strand having:

(i) a length of 21 nucleotides;

(ii) optionally an ASGPR ligand attached to the 3'-end, wherein said ASGPR ligand comprises three GalNAc derivatives attached through a trivalent branched linker;

(iii) 2'-F modifications at positions 1, 3, 5, 7, 9 to 11, and 13, and 2'-OMe modifications at positions 2, 4, 6, 8, 12, and 14 to 21; and

(iv) phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, and between nucleotide positions 2 and 3 (counting from the 5' end);

and

(b) an antisense strand having:

(i) a length of 23 nucleotides;

(ii) 2'-OMe modifications at positions 1, 3, 5 to 7, 9, 11 to 13, 15, 17 to 19, and 21 to 23, and 2'-F modifications at positions 2, 4, 8, 10, 14, 16, and 20 (counting from the 5' end); and

(iii) phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, between nucleotide positions 2 and 3, between nucleotide positions 21 and 22, and between nucleotide positions 22 and 23 (counting from the 5' end);

wherein the dsRNA agents have a two nucleotide overhang at the 3'-end of the antisense strand, and a blunt end at the 5'-end of the antisense strand.

In another particular embodiment, the dsRNA agents of the present invention comprise:

(a) a sense strand having:

(i) a length of 21 nucleotides;

(ii) optionally an ASGPR ligand attached to the 3'-end, wherein said ASGPR ligand comprises three GalNAc derivatives attached through a trivalent branched linker;

(iii) 2'-OMe modifications at positions 1, 2, 4, 6, 8, 12, 14, 15, 17, and 19 to 21, and 2'-F modifications at positions 3, 5, 7, 9 to 11, 13, 16, and 18; and

(iv) phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, and between nucleotide positions 2 and 3 (counting from the 5' end);

and

(b) an antisense strand having:

(i) a length of 25 nucleotides;

(ii) 2'-OMe modifications at positions 1, 4, 6, 7, 9, 11 to 13, 15, 17, and 19 to 23, 2'-F modifications at positions 2, 3, 5, 8, 10, 14, 16, and 18, and desoxy-nucleotides (*e.g.* dT) at positions 24 and 25 (counting from the 5' end); and

(iii) phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, between nucleotide positions 2 and 3, between nucleotide positions 21 and 22, and between nucleotide positions 22 and 23 (counting from the 5' end);

wherein the dsRNA agents have a four nucleotide overhang at the 3'-end of the antisense strand, and a blunt end at the 5'-end of the antisense strand.

In another particular embodiment, the dsRNA agents of the present invention comprise:

(a) a sense strand having:

(i) a length of 21 nucleotides;

(ii) optionally an ASGPR ligand attached to the 3'-end, wherein said ASGPR ligand comprises three GalNAc derivatives attached through a trivalent branched linker;

(iii) 2'-OMe modifications at positions 1 to 6, 8, and 12 to 21, and 2'-F modifications at positions 7, and 9 to 11; and

(iv) phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, and between nucleotide positions 2 and 3 (counting from the 5' end);

and

(b) an antisense strand having:

(i) a length of 23 nucleotides;

(ii) 2'-OMe modifications at positions 1, 3 to 5, 7, 8, 10 to 13, 15, and 17 to 23, and 2'-F modifications at positions 2, 6, 9, 14, and 16 (counting from the 5' end); and

(iii) phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, between nucleotide positions 2 and 3, between nucleotide positions 21 and 22, and between nucleotide positions 22 and 23 (counting from the 5' end);

wherein the dsRNA agents have a two nucleotide overhang at the 3'-end of the antisense strand, and a blunt end at the 5'-end of the antisense strand.

In another particular embodiment, the dsRNA agents of the present invention comprise:

(a) a sense strand having:

(i) a length of 21 nucleotides;

(ii) optionally an ASGPR ligand attached to the 3'-end, wherein said ASGPR ligand comprises three GalNAc derivatives attached through a trivalent branched linker;

(iii) 2'-OMe modifications at positions 1 to 6, 8, and 12 to 21, and 2'-F modifications at positions 7, and 9 to 11; and

(iv) phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, and between nucleotide positions 2 and 3 (counting from the 5' end);

and

(b) an antisense strand having:

(i) a length of 23 nucleotides;

(ii) 2'-OMe modifications at positions 1, 3 to 5, 7, 10 to 13, 15, and 17 to 23, and 2'-F modifications at positions 2, 6, 8, 9, 14, and 16 (counting from the 5' end); and

(iii) phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, between nucleotide positions 2 and 3, between nucleotide positions 21 and 22, and between nucleotide positions 22 and 23 (counting from the 5' end);

wherein the dsRNA agents have a two nucleotide overhang at the 3'-end of the antisense strand, and a blunt end at the 5'-end of the antisense strand.

In another particular embodiment, the dsRNA agents of the present invention comprise:

(a) a sense strand having:

(i) a length of 19 nucleotides;

(ii) optionally an ASGPR ligand attached to the 3'-end, wherein said ASGPR ligand comprises three GalNAc derivatives attached through a trivalent branched linker;

(iii) 2'-OMe modifications at positions 1 to 4, 6, and 10 to 19, and 2'-F modifications at positions 5, and 7 to 9; and

(iv) phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, and between nucleotide positions 2 and 3 (counting from the 5' end);

and

(b) an antisense strand having:

(i) a length of 21 nucleotides;

(ii) 2'-OMe modifications at positions 1, 3 to 5, 7, 10 to 13, 15, and 17 to 21, and 2'-F modifications at positions 2, 6, 8, 9, 14, and 16 (counting from the 5' end); and

(iii) phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, between nucleotide positions 2 and 3, between nucleotide positions 19 and 20, and between nucleotide positions 20 and 21 (counting from the 5' end);

wherein the dsRNA agents have a two nucleotide overhang at the 3'-end of the antisense strand, and a blunt end at the 5'-end of the antisense strand.

In one embodiment, the dsRNA agents of the present invention comprise:

(a) a sense strand having:

(i) a length of 18-23 nucleotides;

(ii) three consecutive 2'-F modifications at positions 7-15; and

(b) an antisense strand having:

(i) a length of 18-23 nucleotides;

(ii) at least 2'-F modifications anywhere on the strand; and

(iii) at least two phosphorothioate internucleotide linkages at the first five nucleotides (counting from the 5' end);

wherein the dsRNA agents have one or more lipophilic moieties conjugated to one or more positions on at least one strand; and either have two nucleotides overhang at the 3'-end of the antisense strand, and a blunt end at the 5'-end of the antisense strand; or blunt end both ends of the duplex.

In one embodiment, the dsRNA agents of the present invention comprise:

(a) a sense strand having:

(i) a length of 18-23 nucleotides;

(ii) less than four 2'-F modifications;

(b) an antisense strand having:

(i) a length of 18-23 nucleotides;

(ii) at less than twelve 2'-F modfication; and

(iii) at least two phosphorothioate internucleotide linkages at the first five nucleotides (counting from the 5' end);

wherein the dsRNA agents have one or more lipophilic moieties conjugated to one or more positions on at least one strand; and either have two nucleotides overhang at the 3'-end of the antisense strand, and a blunt end at the 5'-end of the antisense strand; or blunt end both ends of the duplex.

In one embodiment, the dsRNA agents of the present invention comprise:

(a) a sense strand having:

(i) a length of 19-35 nucleotides;

(ii) less than four 2'-F modifications;

(b) an antisense strand having:

(i) a length of 19-35 nucleotides;

(ii) at less than twelve 2'-F modfication; and

(iii) at least two phosphorothioate internucleotide linkages at the first five nucleotides (counting from the 5' end);

wherein the duplex region is between 19 to 25 base pairs (preferably 19, 20, 21 or 22); and wherein the dsRNA agents have one or more lipophilic moieties conjugated to one or more positions on at least one strand; and either have two nucleotides overhang at the 3'-end of the antisense strand, and a blunt end at the 5'-end of the antisense strand; or blunt end both ends of the duplex.

In one embodiment, the dsRNA agents of the present invention comprise a sense strand and antisense strands having a length of 15-30 nucleotides; at least two phosphorothioate internucleotide linkages at the first five nucleotides on the antisense strand (counting from the 5' end); wherein the

duplex region is between 19 to 25 base pairs (preferably 19, 20, 21 or 22); wherein the dsRNA agents have one or more lipophilic moieties conjugated to one or more positions on at least one strand; and wherein the dsRNA agents have less than 20% , less than 15% and less than 10% non-natural nucleotide.

Examples of non-natural nucleotide includes acyclic nucleotides, LNA, HNA, CeNA, 2'-methoxyethyl, , 2'-O-allyl, 2'-C-allyl, 2'-deoxy, 2'-fluoro, 2'-O-N-methylacetamido (2'-O-NMA), a 2'-O-dimethylaminoethoxyethyl (2'-O-DMAEOE), 2'-O-aminopropyl (2'-O-AP), or 2'-ara-F, and others.

In one embodiment, the dsRNA agents of the present invention comprise a sense strand and antisense strands having a length of 15-30 nucleotides; at least two phosphorothioate internucleotide linkages at the first five nucleotides on the antisense strand (counting from the 5' end); wherein the duplex region is between 19 to 25 base pairs (preferably 19, 20, 21 or 22); wherein the dsRNA agents have one or more lipophilic moieties conjugated to one or more positions on at least one strand; and wherein the dsRNA agents have greater than 80% , greater than 85% and greater than 90% natural nucleotide, such as 2'-OH, 2'-deoxy and 2'-OMe are natural nucleotides.

In one embodiment, the dsRNA agents of the present invention comprise a sense strand and antisense strands having a length of 15-30 nucleotides; at least two phosphorothioate internucleotide linkages at the first five nucleotides on the antisense strand (counting from the 5' end); wherein the duplex region is between 19 to 25 base pairs (preferably 19, 20, 21 or 22); wherein the dsRNA agents have one or more lipophilic moieties conjugated to one or more positions on at least one strand; and wherein the dsRNA agents have 100% natural nucleotide, such as 2'-OH, 2'-deoxy and 2'-OMe are natural nucleotides.

Various publications described multimeric siRNA and can all be used with the iRNA of the invention. Such publications include WO2007/091269, US Patent No. 7858769, WO2010/141511, WO2007/117686, WO2009/014887 and WO2011/031520, which are hereby incorporated by reference in their entirety.

In some embodiments, 100%, 95%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35% or 30% of the iRNA agent of the invention is modified.

In some embodiments, each of the sense and antisense strands of the iRNA agent is independently modified with acyclic nucleotides, LNA, HNA, CeNA, 2'-methoxyethyl, 2'- O-methyl, 2'-O-allyl, 2'-C-allyl, 2'-deoxy, 2'-fluoro, 2'-O-N-methylacetamido (2'-O-NMA), a 2'-O-dimethylaminoethoxyethyl (2'-O-DMAEOE), 2'-O-aminopropyl (2'-O-AP), or 2'-ara-F.

In some embodiments, each of the sense and antisense strands of the iRNA agent contains at least two different modifications.

In some embodiments, the dsRNA agent of the invention of the invention does not contain any 2'-F modification.

In some embodiments, the dsRNA agent of the invention contains one, two, three, four, five, six, seven, eight, nine, ten, eleven or twelve 2'-F modification(s). In one example, dsRNA agent of the invention contains nine or ten 2'-F modifications.

The iRNA agent of the invention 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 may contain 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 one embodiment, the iRNA comprises the phosphorothioate or methylphosphonate internucleotide linkage modification in the overhang region. For example, the overhang region may contain 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 paried nucleotide next to the overhang nucleotide. Preferably, these terminal three nucleotides may be at the 3'-end of the antisense strand.

In some embodiments, the sense strand and/or antisense strand of the iRNA agent comprises one or more blocks of phosphorothioate or methylphosphonate internucleotide linkages. In one example, the sense strand comprises one block of two phosphorothioate or methylphosphonate internucleotide linkages. In one example, the antisense strand comprises two blocks of two phosphorothioate or methylphosphonate internucleotide linkages. For example, the two blocks of phosphorothioate or methylphosphonate internucleotide linkages are separated by 16-18 phosphate internucleotide linkages.

In some embodiments, the antisense strand of the iRNA agent of the invention is 100% complementary to a target RNA to hybridize thereto and inhibits its expression through RNA interference. In another embodiment, the antisense strand of the iRNA agent of the invention is at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55%, or at least 50% complementary to a target RNA.

In one aspect, the invention relates to a iRNA agent capable of inhibiting the expression of a target gene. The iRNA agent comprises a sense strand and an antisense strand, each strand having 14 to 40 nucleotides. The sense strand contains at least one thermally destabilizing nucleotide, wherein at at least one said thermally destabilizing nucleotide occurs at or near the site that is opposite to the

seed region of the antisense strand (i.e .at position 2-8 of the 5'-end of the antisense strand, or at positions 2-9 of the 5'-end of the antisense strand). For example, the thermally destabilizing nucleotide occurs between positions 14-17 of the 5'-end of the sense strand when the sense strand is 21 nucleotides in length. The antisense strand contains at least two modified nucleic acids that are smaller than a sterically demanding 2'-OMe modification. Preferably, the two modified nucleic acids that is smaller than a sterically demanding 2'-OMe are separated by 11 nucleotides in length. For example, the two modified nucleic acids are at positions 2 and 14 of the 5'end of the antisense strand.

In some embodiments, the compound of the invention disclosed herein is a miRNA mimic. In one design, miRNA mimics are double stranded molecules (*e.g.*, with a duplex region of between about 16 and about 31 nucleotides in length) and contain one or more sequences that have identity with the mature strand of a given miRNA. Double-stranded miRNA mimics have designs similar to as described above for double-stranded iRNAs. In some embodiments, a miRNA mimic comprises a duplex region of between 16 and 31 nucleotides and one or more of the following chemical modification patterns: the sense strand contains 2'-O-methyl modifications of nucleotides 1 and 2 (counting from the 5' end of the sense oligonucleotide), and all of the Cs and Us; the antisense strand modifications can comprise 2' F modification of all of the Cs and Us, phosphorylation of the 5' end of the oligonucleotide, and stabilized internucleotide linkages associated with a 2 nucleotide 3 ' overhang.

V. C_{22} Hydrocarbon Chains

As described In U.S. Provisional Application No. 63/255,984, filed on October 15, 2021 (the entire contents of which are incorporated herein by reference), including a C_{22} hydrocarbon chain, *e.g.,* saturated or unsaturated, on one or more internal position(s) of the dsRNA agent increases lipophilicity of the dsRNA agent and provides optimal hydrophobicity for the enhanced *in vivo* delivery of dsRNA to, *e.g.,* muscle tissue and/or adipose tissue.

One way to characterize lipophilicity 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 C_{22} hydrocarbon chain can increase or decrease the partition coefficient (*e.g.*, $\log K_{ow}$) value of the C_{22} hydrocarbon chain.

Alternatively, the hydrophobicity of the dsRNA agent, conjugated to one or more C_{22} hydrocarbon chains, can be measured by its protein binding characteristics. For instance, the unbound fraction in the plasma protein binding assay of the dsRNA agent can be determined to positively correlate to the relative hydrophobicity of the dsRNA agent, which can positively correlate to the silencing activity of the dsRNA agent.

In one embodiment, the plasma protein binding assay determined is an electrophoretic mobility shift assay (EMSA) using human serum albumin protein. The hydrophobicity of the dsRNA agent, measured by fraction of unbound dsRNA 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.

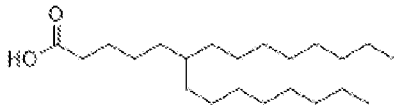
In certain embodiments, the one or more C_{22} hydrocarbon chains is an aliphatic, alicyclic, or polyalicyclic compound is an aliphatic, cyclic such as alicyclic, or polycyclic such as polyalicyclic compound. The hydrocarbon chain may comprise various substituents and/or one or more heteroatoms, such as an oxygen or nitrogen atom.

The one or more C_{22} hydrocarbon chains may be attached to the iRNA agent by any method known in the art, including via a functional grouping already present in the lipophilic moiety or introduced into the iRNA agent, such as a hydroxy group (*e.g.*, —CO—CH_2—OH). The functional groups already present in the C_{22} hydrocarbon chain or introduced into the dsRNA agent include, but are not limited to, hydroxyl, amine, carboxylic acid, sulfonate, phosphate, thiol, azide, and alkyne.

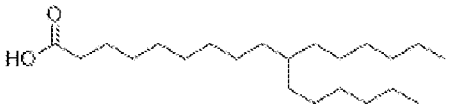
Conjugation of the dsRNA agent and the C_{22} hydrocarbon chain may occur, for example, through formation of an ether or a carboxylic or carbamoyl ester linkage between the hydroxy and an alkyl group R—, an alkanoyl group RCO— or a substituted carbamoyl group RNHCO—. The alkyl group R may be cyclic (*e.g.*, 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 C_{22} hydrocarbon chain is conjugated to the dsRNA 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 one embodiment, the one or more C_{22} hydrocarbon chains is a C_{22} acid, *e.g.*, the C_{22} acid is selected from the group consisting of docosanoic acid, 6-octyltetradecanoic acid, 10-hexylhexadecanoic acid, all-cis-7,10,13,16,19-docosapentaenoic acid, all-cis-4,7,10,13,16,19-docosahexaenoic acid, all-cis-13,16-docosadienoic acid, all-cis-7,10,13,16-docosatetraenoic acid, all-cis-4,7,10,13,16-docosapentaenoic acid, and cis-13-docosenoic acid.

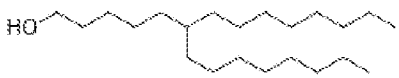


6-octyltetradecanoic acid



10-hexylhexadecanoic acid

In one embodiment, the one or more C_{22} hydrocarbon chains is a C_{22} alcohol, *e.g.* the C_{22} alcohol is selected from the group consisting of 1-docosanol, 6-octyltetradecan-1-ol, 10-hexylhexadecan-1-ol, cis-13-docosen-1-ol, docosan-9-ol, docosan-2-ol, docosan-10-ol, docosan-11-ol, and cis-4,7,10,13,16,19-docosahexanol.



6-octyltetradecan-1-ol



10-hexylhexadecan-1-ol

In one embodiment, the one or more C_{22} hydrocarbon chains is not cis-4,7,10,13,16,19-docosahexanoic acid. In one embodiment, the one or more C_{22} hydrocarbon chains is not cis-4,7,10,13,16,19-docosahexanol. In one embodiment, the one or more C_{22} hydrocarbon chains is not cis-4,7,10,13,16,19-docosahexanoic acid and is not cis-4,7,10,13,16,19-docosahexanol.

In one embodiment, the one or more C_{22} hydrocarbon chains is a C_{22} amide, *e.g.,* the C_{22} amide is selected from the group consisting of (E)-Docos-4-enamide, (E)-Docos-5-enamide, (Z)-Docos-9-enamide, (E)-Docos-11-enamide,12-Docosenamide, (Z)-Docos-13-enamide, (Z)-N-Hydroxy-13-docoseneamide, (E)-Docos-14-enamide, 6-cis-Docosenamide, 14-Docosenamide Docos-11-enamide, (4E,13E)-Docosa-4,13-dienamide, and (5E,13E)-Docosa-5,13-dienamide.

In certain embodiments, more than one C_{22} hydrocarbon chains can be incorporated into the double-strand iRNA agent, particularly when the C_{22} hydrocarbon chains has a low lipophilicity or hydrophobicity. In one embodiment, two or more C_{22} hydrocarbon chains are incorporated into the same strand of the double-strand iRNA agent. In one embodiment, each strand of the double-strand iRNA agent has one or more C_{22} hydrocarbon chains incorporated. In one embodiment, two or more C_{22} hydrocarbon chains are incorporated into the same position (*i.e.*, the same nucleobase, same sugar moiety, or same internucleosidic linkage) of the double-stranded iRNA agent. This can be achieved

by, *e.g.*, conjugating the two or more aturated or unsaturated C_{22} hydrocarbon chains via a carrier, and/or conjugating the two or more C_{22} hydrocarbon chains via a branched linker, and/or conjugating the two or more C_{22} hydrocarbon chains via one or more linkers, with one or more linkers linking the C_{22} hydrocarbon chains consecutively.

The one or more C_{22} hydrocarbon chains may be conjugated to the iRNA agent *via* a direct attachment to the ribosugar of the iRNA agent. Alternatively, the one or more C_{22} hydrocarbon chains may be conjugated to the double-strand iRNA agent *via* a linker or a carrier.

In certain embodiments, the one or more C_{22} hydrocarbon chains may be conjugated to the iRNA agent *via* one or more linkers (tethers).

In one embodiment, the one or more C_{22} hydrocarbon chains is conjugated to the dsRNA 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.

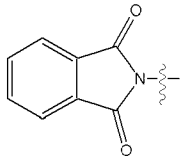
A. Linkers/Tethers

Linkers/Tethers are connected to the one or more C_{22} hydrocarbon chains at a "tethering attachment point (TAP)." Linkers/Tethers may include any C_1-C_{100} carbon-containing moiety, (*e.g.* C_1-C_{75}, C_1-C_{50}, C_1-C_{20}, C_1-C_{10}; C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, or C_{10}), and may have at least one nitrogen atom. In certain embodiments, the nitrogen atom forms part of a terminal amino or amido (NHC(O)-) group on the linker/tether, which may serve as a connection point for the lipophilic moiety. Non-limited examples of linkers/tethers (underlined) include TAP-$(CH_2)_nNH$-; TAP-$C(O)(CH_2)_nNH$-; TAP-$NR''''(CH_2)_nNH$-, TAP-$C(O)$-$(CH_2)_n$-$C(O)$-; TAP-$C(O)$-$(CH_2)_n$-$C(O)O$-; TAP-$C(O)$-O-; TAP-$C(O)$-$(CH_2)_n$-NH-$C(O)$-; TAP-$C(O)$-$(CH_2)_n$-; TAP-$C(O)$-NH-; TAP-$C(O)$-; TAP-$(CH_2)_n$-$C(O)$-; TAP-$(CH_2)_n$-$C(O)O$-; TAP-$(CH_2)_n$-; or TAP-$(CH_2)_n$-NH-$C(O)$-; in which n is 1-20 (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) and R'''' is C_1-C_6 alkyl. Preferably, n is 5, 6, or 11. In other embodiments, the nitrogen may form part of a terminal oxyamino group, *e.g.*, -ONH_2, or hydrazino group, -$NHNH_2$. The linker/tether may optionally be substituted, *e.g.*, with hydroxy, alkoxy, perhaloalkyl, and/or optionally inserted with one or more additional heteroatoms, *e.g.*, N, O, or S. Preferred tethered ligands may include, *e.g.*, TAP-$(CH_2)_nNH(LIGAND)$; TAP-$C(O)(CH_2)_nNH(LIGAND)$; TAP-$NR''''(CH_2)_nNH(LIGAND)$; TAP-$(CH_2)_nONH(LIGAND)$; TAP-$C(O)(CH_2)_nONH(LIGAND)$; TAP-$NR''''(CH_2)_nONH(LIGAND)$; TAP-$(CH_2)_nNHNH_2(LIGAND)$, TAP-$C(O)(CH_2)_nNHNH_2(LIGAND)$; TAP-$NR''''(CH_2)_nNHNH_2(LIGAND)$; TAP-$C(O)$-$(CH_2)_n$-$C(O)(LIGAND)$; TAP-$C(O)$-$(CH_2)_n$-$C(O)O(LIGAND)$; TAP-$C(O)$-$O(LIGAND)$; TAP-$C(O)$-$(CH_2)_n$-$NH$-$C(O)(LIGAND)$; TAP-$C(O)$-$(CH_2)_n(LIGAND)$; TAP-$C(O)$-$NH(LIGAND)$; TAP-$C(O)(LIGAND)$; TAP-$(CH_2)_n$-$C(O)$ $(LIGAND)$; TAP-$(CH_2)_n$-$C(O)O(LIGAND)$; TAP-$(CH_2)_n(LIGAND)$; or TAP-$(CH_2)_n$-NH-$C(O)(LIGAND)$. In some embodiments, amino terminated linkers/tethers (*e.g.*, NH_2, ONH_2, NH_2NH_2) can form an imino bond (*i.e.*, C=N) with the ligand. In some embodiments, amino terminated linkers/tethers (*e.g.*, NH_2, ONH_2, NH_2NH_2) can acylated, *e.g.*, with $C(O)CF_3$.

In some embodiments, the linker/ tether can terminate with a mercapto group (*i.e.*, SH) or an olefin (*e.g.*, $CH=CH_2$). For example, the tether can be TAP-$(CH_2)_n$-SH, TAP-$C(O)(CH_2)_n$SH, TAP-$(CH_2)_n$-$(CH=CH_2)$, or TAP-$C(O)(CH_2)_n(CH=CH_2)$, in which n can be as described elsewhere. The tether may optionally be substituted, *e.g.*, with hydroxy, alkoxy, perhaloalkyl, and/or optionally inserted with one or more additional heteroatoms, *e.g.*, N, O, or S. The double bond can be *cis* or *trans* or *E* or *Z*.

In other embodiments, the linker/tether may include an electrophilic moiety, preferably at the terminal position of the linker/tether. Exemplary electrophilic moieties include, *e.g.*, an aldehyde, alkyl halide, mesylate, tosylate, nosylate, or brosylate, or an activated carboxylic acid ester, *e.g.* an NHS ester, or a pentafluorophenyl ester. Preferred linkers/tethers (underlined) include TAP-$(CH_2)_n$CHO; TAP-$C(O)(CH_2)_n$CHO; or TAP-NR''''$(CH_2)_n$CHO, in which n is 1-6 and R'''' is C_1-C_6 alkyl; or TAP-$(CH_2)_n$C(O)ONHS; TAP-$C(O)(CH_2)_n$C(O)ONHS; or TAP-NR''''$(CH_2)_n$C(O)ONHS, in which n is 1-6 and R'''' is C_1-C_6 alkyl; TAP-$(CH_2)_n$C(O)OC_6F_5; TAP-$C(O)(CH_2)_n$C(O) OC_6F_5; or TAP-NR''''$(CH_2)_n$C(O) OC_6F_5, in which n is 1-11 and R'''' is C_1-C_6 alkyl; or -$(CH_2)_n$$CH_2$LG; TAP-$C(O)(CH_2)_n$$CH_2$LG; or TAP-NR''''$(CH_2)_n$$CH_2$LG, in which n can be as described elsewhere and R'''' is C_1-C_6 alkyl (LG can be a leaving group, *e.g.*, halide, mesylate, tosylate, nosylate, brosylate). Tethering can be carried out by coupling a nucleophilic group of a ligand, *e.g.*, a thiol or amino group with an electrophilic group on the tether.

In other embodiments, it can be desirable for the monomer to include a phthalimido group (K)



at the terminal position of the linker/tether. K .

In other embodiments, other protected amino groups can be at the terminal position of the linker/tether, *e.g.*, alloc, monomethoxy trityl (MMT), trifluoroacetyl, Fmoc, or aryl sulfonyl (*e.g.*, the aryl portion can be *ortho*-nitrophenyl or *ortho, para*-dinitrophenyl).

Any of the linkers/tethers described herein may further include one or more additional linking groups, *e.g.*, -O-$(CH_2)_n$-, -$(CH_2)_n$-SS-, -$(CH_2)_n$-, or -(CH=CH)-.

B. Cleavable linkers/tethers

In some embodiments, at least one of the linkers/tethers can be a redox cleavable linker, an acid cleavable linker, an esterase cleavable linker, a phosphatase cleavable linker, or a peptidase cleavable linker.

In one embodiment, at least one of the linkers/tethers can be a reductively cleavable linker (*e.g.*, a disulfide group).

In one embodiment, at least one of the linkers/tethers can be an acid cleavable linker (*e.g.*, a hydrazone group, an ester group, an acetal group, or a ketal group).

In one embodiment, at least one of the linkers/tethers can be an esterase cleavable linker (*e.g.*, an ester group).

In one embodiment, at least one of the linkers/tethers can be a phosphatase cleavable linker (*e.g.*, a phosphate group).

In one embodiment, at least one of the linkers/tethers can be a peptidase cleavable linker (*e.g.*, a peptide bond).

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 tethers will have a linkage group that is cleaved at a preferred pH, thereby releasing the iRNA agent from a ligand (*e.g.*, a targeting or cell-permeable ligand, such as cholesterol) inside the cell, or into the desired compartment of the cell.

A chemical junction (*e.g.*, a linking group) that links a ligand to an iRNA agent can include a disulfide bond. When the iRNA agent/ligand complex is taken up into the cell by endocytosis, the acidic environment of the endosome will cause the disulfide bond to be cleaved, thereby releasing the iRNA agent from the ligand (Quintana et al., *Pharm Res.* 19:1310-1316, 2002; Patri et al., *Curr. Opin. Curr. Biol.* 6:466-471, 2002). The ligand can be a targeting ligand or a second therapeutic agent that may complement the therapeutic effects of the iRNA agent.

A tether can include a linking group that is cleavable by a particular enzyme. The type of linking group incorporated into a tether can depend on the cell to be targeted by the iRNA agent. For example, an iRNA agent that targets an mRNA in liver cells can be conjugated to a tether that includes an ester group. Liver cells are rich in esterases, and therefore the tether will be cleaved more efficiently in liver cells than in cell types that are not esterase-rich. Cleavage of the tether releases the iRNA agent from a ligand that is attached to the distal end of the tether, thereby potentially enhancing silencing activity of the iRNA agent. Other cell-types rich in esterases include cells of the lung, renal cortex, and testis.

Tethers that contain peptide bonds can be conjugated to iRNA agents target to cell types rich in peptidases, such as liver cells and synoviocytes. For example, an iRNA agent targeted to synoviocytes, such as for the treatment of an inflammatory disease (*e.g.*, rheumatoid arthritis), can be conjugated to a tether containing a peptide bond.

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, *e.g.*, tissue the iRNA agent would be exposed to when administered to a subject. 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 may be useful to make initial evaluations in cell-free or culture conditions and to confirm by further evaluations in whole animals. In preferred embodiments, useful candidate compounds are cleaved at least 2, 4, 10 or 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).

C. Redox Cleavable Linking Groups

One class of cleavable linking groups are redox cleavable linking groups that are 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 a preferred embodiment, candidate compounds are cleaved by at most 10% in the blood. In preferred embodiments, useful candidate compounds are degraded at least 2, 4, 10 or 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.

D. Phosphate-Based Cleavable Linking Groups

Phosphate-based linking groups are 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—. Preferred embodiments 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—. A preferred embodiment is —O—P(O)(OH)—O—. These candidates can be evaluated using methods analogous to those described above.

E. Acid Cleavable Linking Groups

Acid cleavable linking groups are linking groups that are cleaved under acidic conditions. In preferred 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, 5.5, 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, ketals, acetals, esters, and esters of amino acids. Acid cleavable groups can have the general formula —C=NN—, C(O)O, or —OC(O). A preferred embodiment is when 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.

F. Ester-Based Linking Groups

Ester-based linking groups are 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.

G. Peptide-Based Cleaving Groups

Peptide-based linking groups are 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 cleavable linking groups have the general formula —NHCHR^{1}C(O)NHCHR^{2}C(O)—, where R^1 and R^2 are the R groups of the two adjacent amino acids. These candidates can be evaluated using methods analogous to those described above.

H. Biocleavable linkers/tethers

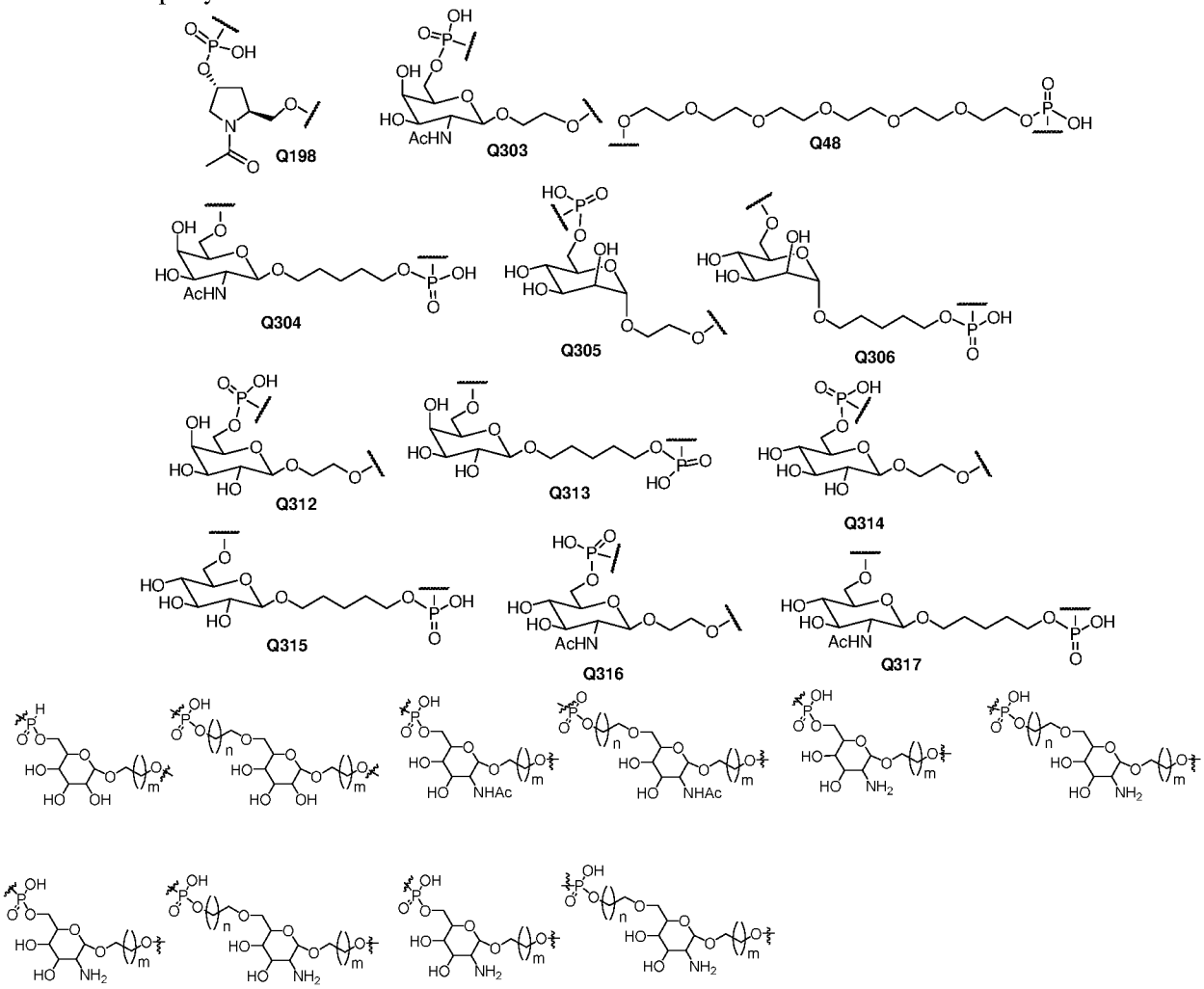
The linkers can also includes biocleavable linkers that are nucleotide and non-nucleotide linkers or combinations thereof that connect two parts of a molecule, for example, one or both strands of two individual siRNA molecules to generate a bis(siRNA). In some embodiments, mere

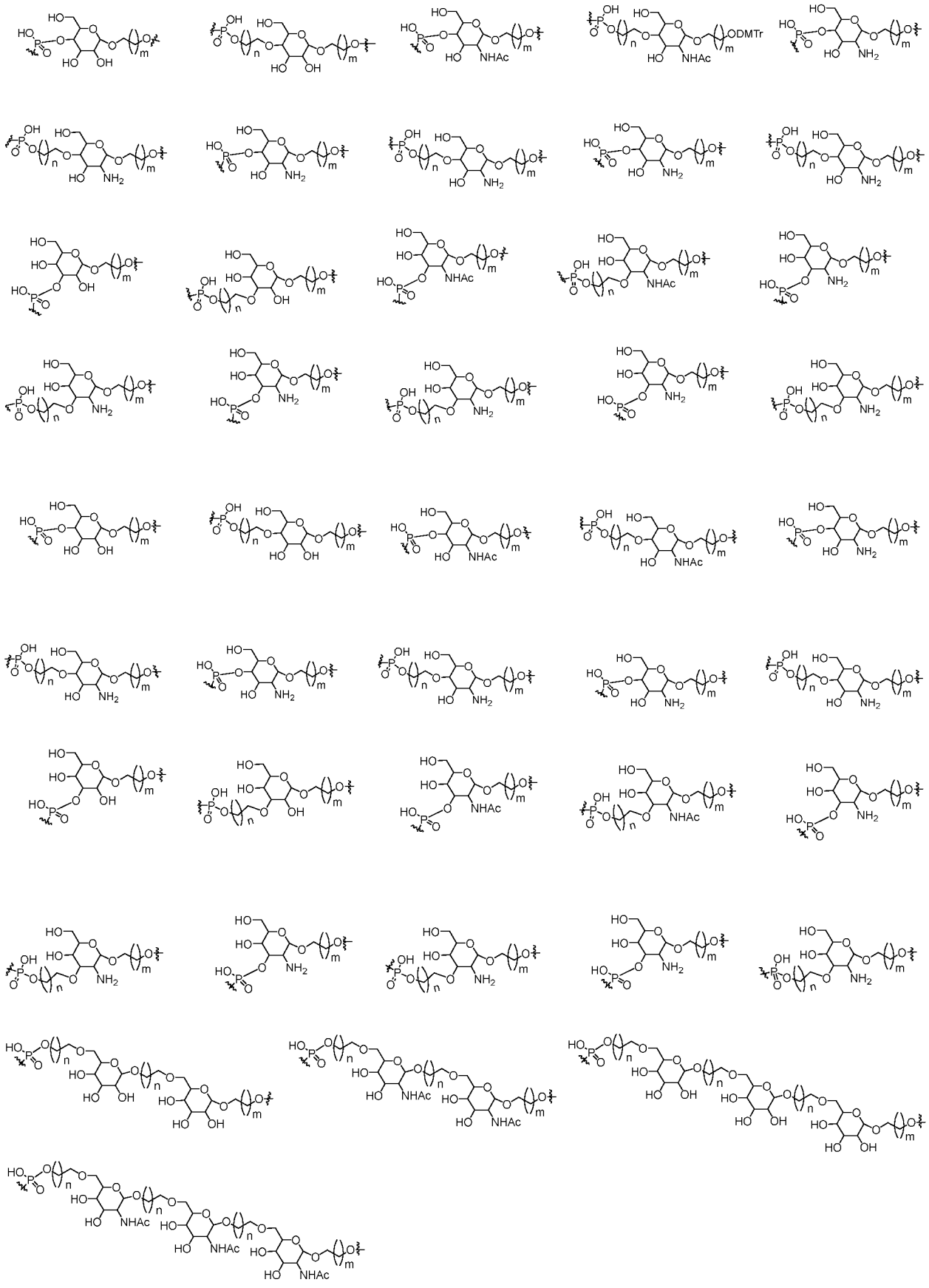
electrostatic or stacking interaction between two individual siRNAs can represent a linker. The non-nucleotide linkers include tethers or linkers derived from monosaccharides, disaccharides, oligosaccharides, and derivatives thereof, aliphatic, alicyclic, hetercyclic, and combinations thereof.

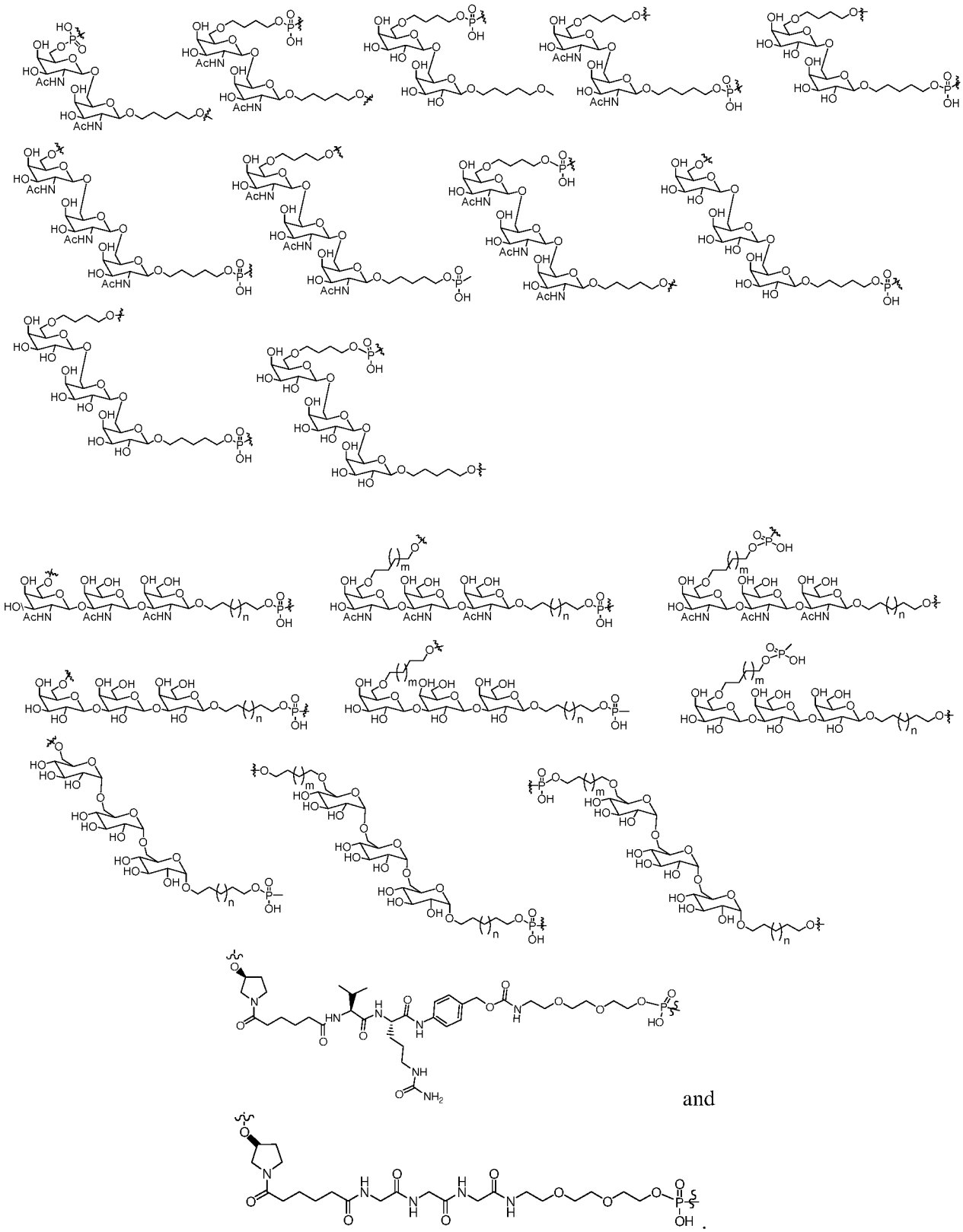
In some embodiments, at least one of the linkers (tethers) is a bio-clevable linker selected from the group consisting of DNA, RNA, disulfide, amide, functionalized monosaccharides or oligosaccharides of galactosamine, glucosamine, glucose, galactose, and mannose, and combinations thereof.

In one embodiment, the bio-cleavable carbohydrate linker may have 1 to 10 saccharide units, which have at least one anomeric linkage capable of connecting two siRNA units. When two or more saccharides are present, these units can be linked via 1-3, 1-4, or 1-6 sugar linkages, or via alkyl chains.

Exemplary bio-cleavable linkers include:







and

More discussion about the biocleavable linkers may be found in PCT application No. PCT/US18/14213, entitled "Endosomal Cleavable Linkers," filed on January 18, 2018, the entire contents of which are incorporated herein by reference.

I. Carriers

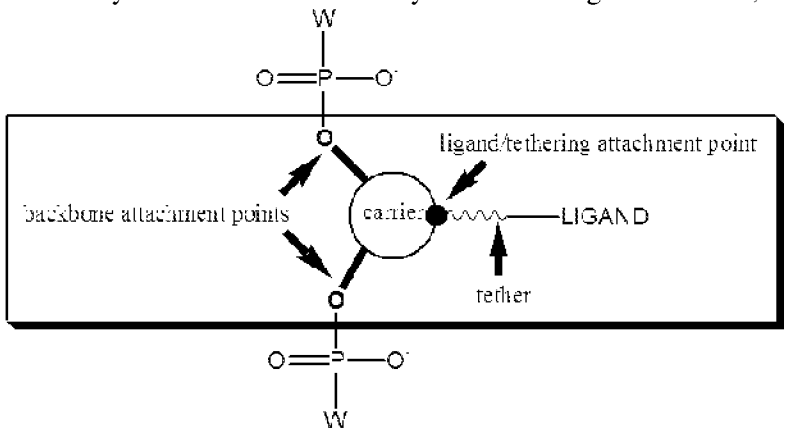
In certain embodiments, the one or more C_{22} hydrocarbon chains is conjugated to the iRNA agent via a carrier that replaces one or more nucleotide(s).

The carrier can be a cyclic group or an acyclic group. In one embodiment, the cyclic group is selected from the group consisting of pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, [1,3]dioxolane, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl, tetrahydrofuryl, and decalin. In one embodiment, the acyclic group is a moiety based on a serinol backbone or a diethanolamine backbone.

In some embodiments, the carrier replaces one or more nucleotide(s) in the internal position(s) of the dsRNA agent.

In other embodiments, the carrier replaces the nucleotides at the terminal end of the sense strand or antisense strand. In one embodiment, the carrier replaces the terminal nucleotide on the 3' end of the sense strand, thereby functioning as an end cap protecting the 3' end of the sense strand. In one embodiment, the carrier is a cyclic group having an amine, for instance, the carrier may be pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, [1,3]dioxolanyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl, tetrahydrofuranyl, or decalinyl.

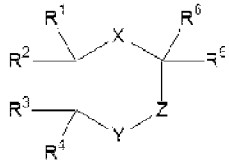
A ribonucleotide subunit in which the ribose sugar of the subunit has been so replaced is referred to herein as a ribose replacement modification subunit (RRMS). The carrier can be a cyclic or acyclic moiety and include two "backbone attachment points" (*e.g.*, hydroxyl groups) and a ligand (*e.g.*, the lipophilic moiety). The one or more C_{22} hydrocarbon chains can be directly attached to the carrier or indirectly attached to the carrier by an intervening linker/tether, as described above.



The ligand-conjugated monomer subunit may be the 5' or 3' terminal subunit of the iRNA molecule, *i.e.*, one of the two "W" groups may be a hydroxyl group, and the other "W" group may be a chain of two or more unmodified or modified ribonucleotides. Alternatively, the ligand-conjugated monomer subunit may occupy an internal position, and both "W" groups may be one or more unmodified or modified ribonucleotides. More than one ligand-conjugated monomer subunit may be present in an iRNA agent.

a. Sugar Replacement-Based Monomers, e.g., Ligand-Conjugated Monomers (Cyclic)

Cyclic sugar replacement-based monomers, *e.g.*, sugar replacement-based ligand-conjugated monomers, are also referred to herein as RRMS monomer compounds. The carriers may have the general formula (**LCM-2**) provided below (in that structure preferred backbone attachment points can be chosen from R^1 or R^2; R^3 or R^4; or R^9 and R^{10} if Y is CR^9R^{10} (two positions are chosen to give two backbone attachment points, *e.g.*, R^1 and R^4, or R^4 and R^9)). Preferred tethering attachment points include R^7; R^5 or R^6 when X is CH_2. The carriers are described below as an entity, which can be incorporated into a strand. Thus, it is understood that the structures also encompass the situations wherein one (in the case of a terminal position) or two (in the case of an internal position) of the attachment points, *e.g.*, R^1 or R^2; R^3 or R^4; or R^9 or R^{10} (when Y is CR^9R^{10}), is connected to the phosphate, or modified phosphate, *e.g.*, sulfur containing, backbone. *E.g.*, one of the above-named R groups can be -CH_2-, wherein one bond is connected to the carrier and one to a backbone atom, *e.g.*, a linking oxygen or a central phosphorus atom.



(**LCM-2**)

wherein:

X is $N(CO)R^7$, NR^7 or CH_2;

Y is NR^8, O, S, CR^9R^{10};

Z is $CR^{11}R^{12}$ or absent;

Each of R^1, R^2, R^3, R^4, R^9, and R^{10} is, independently, H, OR^a, or $(CH_2)_nOR^b$, provided that at least two of R^1, R^2, R^3, R^4, R^9, and R^{10} are OR^a and/or $(CH_2)_nOR^b$;

Each of R^5, R^6, R^{11}, and R^{12} is, independently, a ligand, H, C_1-C_6 alkyl optionally substituted with 1-3 R^{13}, or $C(O)NHR^7$; or R^5 and R^{11} together are C_3-C_8 cycloalkyl optionally substituted with R^{14};

R^7 can be a ligand, *e.g.*, R^7 can be R^d , or R^7 can be a ligand tethered indirectly to the carrier, *e.g.*, through a tethering moiety, *e.g.*, C_1-C_{20} alkyl substituted with NR^cR^d; or C_1-C_{20} alkyl substituted with $NHC(O)R^d$;

R^8 is H or C_1-C_6 alkyl;

R^{13} is hydroxy, C_1-C_4 alkoxy, or halo;

R^{14} is NR^cR^7;

R^{15} is C_1-C_6 alkyl optionally substituted with cyano, or C_2-C_6 alkenyl;

R^{16} is C_1-C_{10} alkyl;

R^{17} is a liquid or solid phase support reagent;

L is $-C(O)(CH_2)_qC(O)-$, or $-C(O)(CH_2)_qS-$;

R^a is a protecting group, *e.g.*, CAr_3; (*e.g.*, a dimethoxytrityl group) or $Si(X^{5'})(X^{5''})(X^{5'''})$ in which $(X^{5'})$,$(X^{5''})$, and $(X^{5'''})$ are as described elsewhere.

R^b is $P(O)(O^-)H$, $P(OR^{15})N(R^{16})_2$ or L-R^{17};

R^c is H or C_1-C_6 alkyl;

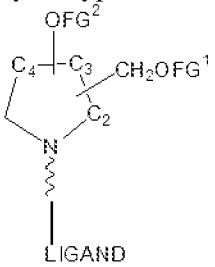
R^d is H or a ligand;

Each Ar is, independently, C_6-C_{10} aryl optionally substituted with C_1-C_4 alkoxy;

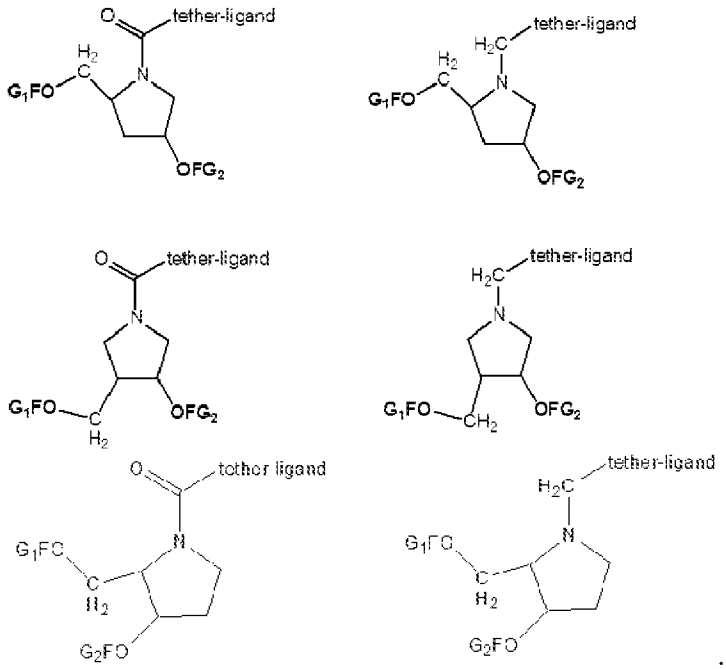
n is 1-4; and q is 0-4.

Exemplary carriers include those in which, *e.g.*, X is $N(CO)R^7$ or NR^7, Y is CR^9R^{10}, and Z is absent; or X is $N(CO)R^7$ or NR^7, Y is CR^9R^{10}, and Z is $CR^{11}R^{12}$; or X is $N(CO)R^7$ or NR^7, Y is NR^8, and Z is $CR^{11}R^{12}$; or X is $N(CO)R^7$ or NR^7, Y is O, and Z is $CR^{11}R^{12}$; or X is CH_2; Y is CR^9R^{10}; Z is $CR^{11}R^{12}$, and R^5 and R^{11} together form C_6 cycloalkyl (**H**, z = 2), or the indane ring system, *e.g.*, X is CH_2; Y is CR^9R^{10}; Z is $CR^{11}R^{12}$, and R^5 and R^{11} together form C_5 cycloalkyl (**H**, z = 1).

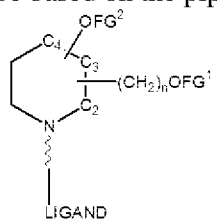
In certain embodiments, the carrier may be based on the pyrroline ring system or the 4-hydroxyproline ring system, *e.g.*, X is $N(CO)R^7$ or NR^7, Y is CR^9R^{10}, and Z is absent (**D**).



D . OFG^1 is preferably attached to a primary carbon, *e.g.*, an exocyclic alkylene group, *e.g.*, a methylene group, connected to one of the carbons in the five-membered ring (-CH_2OFG^1 in **D**). OFG^2 is preferably attached directly to one of the carbons in the five-membered ring (-OFG^2 in **D**). For the pyrroline-based carriers, -CH_2OFG^1 may be attached to C-2 and OFG^2 may be attached to C-3; or -CH_2OFG^1 may be attached to C-3 and OFG^2 may be attached to C-4. In certain embodiments, CH_2OFG^1 and OFG^2 may be geminally substituted to one of the above-referenced carbons. For the 3-hydroxyproline-based carriers, -CH_2OFG^1 may be attached to C-2 and OFG^2 may be attached to C-4. The pyrroline- and 4-hydroxyproline-based monomers may therefore contain linkages (*e.g.*, carbon-carbon bonds) wherein bond rotation is restricted about that particular linkage, *e.g.* restriction resulting from the presence of a ring. Thus, CH_2OFG^1 and OFG^2 may be *cis* or *trans* with respect to one another in any of the pairings delineated above Accordingly, all *cis/trans* isomers are expressly included. The monomers may also contain one or more asymmetric centers and thus occur as racemates and racemic mixtures, single enantiomers, individual diastereomers and diastereomeric mixtures. All such isomeric forms of the monomers are expressly included (*e.g.*, the centers bearing CH_2OFG^1 and OFG^2 can both have the R configuration; or both have the S configuration; or one center can have the R configuration and the other center can have the S configuration and *vice versa*). The tethering attachment point is preferably nitrogen. Preferred examples of carrier **D** include the following:



In certain embodiments, the carrier may be based on the piperidine ring system (**E**), *e.g.*, X is

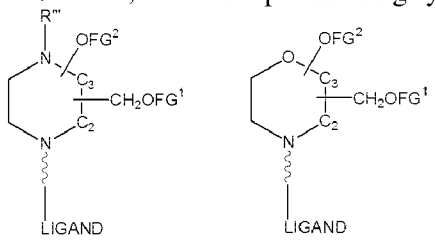


$N(CO)R^7$ or NR^7, Y is CR^9R^{10}, and Z is $CR^{11}R^{12}$. E .

OFG^1 is preferably attached to a primary carbon, *e.g.*, an exocyclic alkylene group, *e.g.*, a methylene group (n=1) or ethylene group (n=2), connected to one of the carbons in the six-membered ring [$-(CH_2)_nOFG^1$ in **E**]. OFG^2 is preferably attached directly to one of the carbons in the six-membered ring ($-OFG^2$ in **E**). $-(CH_2)_nOFG^1$ and OFG^2 may be disposed in a geminal manner on the ring, *i.e.*, both groups may be attached to the same carbon, *e.g.*, at C-2, C-3, or C-4. Alternatively, $-(CH_2)_nOFG^1$ and OFG^2 may be disposed in a vicinal manner on the ring, *i.e.*, both groups may be attached to adjacent ring carbon atoms, *e.g.*, $-(CH_2)_nOFG^1$ may be attached to C-2 and OFG^2 may be attached to C-3; $-(CH_2)_nOFG^1$ may be attached to C-3 and OFG^2 may be attached to C-2; $-(CH_2)_nOFG^1$ may be attached to C-3 and OFG^2 may be attached to C-4; or $-(CH_2)_nOFG^1$ may be attached to C-4 and OFG^2 may be attached to C-3. The piperidine-based monomers may therefore contain linkages (*e.g.*, carbon-carbon bonds) wherein bond rotation is restricted about that particular linkage, *e.g.* restriction resulting from the presence of a ring. Thus, $-(CH_2)_nOFG^1$ and OFG^2 may be *cis* or *trans* with respect to one another in any of the pairings delineated above. Accordingly, all *cis/trans* isomers are expressly included. The monomers may also contain one or more asymmetric centers and thus occur as racemates and racemic mixtures, single enantiomers, individual diastereomers and diastereomeric mixtures. All such isomeric forms of the monomers are expressly included (*e.g.*, the centers bearing CH_2OFG^1 and OFG^2 can both have the R configuration; or both

have the S configuration; or one center can have the R configuration and the other center can have the S configuration and *vice versa*). The tethering attachment point is preferably nitrogen.

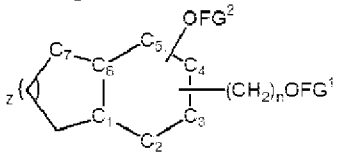
In certain embodiments, the carrier may be based on the piperazine ring system (**F**), *e.g.*, X is $N(CO)R^7$ or NR^7, Y is NR^8, and Z is $CR^{11}R^{12}$, or the morpholine ring system (**G**), *e.g.*, X is $N(CO)R^7$



F G

or NR^7, Y is O, and Z is $CR^{11}R^{12}$. . OFG^1 is preferably attached to a primary carbon, *e.g.*, an exocyclic alkylene group, *e.g.*, a methylene group, connected to one of the carbons in the six-membered ring ($-CH_2OFG^1$ in **F** or **G**). OFG^2 is preferably attached directly to one of the carbons in the six-membered rings ($-OFG^2$ in **F** or **G**). For both **F** and **G**, $-CH_2OFG^1$ may be attached to C-2 and OFG^2 may be attached to C-3; or *vice versa*. In certain embodiments, CH_2OFG^1 and OFG^2 may be geminally substituted to one of the above-referenced carbons.The piperazine- and morpholine-based monomers may therefore contain linkages (*e.g.*, carbon-carbon bonds) wherein bond rotation is restricted about that particular linkage, *e.g.* restriction resulting from the presence of a ring. Thus, CH_2OFG^1 and OFG^2 may be *cis* or *trans* with respect to one another in any of the pairings delineated above. Accordingly, all *cis/trans* isomers are expressly included. The monomers may also contain one or more asymmetric centers and thus occur as racemates and racemic mixtures, single enantiomers, individual diastereomers and diastereomeric mixtures. All such isomeric forms of the monomers are expressly included (*e.g.*, the centers bearing CH_2OFG^1 and OFG^2 can both have the R configuration; or both have the S configuration; or one center can have the R configuration and the other center can have the S configuration and *vice versa*). R''' can be, *e.g.*, C_1-C_6 alkyl, preferably CH_3. The tethering attachment point is preferably nitrogen in both **F** and **G**.

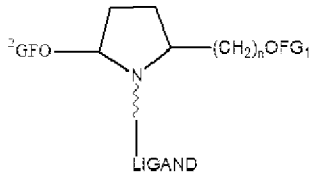
In certain embodiments, the carrier may be based on the decalin ring system, *e.g.*, X is CH_2; Y is CR^9R^{10}; Z is $CR^{11}R^{12}$, and R^5 and R^{11} together form C_6 cycloalkyl (**H**, z = 2), or the indane ring system, *e.g.*, X is CH_2; Y is CR^9R^{10}; Z is $CR^{11}R^{12}$, and R^5 and R^{11} together form C_5 cycloalkyl (**H**, z = 1).



H

. OFG^1 is preferably attached to a primary carbon, *e.g.*, an exocyclic methylene group (n=1) or ethylene group (n=2) connected to one of C-2, C-3, C-4, or C-5 [$-(CH_2)_nOFG^1$ in **H**]. OFG^2 is preferably attached directly to one of C-2, C-3, C-4, or C-5 ($-OFG^2$ in **H**). $-(CH_2)_nOFG^1$ and OFG^2 may be disposed in a geminal manner on the ring, *i.e.*, both groups may be attached to the same carbon, *e.g.*, at C-2, C-3, C-4, or C-5. Alternatively, $-(CH_2)_nOFG^1$ and OFG^2 may be disposed in a vicinal manner on the ring, *i.e.*, both groups may be attached to adjacent ring carbon atoms, *e.g.*, $-(CH_2)_nOFG^1$ may be attached to C-2 and OFG^2 may be attached to C-3; $-(CH_2)_nOFG^1$ may be attached to C-3 and OFG^2 may be attached to C-2; $-(CH_2)_nOFG^1$ may be attached

to C-3 and OFG^2 may be attached to C-4; or -$(CH_2)_nOFG^1$ may be attached to C-4 and OFG^2 may be attached to C-3; -$(CH_2)_nOFG^1$ may be attached to C-4 and OFG^2 may be attached to C-5; or -$(CH_2)_nOFG^1$ may be attached to C-5 and OFG^2 may be attached to C-4. The decalin or indane-based monomers may therefore contain linkages (*e.g.*, carbon-carbon bonds) wherein bond rotation is restricted about that particular linkage, *e.g.* restriction resulting from the presence of a ring. Thus, -$(CH_2)_nOFG^1$ and OFG^2 may be *cis* or *trans* with respect to one another in any of the pairings delineated above. Accordingly, all *cis/trans* isomers are expressly included. The monomers may also contain one or more asymmetric centers and thus occur as racemates and racemic mixtures, single enantiomers, individual diastereomers and diastereomeric mixtures. All such isomeric forms of the monomers are expressly included (*e.g.*, the centers bearing CH_2OFG^1 and OFG^2 can both have the R configuration; or both have the S configuration; or one center can have the R configuration and the other center can have the S configuration and *vice versa*). In a preferred embodiment, the substituents at C-1 and C-6 are *trans* with respect to one another. The tethering attachment point is preferably C-6 or C-7.



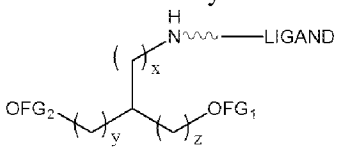
J

Other carriers may include those based on 3-hydroxyproline (**J**). Thus, -$(CH_2)_nOFG^1$ and OFG^2 may be *cis* or *trans* with respect to one another. Accordingly, all *cis/trans* isomers are expressly included. The monomers may also contain one or more asymmetric centers and thus occur as racemates and racemic mixtures, single enantiomers, individual diastereomers and diastereomeric mixtures. All such isomeric forms of the monomers are expressly included (*e.g.*, the centers bearing CH_2OFG^1 and OFG^2 can both have the R configuration; or both have the S configuration; or one center can have the R configuration and the other center can have the S configuration and *vice versa*). The tethering attachment point is preferably nitrogen.

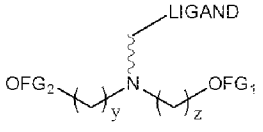
Details about more representative cyclic, sugar replacement-based carriers can be found in U.S. Patent Nos. 7,745,608 and 8,017,762, which are herein incorporated by reference in their entireties.

b. Sugar Replacement-Based Monomers (Acyclic)

Acyclic sugar replacement-based monomers, *e.g.*, sugar replacement-based ligand-conjugated monomers, are also referred to herein as ribose replacement monomer subunit (RRMS) monomer compounds. Preferred acyclic carriers can have formula **LCM-3** or **LCM-4**:



LCM-3



LCM-4

In some embodiments, each of x, y, and z can be, independently of one another, 0, 1, 2, or 3. In formula **LCM-3**, when y and z are different, then the tertiary carbon can have either the R or S configuration. In preferred embodiments, x is zero and y and z are each 1 in formula **LCM-3** (*e.g.*, based on serinol), and y and z are each 1 in formula **LCM-3**. Each of formula **LCM-3** or **LCM-4** below can optionally be substituted, *e.g.*, with hydroxy, alkoxy, perhaloalkyl.

Details about more representative acyclic, sugar replacement-based carriers can be found in U.S. Patent Nos. 7,745,608 and 8,017,762, which are herein incorporated by reference in their entireties.

The one or more C_{22} hydrocarbon chains is conjugated to one or more internal positions on at least one strand. Internal positions of a strand refers to the nucleotide on any position of the strand, except the terminal position from the 3' end and 5' end of the strand (*e.g.*, excluding 2 positions: position 1 counting from the 3' end and position 1 counting from the 5' end).

In one embodiment, the one or more C_{22} hydrocarbon chains is conjugated to one or more internal positions on at least one strand, which include all positions except the terminal two positions from each end of the strand (*e.g.*, excluding 4 positions: positions 1 and 2 counting from the 3' end and positions 1 and 2 counting from the 5' end). In one embodiment, the one or more C_{22} hydrocarbon chains is conjugated to one or more internal positions on at least one strand, which include all positions except the terminal three positions from each end of the strand (*e.g.*, excluding 6 positions: positions 1, 2, and 3 counting from the 3' end and positions 1, 2, and 3 counting from the 5' end).

In one embodiment, the one or more C_{22} hydrocarbon chains is conjugated to one or more internal positions on at least one strand, except the cleavage site region of the sense strand, for instance, the one or more C_{22} hydrocarbon chains is not conjugated to positions 9-12 counting from the 5'-end of the sense strand, for example, the one or more C_{22} hydrocarbon chains is not conjugated to positions 9-11 counting from the 5'-end of the sense strand. Alternatively, the internal positions exclude positions 11-13 counting from the 3'-end of the sense strand.

In one embodiment, the one or more C_{22} hydrocarbon chains is conjugated to one or more internal positions on at least one strand, which exclude the cleavage site region of the antisense strand. For instance, the internal positions exclude positions 12-14 counting from the 5'-end of the antisense strand.

In one embodiment, the one or more C_{22} hydrocarbon chains is conjugated to one or more internal positions on at least one strand, which exclude 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 one embodiment, the one or more C_{22} hydrocarbon chains is conjugated to one or more of the following internal positions: 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 one embodiment, the one or more C_{22} hydrocarbon chains is conjugated to one or more of the following internal positions: 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 one embodiment, the one or more C_{22} hydrocarbon chains is conjugated to position 6 on the sense strand, counting from the 5'end of each strand.

In some embodiments, the one or more C_{22} hydrocarbon chains is conjugated to a nucleobase, sugar moiety, or internucleosidic phosphate linkage of the dsRNA agent.

VI. Synthesis of RNAi Agents of the Invention

The nucleic acids featured in the disclosure can be synthesized 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.

An siRNA can be produced, *e.g.*, in bulk, by a variety of methods. Exemplary methods include: organic synthesis and RNA cleavage, *e.g.*, *in vitro* cleavage.

A. Organic Synthesis

An siRNA can be made by separately synthesizing a single stranded RNA molecule, or each respective strand of a double-stranded RNA molecule, after which the component strands can then be annealed.

A large bioreactor, *e.g.*, the OligoPilot II from Pharmacia Biotec AB (Uppsala Sweden), can be used to produce a large amount of a particular RNA strand for a given siRNA. The OligoPilotII reactor can efficiently couple a nucleotide using only a 1.5 molar excess of a phosphoramidite nucleotide. To make an RNA strand, ribonucleotides amidites are used. Standard cycles of monomer addition can be used to synthesize the 21 to 23 nucleotide strand for the siRNA. Typically, the two complementary strands are produced separately and then annealed, *e.g.*, after release from the solid support and deprotection.

Organic synthesis can be used to produce a discrete siRNA species. The complementary of the species to a particular target gene can be precisely specified. For example, the species may be complementary to a region that includes a polymorphism, *e.g.*, a single nucleotide polymorphism. Further the location of the polymorphism can be precisely defined. In some embodiments, the polymorphism is located in an internal region, *e.g.*, at least 4, 5, 7, or 9 nucleotides from one or both of the termini.

B. dsiRNA Cleavage

siRNAs can also be made by cleaving a larger siRNA. The cleavage can be mediated *in vitro* or *in vivo*. For example, to produce iRNAs by cleavage *in vitro*, the following method can be used:

1. In vitro transcription.

dsiRNA is produced by transcribing a nucleic acid (DNA) segment in both directions. For example, the HiScribe™ RNAi transcription kit (New England Biolabs) provides a vector and a method for producing a dsiRNA for a nucleic acid segment that is cloned into the vector at a position flanked on either side by a T7 promoter. Separate templates are generated for T7 transcription of the

two complementary strands for the dsiRNA. The templates are transcribed *in vitro* by addition of T7 RNA polymerase and dsiRNA is produced. Similar methods using PCR and/or other RNA polymerases (*e.g.*, T3 or SP6 polymerase) can also be dotoxins that may contaminate preparations of the recombinant enzymes. In one embodiment, RNA generated by this method is carefully purified to remove endotoxins that may contaminate preparations of the recombinant enzymes.

2. In vitro Cleavage.

dsRNA is cleaved *in vitro* into siRNAs, for example, using a Dicer or comparable RNAse III-based activity. For example, the dsiRNA can be incubated in an *in vitro* extract from Drosophila or using purified components, *e.g.,* a purified RNAse or RISC complex (RNA-induced silencing complex). See, *e.g.*, Ketting *et al. Genes Dev* 2001 Oct 15;15(20):2654-9 and Hammond *Science* 2001 Aug 10;293(5532):1146-50.

dsiRNA cleavage generally produces a plurality of siRNA species, each being a particular 21 to 23 nt fragment of a source dsiRNA molecule. For example, siRNAs that include sequences complementary to overlapping regions and adjacent regions of a source dsiRNA molecule may be present.

Regardless of the method of synthesis, the siRNA preparation can be prepared in a solution (*e.g.*, an aqueous and/or organic solution) that is appropriate for formulation. For example, the siRNA preparation can be precipitated and redissolved in pure double-distilled water, and lyophilized. The dried siRNA can then be resuspended in a solution appropriate for the intended formulation process.

C. Making dsRNA agents conjugated to one or more C_{22} hydrocarbon chains

In some embodiments, the one or more C_{22} hydrocarbon chains is conjugated to the dsRNA agent via a nucleobase, sugar moiety, or internucleosidic linkage.

Conjugation to purine nucleobases or derivatives thereof can occur at any position including, endocyclic and exocyclic atoms. In some embodiments, the 2-, 6-, 7-, or 8-positions of a purine nucleobase are attached to a C_{22} hydrocarbon chain. Conjugation to pyrimidine nucleobases or derivatives thereof can also occur at any position. In some embodiments, the 2-, 5-, and 6-positions of a pyrimidine nucleobase can be substituted with a C_{22} hydrocarbon chain. When one or more C_{22} hydrocarbon chains is conjugated to a nucleobase, the preferred position is one that does not interfere with hybridization, *i.e.*, does not interfere with the hydrogen bonding interactions needed for base pairing. In one embodiment, the one or more C_{22} hydrocarbon chains may be conjugated to a nucleobase via a linker containing an alkyl, alkenyl or amide linkage. .

Conjugation to sugar moieties of nucleosides can occur at any carbon atom. Exemplary carbon atoms of a sugar moiety that the one or more C_{22} hydrocarbon chains can be attached to include the 2', 3', and 5' carbon atoms. The one or more C_{22} hydrocarbon chains can also be attached to the 1' position, such as in an abasic residue. In one embodiment, the the one or more C_{22}

hydrocarbon chains may be conjugated to a sugar moiety, via a 2'-O modification, with or without a linker.

Internucleosidic linkages can also bear the one or more C_{22} hydrocarbon chains. For phosphorus-containing linkages (*e.g.*, phosphodiester, phosphorothioate, phosphorodithiotate, phosphoroamidate, and the like), the the one or more C_{22} hydrocarbon chains can be attached directly to the phosphorus atom or to an O, N, or S atom bound to the phosphorus atom. For amine- or amide-containing internucleosidic linkages (*e.g.*, PNA), the the one or more C_{22} hydrocarbon chains can be attached to the nitrogen atom of the amine or amide or to an adjacent carbon atom.

There are numerous methods for preparing conjugates of oligonuclotides. Generally, an oligonucleotide is attached to a conjugate moiety by contacting a reactive group (*e.g.*, OH, SH, amine, carboxyl, aldehyde, and the like) on the oligonucleotide with a reactive group on the conjugate moiety. In some embodiments, one reactive group is electrophilic and the other is nucleophilic.

For example, an electrophilic group can be a carbonyl-containing functionality and a nucleophilic group can be an amine or thiol. Methods for conjugation of nucleic acids and related oligomeric compounds with and without linking groups are well described in the literature such as, for example, in Manoharan in Antisense Research and Applications, Crooke and LeBleu, eds., CRC Press, Boca Raton, Fla., 1993, Chapter 17, which is incorporated herein by reference in its entirety.

In one embodiment, a first (complementary) RNA strand and a second (sense) RNA strand can be synthesized separately, wherein one of the RNA strands comprises a pendant C_{22} hydrocarbon chain, and the first and second RNA strands can be mixed to form a dsRNA. The step of synthesizing the RNA strand preferably involves solid-phase synthesis, wherein individual nucleotides are joined end to end through the formation of internucleotide 3′-5′ phosphodiester bonds in consecutive synthesis cycles.

In one embodiment, the C_{22} hydrocarbon chain having a phosphoramidite group is coupled to the 3'-end or 5′-end of either the first (complementary) or second (sense) RNA strand in the last synthesis cycle. In the solid-phase synthesis of an RNA, the nucleotides are initially in the form of nucleoside phosphoramidites. In each synthesis cycle, a further nucleoside phosphoramidite is linked to the -OH group of the previously incorporated nucleotide. If the the one or more C_{22} hydrocarbon chains has a phosphoramidite group, it can be coupled in a manner similar to a nucleoside phosphoramidite to the free OH end of the RNA synthesized previously in the solid-phase synthesis. The synthesis can take place in an automated and standardized manner using a conventional RNA synthesizer. Synthesis of the molecule having the phosphoramidite group may include phosphitylation of a free hydroxyl to generate the phosphoramidite group.

Synthesis procedures of the one or more C_{22} hydrocarbon chain-conjugated phosphoramidites are exemplified in Example 1.

In general, the oligonucleotides can be synthesized using protocols known in the art, for example, as described in Caruthers et al., Methods in Enzymology (1992) 211:3-19; WO 99/54459; Wincott et al., Nucl. Acids Res. (1995) 23:2677-2684; Wincott et al., Methods Mol. Bio., (1997) 74:59; Brennan et al., Biotechnol. Bioeng. (1998) 61:33-45; and U.S. Pat. No. 6,001,311; each of

which is hereby incorporated by reference in its entirety. In general, the synthesis of oligonucleotides involves conventional nucleic acid protecting and coupling groups, such as dimethoxytrityl at the 5′-end, and phosphoramidites at the 3′-end. In a non-limiting example, small scale syntheses are conducted on a Expedite 8909 RNA synthesizer sold by Applied Biosystems, Inc. (Weiterstadt, Germany), using ribonucleoside phosphoramidites sold by ChemGenes Corporation (Ashland, Mass.). Alternatively, syntheses can be performed on a 96-well plate synthesizer, such as the instrument produced by Protogene (Palo Alto, Calif.), or by methods such as those described in Usman et al., J. Am. Chem. Soc. (1987) 109:7845; Scaringe, et al., Nucl. Acids Res. (1990) 18:5433; Wincott, et al., Nucl. Acids Res. (1990) 23:2677-2684; and Wincott, et al., Methods Mol. Bio. (1997) 74:59, each of which is hereby incorporated by reference in its entirety.

The nucleic acid molecules of the present invention may be synthesized separately and joined together post-synthetically, for example, by ligation (Moore et al., Science (1992) 256:9923; WO 93/23569; Shabarova et al., Nucl. Acids Res. (1991) 19:4247; Bellon et al., Nucleosides & Nucleotides (1997) 16:951; Bellon et al., Bioconjugate Chem. (1997) 8:204; or by hybridization following synthesis and/or deprotection. The nucleic acid molecules can be purified by gel electrophoresis using conventional methods or can be purified by high pressure liquid chromatography (HPLC; see Wincott et al., supra, the totality of which is hereby incorporated herein by reference) and re-suspended in water.

VII. Ligands

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

In some embodiments, the dsRNA agent further comprises a targeting ligand that targets a receptor which mediates delivery to a specific tissue, *e.g.,* liver tissue. These targeting ligands can be conjugated in combination with the one or more C_{22} hydrocarbon chains to enable specific systemic delivery. In one embodiment, a targeting ligand, *e.g.,* one or more GalNAc derivatives, is conjugated to a dsRNA agent of the invention in combination with the one or more C_{22} hydrocarbon chains. In another embodiment, a targeting ligand, *e.g.,* one or more GalNAc derivatives, is not conjugated to a dsRNA agent of the invention in combination with the one or more C_{22} hydrocarbon chains.

Exemplary targeting ligands that targets the receptor mediated delivery to an adipose tissue are peptide ligands such as Angiopep-2, lipoprotein receptor related protein (LRP) ligand, bEnd.3 cell

binding ligand; transferrin receptor (TfR) ligand (which can utilize iron transport system in brain and cargo transport into the brain parenchyma); manose receptor ligand (which targets olfactory ensheathing cells, glial cells), glucose transporter protein, and LDL receptor ligand.

Preferred conjugate groups amenable to the present invention include lipid moieties such as a cholesterol moiety (Letsinger et al., Proc. Natl. Acad. Sci. USA, 1989, 86, 6553); cholic acid (Manoharan et al., Bioorg. Med. Chem. Lett., 1994, 4, 1053); a thioether, *e.g.*, hexyl-S-tritylthiol (Manoharan et al., Ann. N.Y. Acad. Sci., 1992, 660, 306; Manoharan et al., Bioorg. Med. Chem. Let., 1993, 3, 2765); a thiocholesterol (Oberhauser et al., Nucl. Acids Res., 1992, 20, 533); an aliphatic chain, *e.g.*, dodecandiol or undecyl residues (Saison-Behmoaras et al., EMBO J., 1991, 10, 111; Kabanov et al., FEBS Lett., 1990, 259, 327; Svinarchuk et al., Biochimie, 1993, 75, 49); a phospholipid, *e.g.*, di-hexadecyl-rac-glycerol or 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); 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).

Generally, a wide variety of entities, *e.g.*, ligands, can be coupled to the oligomeric compounds described herein. Ligands can include naturally occurring molecules, or recombinant or synthetic molecules. Exemplary ligands include, but are not limited to, 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, *e.g.*, PEG-2K, PEG-5K, PEG-10K, PEG-12K, PEG-15K, PEG-20K, PEG-40K), MPEG, $[MPEG]_2$, polyvinyl alcohol (PVA), polyurethane, poly(2-ethylacryllic acid), N-isopropylacrylamide polymers, polyphosphazine, polyethylenimine, cationic groups, spermine, spermidine, polyamine, pseudopeptide-polyamine, peptidomimetic polyamine, dendrimer polyamine, arginine, amidine, protamine, cationic lipid, cationic porphyrin, quaternary salt of a polyamine, thyrotropin, melanotropin, lectin, glycoprotein, surfactant protein A, mucin, glycosylated polyaminoacids, transferrin, bisphosphonate, polyglutamate, polyaspartate, aptamer, asialofetuin, hyaluronan, procollagen, immunoglobulins (*e.g.*, antibodies), insulin, transferrin, albumin, sugar-albumin conjugates, intercalating agents (*e.g.*, acridines), cross-linkers (*e.g.* psoralen, mitomycin C), porphyrins (*e.g.*, TPPC4, texaphyrin, Sapphyrin), polycyclic aromatic hydrocarbons (*e.g.*, phenazine, dihydrophenazine), artificial endonucleases (*e.g.*, EDTA), lipophilic molecules (e.g, steroids, bile acids, 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), peptides (*e.g.*, an alpha helical peptide, amphipathic peptide, RGD peptide, cell permeation peptide, endosomolytic/fusogenic peptide), alkylating agents, phosphate, amino,

mercapto, polyamino, alkyl, substituted alkyl, radiolabeled markers, enzymes, haptens (*e.g.* biotin), transport/absorption facilitators (*e.g.*, naproxen, aspirin, vitamin E, folic acid), synthetic ribonucleases (*e.g.*, imidazole, bisimidazole, histamine, imidazole clusters, acridine-imidazole conjugates, Eu3+ complexes of tetraazamacrocycles), dinitrophenyl, HRP, AP, antibodies, hormones and hormone receptors, lectins, carbohydrates, multivalent carbohydrates, vitamins (*e.g.*, vitamin A, vitamin E, vitamin K, vitamin B, *e.g.*, folic acid, B12, riboflavin, biotin and pyridoxal), vitamin cofactors, lipopolysaccharide, an activator of p38 MAP kinase, an activator of NF-κB, taxon, vincristine, vinblastine, cytochalasin, nocodazole, japlakinolide, latrunculin A, phalloidin, swinholide A, indanocine, myoservin, tumor necrosis factor alpha (TNFalpha), interleukin-1 beta, gamma interferon, natural or recombinant low density lipoprotein (LDL), natural or recombinant high-density lipoprotein (HDL), and a cell-permeation agent (*e.g.*, a.helical cell-permeation agent).

Peptide and peptidomimetic ligands include those having naturally occurring or modified peptides, *e.g.*, D or L peptides; α, β, or γ peptides; N-methyl peptides; azapeptides; peptides having one or more amide, *i.e.*, peptide, linkages replaced with one or more urea, thiourea, carbamate, or sulfonyl urea linkages; or cyclic peptides. 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 peptide or peptidomimetic ligand 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.

Exemplary amphipathic peptides include, but are not limited to, cecropins, lycotoxins, paradaxins, buforin, CPF, bombinin-like peptide (BLP), cathelicidins, ceratotoxins, *S. clava* peptides, hagfish intestinal antimicrobial peptides (HFIAPs), magainines, brevinins-2, dermaseptins, melittins, pleurocidin, H_2A peptides, Xenopus peptides, esculentinis-1, and caerins.

As used herein, the term "endosomolytic ligand" refers to molecules having endosomolytic properties. Endosomolytic ligands promote the lysis of and/or transport of the composition of the invention, or its components, from the cellular compartments such as the endosome, lysosome, endoplasmic reticulum (ER), Golgi apparatus, microtubule, peroxisome, or other vesicular bodies within the cell, to the cytoplasm of the cell. Some exemplary endosomolytic ligands include, but are not limited to, imidazoles, poly or oligoimidazoles, linear or branched polyethyleneimines (PEIs), linear and brached polyamines, *e.g.* spermine, cationic linear and branched polyamines, polycarboxylates, polycations, masked oligo or poly cations or anions, acetals, polyacetals, ketals/polyketals, orthoesters, linear or branched polymers with masked or unmasked cationic or anionic charges, dendrimers with masked or unmasked cationic or anionic charges, polyanionic peptides, polyanionic peptidomimetics, pH-sensitive peptides, natural and synthetic fusogenic lipids, natural and synthetic cationic lipids.

Exemplary endosomolytic/fusogenic peptides include, but are not limited to, AALEALAEALEALAEALEALAEAAAAGGC (GALA); AALAEALAEALAEALAEALAEALAAAAGGC (EALA); ALEALAEALEALAEA; GLFEAIEGFIENGWEGMIWDYG (INF-7); GLFGAIAGFIENGWEGMIDGWYG (Inf HA-2); GLFEAIEGFIENGWEGMIDGWYGCGLFEAIEGFIENGWEGMID GWYGC (diINF-7);

GLFEAIEGFIENGWEGMIDGGCGLFEAIEGFIENGWEGMIDGGC (diINF-3); GLFGALAEALAEALAEHLAEALAEALEALAAGGSC (GLF); GLFEAIEGFIENGWEGLAEALAEALEALAAGGSC (GALA-INF3); GLF EAI EGFI ENGW EGnI DG K GLF EAI EGFI ENGW EGnI DG (INF-5, n is norleucine); LFEALLELLESLWELLLEA (JTS-1); GLFKALLKLLKSLWKLLLKA (ppTG1); GLFRALLRLLRSLWRLLLRA (ppTG20); WEAKLAKALAKALAKHLAKALAKALKACEA (KALA); GLFFEAIAEFIEGGWEGLIEGC (HA); GIGAVLKVLTTGLPALISWIKRKRQQ (Melittin); H_5WYG; and CHK_6HC.

Without wishing to be bound by theory, fusogenic lipids fuse with and consequently destabilize a membrane. Fusogenic lipids usually have small head groups and unsaturated acyl chains. Exemplary fusogenic lipids include, but are not limited to, 1,2-dileoyl-sn-3-phosphoethanolamine (DOPE), phosphatidylethanolamine (POPE), palmitoyloleoylphosphatidylcholine (POPC), (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-ol (Di-Lin), N-methyl(2,2-di((9Z,12Z)-octadeca-9,12-dienyl)-1,3-dioxolan-4-yl)methanamine (DLin-k-DMA) and N-methyl-2-(2,2-di((9Z,12Z)-octadeca-9,12-dienyl)-1,3-dioxolan-4-yl)ethanamine (also refered to as XTC herein).

Synthetic polymers with endosomolytic activity amenable to the present invention are described in U.S. Pat. App. Pub. Nos. 2009/0048410; 2009/0023890; 2008/0287630; 2008/0287628; 2008/0281044; 2008/0281041; 2008/0269450; 2007/0105804; 20070036865; and 2004/0198687, contents of which are hereby incorporated by reference in their entirety.

Exemplary cell permeation peptides include, but are not limited to, RQIKIWFQNRRMKWKK (penetratin); GRKKRRQRRRPPQC (Tat fragment 48-60); GALFLGWLGAAGSTMGAWSQPKKKRKV (signal sequence based peptide); LLIILRRRIRKQAHAHSK (PVEC); GWTLNSAGYLLKINLKALAALAKKIL (transportan); KLALKLALKALKAALKLA (amphiphilic model peptide); RRRRRRRRR (Arg9); KFFKFFKFFK (Bacterial cell wall permeating peptide); LLGDFFRKSKEKIGKEFKRIVQRIKDFLRNLVPRTES (LL-37); SWLSKTAKKLENSAKKRISEGIAIAIQGGPR (cecropin P1); ACYCRIPACIAGERRYGTCIYQGRLWAFCC (α-defensin); DHYNCVSSGGQCLYSACPIFTKIQGTCYRGKAKCCK (β-defensin); RRRPRPPYLPRPRPPPFFPPRLPPRIPPGFPPRFPPRFPGKR-NH2 (PR-39); ILPWKWPWWPWRR-NH2 (indolicidin); AAVALLPAVLLALLAP (RFGF); AALLPVLLAAP (RFGF analogue); and RKCRIVVIRVCR (bactenecin).

Exemplary cationic groups include, but are not limited to, protonated amino groups, derived from *e.g.*, O-AMINE (AMINE = NH_2; alkylamino, dialkylamino, heterocyclyl, arylamino, diaryl amino, heteroaryl amino, or diheteroaryl amino, ethylene diamine, polyamino); aminoalkoxy, *e.g.*, $O(CH_2)_nAMINE$, (*e.g.*, AMINE = NH_2; alkylamino, dialkylamino, heterocyclyl, arylamino, diaryl amino, heteroaryl amino, or diheteroaryl amino, ethylene diamine, polyamino); amino (*e.g.* NH_2; alkylamino, dialkylamino, heterocyclyl, arylamino, diaryl amino, heteroaryl amino, diheteroaryl amino, or amino acid); and $NH(CH_2CH_2NH)_nCH_2CH_2$-AMINE (AMINE = NH_2; alkylamino, dialkylamino, heterocyclyl, arylamino, diaryl amino, heteroaryl amino, or diheteroaryl amino).

As used herein the term "targeting ligand" refers to any molecule that provides an enhanced affinity for a selected target, *e.g.*, a cell, cell type, tissue, organ, region of the body, or a compartment, *e.g.*, a cellular, tissue or organ compartment. Some exemplary targeting ligands include, but are not limited to, antibodies, antigens, folates, receptor ligands, carbohydrates, aptamers, integrin receptor ligands, chemokine receptor ligands, transferrin, biotin, serotonin receptor ligands, PSMA, endothelin, GCPII, somatostatin, LDL and HDL ligands.

Carbohydrate based targeting ligands include, but are not limited to, D-galactose, multivalent galactose, N-acetyl-D-galactosamine (GalNAc), multivalent GalNAc, *e.g.* $GalNAc_2$ and $GalNAc_3$ (GalNAc and multivalent GalNAc are collectively referred to herein as GalNAc conjugates); D-mannose, multivalent mannose, multivalent lactose, N-acetyl-glucosamine, Glucose, multivalent Glucose, multivalent fucose, glycosylated polyaminoacids and lectins. The term multivalent indicates that more than one monosaccharide unit is present. Such monosaccharide subunits can be linked to each other through glycosidic linkages or linked to a scaffold molecule.

A number of folate and folate analogs amenable to the present invention as ligands are described in U.S. Pat. Nos. 2,816,110; 5,552,545; 6,335,434 and 7,128,893, contents of which are herein incorporated in their entireties by reference.

As used herein, the terms "PK modulating ligand" and "PK modulator" refers to molecules which can modulate the pharmacokinetics of the composition of the invention. Some exemplary PK modulator include, but are not limited to, lipophilic molecules, bile acids, sterols, phospholipid analogues, peptides, protein binding agents, vitamins, fatty acids, phenoxazine, aspirin, naproxen, ibuprofen, suprofen, ketoprofen, (S)-(+)-pranoprofen, carprofen, PEGs, biotin, and transthyretia-binding ligands (*e.g.*, tetraiidothyroacetic acid, 2, 4, 6-triiodophenol and flufenamic acid). Oligomeric compounds that comprise a number of phosphorothioate intersugar linkages are also known to bind to serum protein, thus short oligomeric compounds, *e.g.* oligonucleotides of comprising from about 5 to 30 nucleotides (*e.g.*, 5 to 25 nucleotides, preferably 5 to 20 nucleotides, *e.g.*, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 nucleotides), and that comprise a plurality of phosphorothioate linkages in the backbone are also amenable to the present invention as ligands (*e.g.* as PK modulating ligands). The PK modulating oligonucleotide can comprise at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or more phosphorothioate and/or phosphorodithioate linkages. In some embodiments, all internucleotide linkages in PK modulating oligonucleotide are phosphorothioate and/or phosphorodithioates linkages. In addition, aptamers that bind serum components (*e.g.* serum proteins) are also amenable to the present invention as PK modulating ligands. Binding to serum components (*e.g.* serum proteins) can be predicted from albumin binding assays, scuh as those described in Oravcova, et al., Journal of Chromatography B (1996), 677: 1-27.

When two or more ligands are present, the ligands can all have same properties, all have different properties or some ligands have the same properties while others have different properties. For example, a ligand can have targeting properties, have endosomolytic activity or have PK modulating properties. In a preferred embodiment, all the ligands have different properties.

The ligand or tethered ligand can be present on a monomer when said monomer is incorporated into a component of the dsRNA agent of the invention (*e.g.*, a dsRNA agent of the invention or linker). In some embodiments, the ligand can be incorporated via coupling to a "precursor" monomer after said "precursor" monomer has been incorporated into a component of the dsRNA agent of the invention (*e.g.*, a dsRNA agent of the invention or linker). For example, a monomer having, *e.g.*, an amino-terminated tether (*i.e.*, having no associated ligand), *e.g.*, monomer-linker-NH_2 can be incorporated into into a component of the compounds of the invention (*e.g.*, a dsRNA agent of the invention or linker). In a subsequent operation, *i.e.*, after incorporation of the precursor monomer into a component of the compounds of the invention (*e.g.*, a dsRNA agent of the invention or linker), a ligand having an electrophilic group, *e.g.*, a pentafluorophenyl ester or aldehyde group, can subsequently be attached to the precursor monomer by coupling the electrophilic group of the ligand with the terminal nucleophilic group of the precursor monomer's tether.

In another example, a monomer having a chemical group suitable for taking part in Click Chemistry reaction can be incorporated *e.g.*, an azide or alkyne terminated tether/linker. In a subsequent operation, *i.e.*, after incorporation of the precursor monomer into the strand, a ligand having complementary chemical group, *e.g.* an alkyne or azide can be attached to the precursor monomer by coupling the alkyne and the azide together.

In some embodiments, ligand can be conjugated to nucleobases, sugar moieties, or internucleosidic linkages of the dsRNA agent of the invention. Conjugation to purine nucleobases or derivatives thereof can occur at any position including, endocyclic and exocyclic atoms. In some embodiments, the 2-, 6-, 7-, or 8-positions of a purine nucleobase are attached to a conjugate moiety. Conjugation to pyrimidine nucleobases or derivatives thereof can also occur at any position. In some embodiments, the 2-, 5-, and 6-positions of a pyrimidine nucleobase can be substituted with a conjugate moiety. When a ligand is conjugated to a nucleobase, the preferred position is one that does not interfere with hybridization, *i.e.*, does not interfere with the hydrogen bonding interactions needed for base pairing.

Conjugation to sugar moieties of nucleosides can occur at any carbon atom. Example carbon atoms of a sugar moiety that can be attached to a conjugate moiety include the 2', 3', and 5' carbon atoms. The 1' position can also be attached to a conjugate moiety, such as in an abasic residue. Internucleosidic linkages can also bear conjugate moieties. For phosphorus-containing linkages (*e.g.*, phosphodiester, phosphorothioate, phosphorodithiotate, phosphoroamidate, and the like), the conjugate moiety can be attached directly to the phosphorus atom or to an O, N, or S atom bound to the phosphorus atom. For amine- or amide-containing internucleosidic linkages (*e.g.*, PNA), the conjugate moiety can be attached to the nitrogen atom of the amine or amide or to an adjacent carbon atom.

There are numerous methods for preparing conjugates of oligonuclotides. Generally, an oligonucleotide is attached to a conjugate moiety by contacting a reactive group (*e.g.*, OH, SH, amine, carboxyl, aldehyde, and the like) on the oligonucleotide with a reactive group on the conjugate moiety. In some embodiments, one reactive group is electrophilic and the other is nucleophilic.

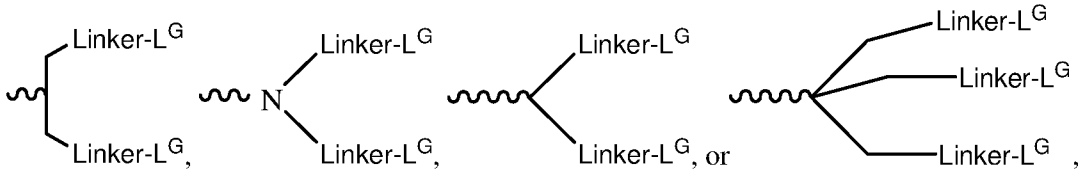
For example, an electrophilic group can be a carbonyl-containing functionality and a nucleophilic group can be an amine or thiol. Methods for conjugation of nucleic acids and related oligomeric compounds with and without linking groups are well described in the literature such as, for example, in Manoharan in Antisense Research and Applications, Crooke and LeBleu, eds., CRC Press, Boca Raton, Fla., 1993, Chapter 17, which is incorporated herein by reference in its entirety.

The ligand can be attached to the dsRNA agent of the inventions via a linker or a carrier monomer, *e.g.*, a ligand carrier. The carriers include (i) at least one "backbone attachment point," preferably 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 monomer into the backbone, *e.g.*, the phosphate, or modified phosphate, *e.g.*, sulfur containing, backbone, of an oligonucleotide. A "tethering attachment point" (TAP) in refers to an atom of the carrier monomer, *e.g.*, a carbon atom or a heteroatom (distinct from an atom which provides a backbone attachment point), that connects a selected moiety. The selected 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 carrier monomer. Thus, the 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 atom.

Representative U.S. patents that teach the preparation of conjugates of nucleic acids 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; 5,580,731; 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; 5,149,782; 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; 5,672,662; 5,688,941; 5,714,166; 6,153, 737; 6,172,208; 6,300,319; 6,335,434; 6,335,437; 6,395, 437; 6,444,806; 6,486,308; 6,525,031; 6,528,631; 6,559, 279; contents of which are herein incorporated in their entireties by reference.

In some embodiments, the dsRNA agent further comprises a targeting ligand that targets a liver tissue. In some embodiments, the targeting ligand is a carbohydrate-based ligand. In one embodiment, the targeting ligand is a GalNAc conjugate.

In certain embodiments, the dsRNA agent of the invention further comprises a ligand having a structure shown below:

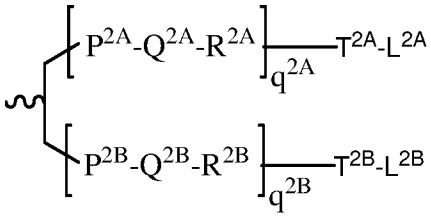


wherein:

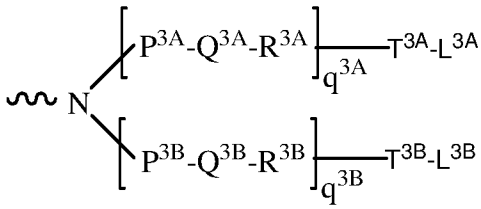
L^G is independently for each occurrence a ligand, *e.g.*, carbohydrate, *e.g.* monosaccharide, disaccharide, trisaccharide, tetrasaccharide, polysaccharide; and

Z', Z", Z"' and Z"" are each independently for each occurrence O or S.

In certain embodiments, the dsRNA agent of the invention comprises a ligand of Formula (II), (III), (IV) or (V):

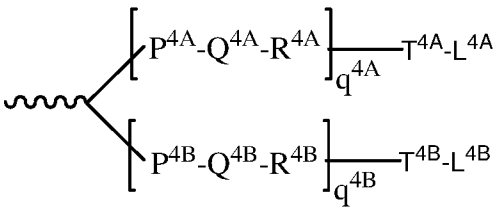


Formula (II)



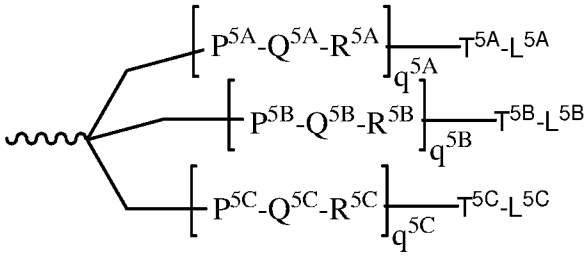
Formula (III)

,



Formula (IV)

, or



Formula (V)

,

wherein:

q^{2A}, q^{2B}, q^{3A}, q^{3B}, $q4^A$, q^{4B}, q^{5A}, q^{5B} and q^{5C} represent independently for each occurrence 0-20 and wherein the repeating unit can be the same or different;

Q and Q' are independently for each occurrence is absent, $-(P^7\text{-}Q^7\text{-}R^7)_p\text{-}T^7\text{-}$ or $-T^7\text{-}Q^7\text{-}T^{7'}\text{-B-}T^{8'}\text{-}Q^8\text{-}T^8$;

P^{2A}, P^{2B}, P^{3A}, P^{3B}, P^{4A}, P^{4B}, P^{5A}, P^{5B}, P^{5C}, P^7, T^{2A}, T^{2B}, T^{3A}, T^{3B}, T^{4A}, T^{4B}, T^{4A}, T^{5B}, T^{5C}, T^7, $T^{7'}$, T^8 and $T^{8'}$ are each independently for each occurrence absent, CO, NH, O, S, OC(O), NHC(O), CH_2, CH_2NH or CH_2O;

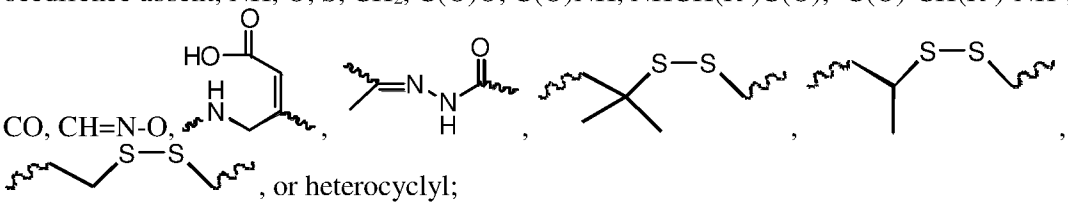
B is $-CH_2\text{-}N(B^L)\text{-}CH_2$-;

B^L is $-T^B\text{-}Q^B\text{-}T^{B'}\text{-}R^x$;

Q^{2A}, Q^{2B}, Q^{3A}, Q^{3B}, Q^{4A}, Q^{4B}, Q^{5A}, Q^{5B}, Q^{5C}, Q^7, Q^8 and Q^B are independently for each occurrence absent, alkylene, substituted alkylene and 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);

T^B and $T^{B'}$ are each independently for each occurrence absent, CO, NH, O, S, OC(O), OC(O)O, NHC(O), NHC(O)NH, NHC(O)O, CH_2, CH_2NH or CH_2O;

R^x is a lipophile (*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), a vitamin (*e.g.*, folate, vitamin A, vitamin E, biotin, pyridoxal), a peptide, a carbohydrate (*e.g.*, monosaccharide, disaccharide, trisaccharide, tetrasaccharide, oligosaccharide, polysaccharide), an endosomolytic component, a steroid (*e.g.*, uvaol, hecigenin, diosgenin), a terpene (*e.g.*, triterpene, *e.g.*, sarsasapogenin, Friedelin, epifriedelanol derivatized lithocholic acid), or a cationic lipid;

R^1, R^2, R^{2A}, R^{2B}, R^{3A}, R^{3B}, R^{4A}, R^{4B}, R^{5A}, R^{5B}, R^{5C}, R^7 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^1, L^{2A}, L^{2B}, L^{3A}, L^{3B}, L^{4A}, L^{4B}, L^{5A}, L^{5B} and L^{5C} are each independently for each occurrence a carbohydrate, *e.g.*, monosaccharide, disaccharide, trisaccharide, tetrasaccharide, oligosaccharide and polysaccharide;

R' and R" are each independently H, C_1-C_6 alkyl, OH, SH, or $N(R^N)_2$;

R^N is independently for each occurrence H, methyl, ethyl, propyl, isopropyl, butyl or benzyl;

R^a is H or amino acid side chain;

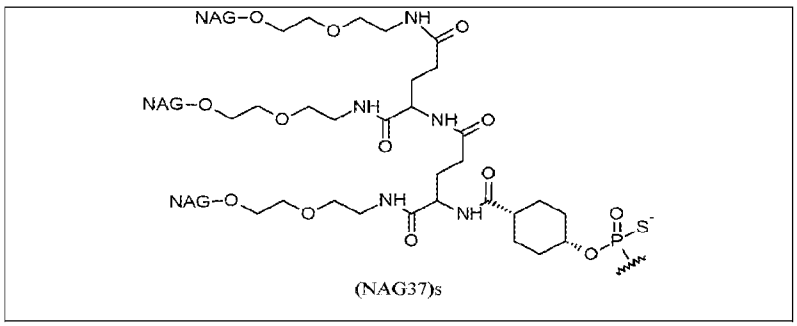
Z', Z", Z"' and Z"" are each independently for each occurrence O or S;

p represent independently for each occurrence 0-20.

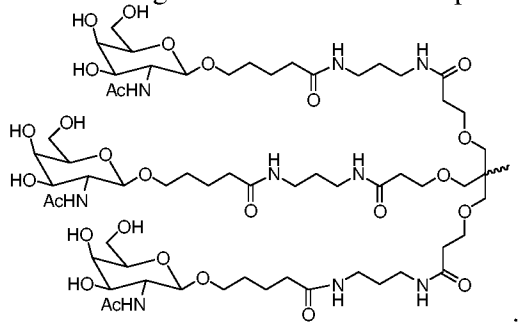
As discussed above, because the ligand can be conjugated to the iRNA agent via a linker or carrier, and because the linker or carrier can contain a branched linker, the iRNA agent can then contain multiple ligands via the same or different backbone attachment points to the carrier, or via the branched linker(s). For instance, the branchpoint of the branched linker may be a bivalent, trivalent, tetravalent, pentavalent ,or hexavalent atom, or a group presenting such multiple valencies. In certain embodiments, the branchpoint is -N, -N(Q)-C, -O-C, -S-C, -SS-C, -C(O)N(Q)-C, -OC(O)N(Q)-C, -N(Q)C(O)-C, or -N(Q)C(O)O-C; wherein Q is independently for each occurrence H or optionally substituted alkyl. In other embodiment, the branchpoint is glycerol or glycerol derivative.

Suitable ligands for use in the compositions of the invention are described in U.S. Patent Nos. 8,106,022, 8,450,467, 8,882,895, 9,352,048, 9,370,581, 9,370,582, 9,867,882, 10,806,791, and 11,110,174, and U.S. Patent Publication Nos. 2009/239814, 200/9247608, 2012/136042, 2013/178512, 2014/179761, 2015/011615, 2015/119444, 2015/119445, 2016/051691, 2016/375137, 2018/326070, 2019/099493, 2019/184018, and 2020/297853, the entire contents of each of which are incorporated herein by reference.

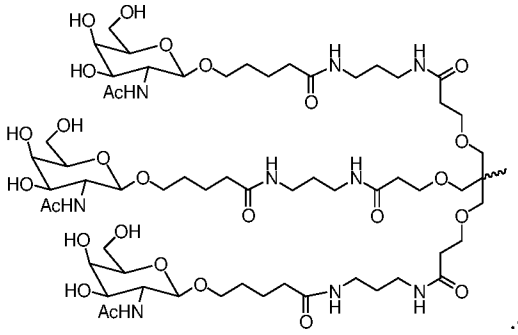
In some embodiments, a suitable ligand is a ligand disclosed in WO 2019/055633, the entire contents of which are incorporated herein by reference. In one embodiment the ligand comprises the structure below:



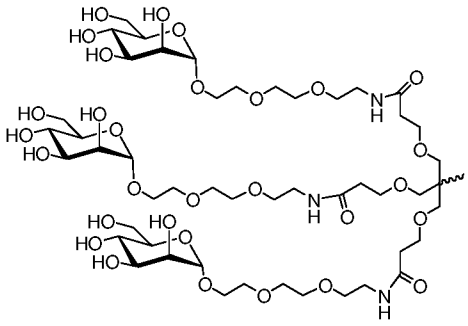
In certain embodiments, the dsRNA agent of the invention comprises a ligand of structure:



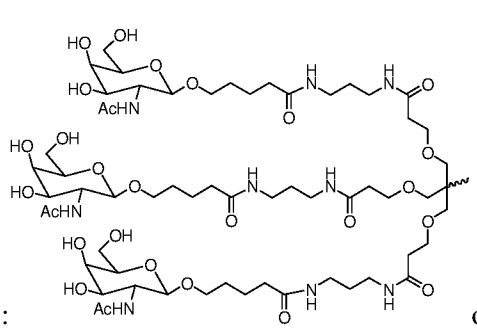
In certain embodiments, the dsRNA agent of the invention is conjugated with a ligand of structure:



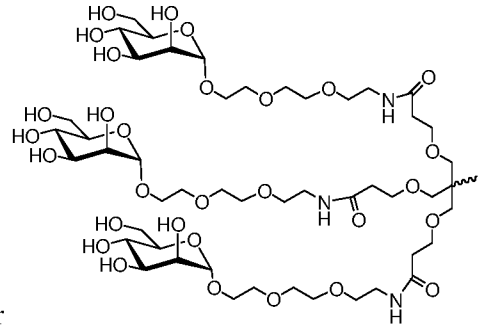
.or



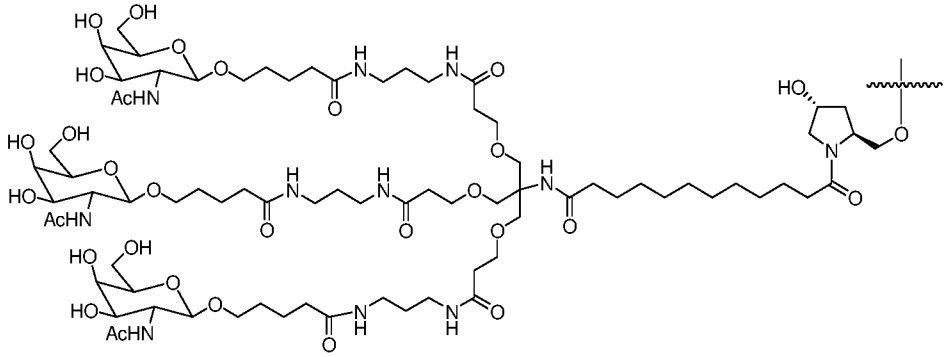
In certain embodiments, the dsRNA agent of the invention comprises a ligand of structure:


:

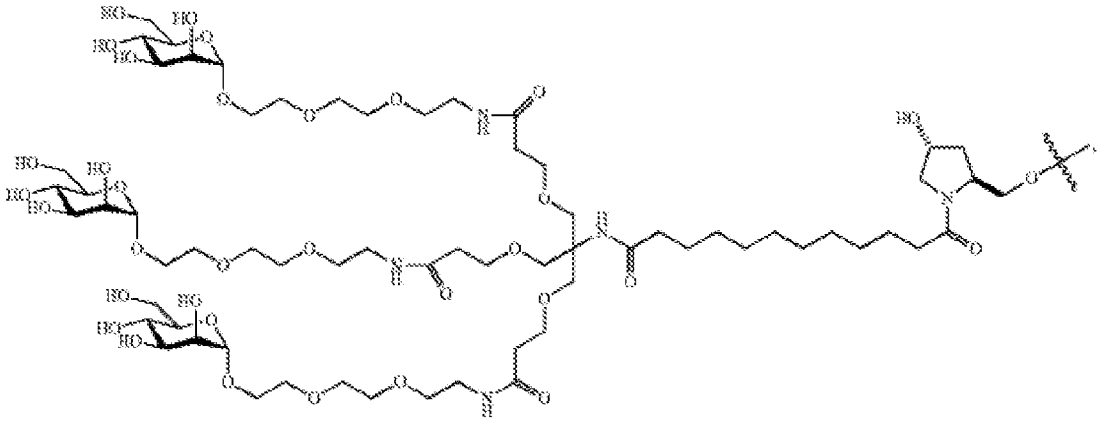
or


.

In certain embodiments, the dsRNA agent of the invention comprises a monomer of structure:

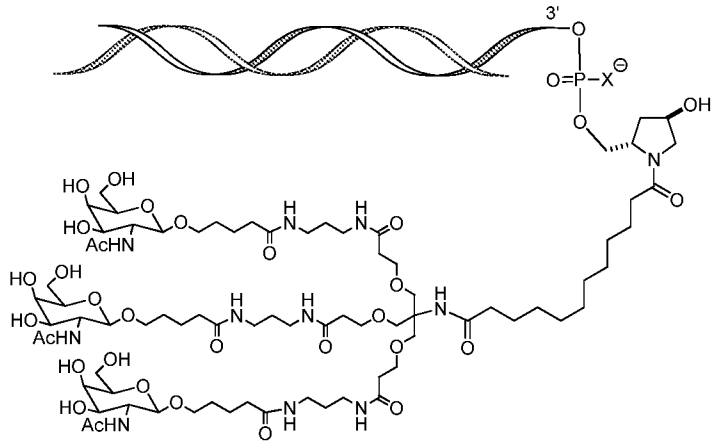


or

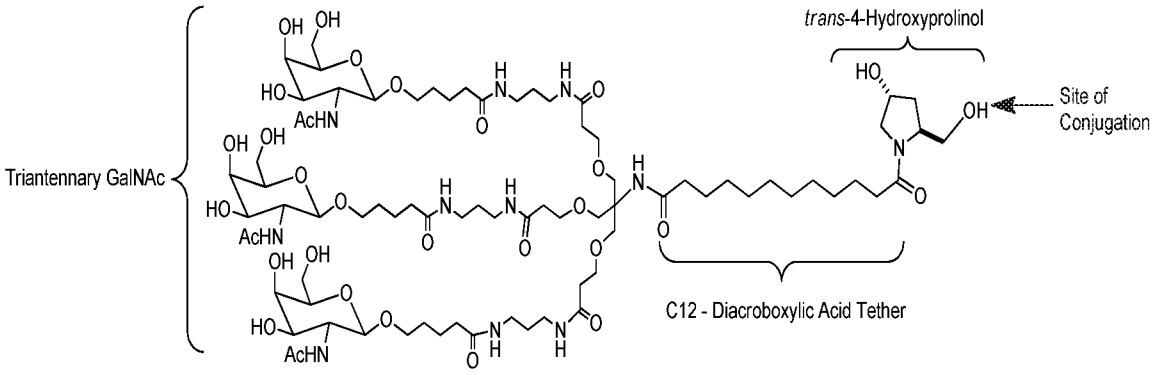


.

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 1 and shown below:



.

Synthesis of above described ligands and monomers is described, for example, in US Patent No. 8,106,022, content of which are incorporated herein by reference in their entirety.

VIII. Delivery of an RNAi Agent of the Disclosure

The delivery of a RNAi agent of the disclosure to a cell *e.g.,* a cell within a subject, such as a human subject (*e.g.,* a subject in need thereof, such as a subject having a metabolic disorder, can be achieved in a number of different ways. For example, delivery may be performed by contacting a cell with an RNAi agent of the disclosure either *in vitro* or *in vivo*. *In vivo* delivery may also be performed directly by administering a composition comprising an RNAi agent, *e.g.,* a dsRNA, to a subject. Alternatively, *in vivo* delivery may be performed indirectly by administering one or more vectors that encode and direct the expression of the RNAi agent. These alternatives are discussed further below.

In general, any method of delivering a nucleic acid molecule (*in vitro* or *in vivo*) can be adapted for use with a RNAi agent of the disclosure (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). For *in vivo* delivery, factors to consider in order to deliver an RNAi agent include, for example, biological stability of the delivered agent, prevention of non-specific effects, and accumulation of the delivered agent in the target tissue. The non-specific effects of an RNAi agent can be minimized by local administration, for example, by direct injection or implantation into a tissue 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 can otherwise be harmed by the agent or that can degrade the agent, and permits a lower total dose of the RNAi agent to be administered. Several studies have shown successful knockdown of gene products when an RNAi agent is administered locally. For example, pulmonary delivery, *e.g.,* inhalation, of a dsRNA, *e.g.,* SOD1, has been shown to effectively knockdown gene and protein expression in lung tissue and that there is excellent uptake of the dsRNA by the bronchioles and alveoli of the lung. Intraocular delivery of a VEGF 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 also 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 a.l* (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 a RNAi agent 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 RNAi agent to the target tissue and avoid undesirable off-target effects (*e.g.,* without wishing to be bound by theory, use of GNAs as described herein has been identified to destabilize the seed region of a dsRNA, resulting in enhanced preference of such dsRNAs for on-target effectiveness, relative to off-target effects, as such off-target effects are significantly weakened by such seed region destabilization). RNAi agents can be modified by chemical conjugation to lipophilic groups such as cholesterol to enhance cellular uptake and prevent degradation. For example, a RNAi agent 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 RNAi agent 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 RNAi agent 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 molecule RNAi agent (negatively charged) and also enhance interactions at the negatively charged cell membrane to permit efficient uptake of an RNAi agent by the cell. Cationic lipids, dendrimers, or polymers can either be bound to an RNAi agent, 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 RNAi agent. The formation of vesicles or micelles further prevents degradation of the RNAi agent when administered systemically. Methods for making and administering cationic- RNAi agent 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 RNAi agents 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, a RNAi agent forms a complex with cyclodextrin for systemic administration. Methods for administration and pharmaceutical compositions of RNAi agents and cyclodextrins can be found in U.S. Patent No. 7, 427, 605, which is herein incorporated by reference in its entirety.

Certain aspects of the instant disclosure relate to a method of reducing the expression of a target gene, *e.g.,* INHBE, ACVR1C, PLIN1, PDE3B, or INHBC, in a cell, comprising contacting said cell with the double-stranded RNAi agent of the disclosure. In one embodiment, the cell is a liver cell. In one embodiment, the cell is an adipocyte.

In certain embodiments, the RNAi agent is taken up on one or more tissue or cell types present in organs, *e.g.,* liver, adipose tissue.

Another aspect of the disclosure relates to a method of reducing the expression and/or activity of a target gene, *e.g.,* INHBE, ACVR1C, PLIN1, PDE3B, or INHBC, in a subject, comprising administering to the subject the double-stranded RNAi agent of the disclosure.

Another aspect of the disclosure relates to a method of treating a subject having a metabolic disorder or at risk of having or at risk of developing a metabolic disorder, comprising administering to the subject a therapeutically effective amount of the double-stranded RNAi agent of the disclosure, thereby treating the subject.

In one embodiment, the double-stranded RNAi agent is administered subcutaneously.

In one embodiment, the double-stranded RNAi agent is administered intramuscularly.

In one embodiment, the double-stranded RNAi agent is administered by intravenously.

In one embodiment, the double-stranded RNAi agent is administered by pulmonary sytem administration, *e.g.*, intranasal administration, or oral inhalative administration.

For ease of exposition the formulations, compositions and methods in this section are discussed largely with regard to modified siRNA compounds. It may be understood, however, that these formulations, compositions and methods can be practiced with other siRNA compounds, *e.g.,* unmodified siRNA compounds, and such practice is within the disclosure. A composition that includes a RNAi agent can be delivered to a subject by a variety of routes. Exemplary routes include pulmonary system, intravenous, subcutaneous, intraventricular, oral, topical, rectal, anal, vaginal, nasal, and ocular.

The RNAi agents of the disclosure can be incorporated into pharmaceutical compositions suitable for administration. Such compositions typically include one or more species of RNAi agent and a pharmaceutically acceptable carrier. As used herein the language "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible

with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

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 intratracheal, intranasal, topical (including ophthalmic, vaginal, rectal, intranasal, transdermal), oral, parenteral, or pulmonary, *e.g.,* by inhalation or insufflation of powders or aerosols, including by nebulizer. Parenteral administration includes intravenous drip, subcutaneous, intraperitoneal, or intramuscular injection, or intrathecal or intraventricular administration.

The route and site of administration may be chosen to enhance targeting. For example, to target muscle cells, intramuscular injection into the muscles of interest would be a logical choice. Lung cells might be targeted by administering the RNAi agent in powder or aerosol form. The vascular endothelial cells could be targeted by coating a balloon catheter with the RNAi agent and mechanically introducing the RNA.

Compositions for pulmonary system delivery may include aqueous solutions, *e.g.,* for intranasal or oral inhalative administration, suitable carriers composed of, *e.g.,* lipids (liposomes, niosomes, microemulsions, lipidic micelles, solid lipid nanoparticles) or polymers (polymer micelles, dendrimers, polymeric nanoparticles, nonogels, nanocapsules), adjuvant, *e.g.,* for oral inhalative administration. Aqueous compositions may be sterile and may optionally contain buffers, diluents, absorbtion enhancers and other suitable additives. Such administration permits both systemic and local delivery of the double stranded RNAi agents of the invention.

Intranasal administration may include instilling or insufflating a double stranded RNAi agent into the nasal cavity with syringes or droppers by applying a few drops at a time or via atomization. Suitable dosage forms for intranasal administration include drops, powders, nebulized mists, and sprays. Nasal delivery devices include, but not limited to, vapor inhaler, nasal dropper, spray bottle, metered dose spray pump, gas driven spray atomizer, nebulizer, mechanical powder sprayer, breath actuated inhaler, and insufflator. Devices for delivery deeper into the respiratory system, *e.g.*, into the lung, include nebulizer, pressured metered-dose inhaler, dry powder inhaler, and thermal vaporization aerosol device. Devices for delivery by inhalation are available from commercial suppliers.Devices can be fixed or variable dose, single or multidose, disposable or reusable depending on, for example, the disease or disorder to be prevented or treated, the volume of the agent to be delivered, the frequency of delivery of the agent, and other considerations in the art.

Oral inhalative administration may include use of device, *e.g.*, a passive breath driven or active power driven single/-multiple dose dry powder inhaler (DPI), to deliver a double stranded RNAi agent to the pulmonary system. Suitable dosage forms for oral inhalative administration include powders and solutions. Suitable devices for oral inhalative administration include nebulizers, metered-dose inhalers, and dry powder inhalers. Dry powder inhalers are of the most popular devices used to deliver drugs, especially proteins to the lungs. Exemplary commercially available dry powder inhalers include Spinhaler (Fisons Pharmaceuticals, Rochester, NY) and Rotahaler (GSK, RTP, NC). Several types of nebulizers are available, namely jet nebulizers, ultrasonic nebulizers, vibrating mesh

nebulizers. Jet nebulizers are driven by compressed air. Ultrasonic nebulizers use a piezoelectric transducer in order to create droplets from an open liquid reservoir. Vibrating mesh nebulizers use perforated membranes actuated by an annular piezoelement to vibrate in resonant bending mode. The holes in the membrane have a large cross-section size on the liquid supply side and a narrow cross-section size on the side from where the droplets emerge. Depending on the therapeutic application, the hole sizes and number of holes can be adjusted. Selection of a suitable device depends on parameters, such as nature of the drug and its formulation, the site of action, and pathophysiology of the lung. Aqueous suspensions and solutions are nebulized effectively. Aerosols based on mechanically generated vibration mesh technologies also have been used successfully to deliver proteins to lungs.

The amount of RNAi agent for pulmonary system administration may vary from one target gene to another target gene and the appropriate amount that has to be applied may have to be determined individually for each target gene. Typically, this amount ranges from 10 μg to 2 mg, or 50 μg to 1500 μg, or 100 μg to 1000 μg.

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.

Compositions for oral administration include powders or granules, suspensions or solutions in water, syrups, elixirs or non-aqueous media, tablets, capsules, lozenges, or troches. In the case of tablets, carriers that can be used include lactose, sodium citrate and salts of phosphoric acid. Various disintegrants such as starch, and lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc, are commonly used in tablets. For oral administration in capsule form, useful diluents are lactose and high molecular weight polyethylene glycols. When aqueous suspensions are required for oral use, the nucleic acid compositions can be combined with emulsifying and suspending agents. If desired, certain sweetening or flavoring agents can be added. Compositions suitable for oral administration of the agents of the invention are further described in PCT Application No. PCT/US20/33156, the entire contents of which are incorporated herein by reference.

Compositions for intrathecal or intraventricular administration may include sterile aqueous solutions which may also contain buffers, diluents, and other suitable additives.

Formulations for parenteral administration may include sterile aqueous solutions which may also contain buffers, diluents, and other suitable additives. Intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir. For intravenous use, the total concentration of solutes may be controlled to render the preparation isotonic.

In one embodiment, the administration of the siRNA compound, *e.g.,* a double-stranded siRNA compound, is parenteral, *e.g.,* intravenous (*e.g.,* as a bolus or as a diffusible infusion), intradermal, intraperitoneal, intramuscular, intrathecal, intraventricular, intracranial, subcutaneous, transmucosal, buccal, sublingual, endoscopic, rectal, oral, vaginal, topical, pulmonary system, intranasal, urethral, or ocular. Administration can be provided by the subject or by another person,

e.g., a health care provider. The medication can be provided in measured doses or in a dispenser which delivers a metered dose. Selected modes of delivery are discussed in more detail below.

A. Vector encoded RNAi agents of the Disclosure

RNAi agents targeting the target gene can be expressed from transcription units inserted into DNA or RNA vectors (see, *e.g.,* Couture, A, *et al.*, *TIG.* (1996), 12:5-10; WO 00/22113, WO 00/22114, and US 6,054,299). Expression can be sustained (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.*, (1995) *Proc. Natl. Acad. Sci. USA* 92:1292).

The individual strand or strands of a RNAi agent 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 one embodiment, a dsRNA is expressed as inverted repeat polynucleotides joined by a linker polynucleotide sequence such that the dsRNA has a stem and loop structure.

RNAi agent expression vectors are generally DNA plasmids or viral vectors. Expression vectors compatible with eukaryotic cells, such as those compatible with vertebrate cells, can be used to produce recombinant constructs for the expression of a RNAi agent as described herein. Delivery of RNAi agent 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.

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) SV 40 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 can be incorporated into vectors capable of episomal replication, *e.g.* EPV and EBV vectors. Constructs for the recombinant expression of a RNAi agent will generally require regulatory elements, *e.g.,* promoters, enhancers, *etc.*, to ensure the expression of the RNAi agent in target cells. Other aspects to consider for vectors and constructs are known in the art.

IX. Pharmaceutical Compositons

The present disclosure also includes pharmaceutical compositions and formulations which include the RNAi agents of the disclosure. In one embodiment, provided herein are pharmaceutical compositions containing an RNAi agent, as described herein, and a pharmaceutically acceptable carrier. The pharmaceutical compositions containing the RNAi agent are useful for treating a subject who would benefit from inhibiting or reducing the expression of a target gene, *e.g.,* INHBE, ACVR1C, PLIN1, PDE3B, or INHBC, *e.g.,* a subject having a metabolic disorder. Such pharmaceutical compositions are formulated based on the mode of delivery. One example is compositions that are formulated for systemic administration *via* parenteral delivery, *e.g.,* by intravenous (IV), intramuscular (IM), or for subcutaneous (subQ) delivery.

In some embodiments, the pharmaceutical compositions of the invention are pyrogen free or non-pyrogenic.

In one embodiment, the delivery vehicle can deliver an iRNA compound, *e.g.*, a double-stranded iRNA compound, or ssiRNA compound, (*e.g.*, a precursor thereof, *e.g.*, a larger siRNA compound which can be processed into a ssiRNA compound, or a DNA which encodes an siRNA compound, *e.g.*, a double-stranded siRNA compound, or ssiRNA compound, or precursor thereof) to a cell by a topical route of administration. The delivery vehicle can be microscopic vesicles. In one example the microscopic vesicles are liposomes. In some embodiments the liposomes are cationic liposomes. In another example the microscopic vesicles are micelles.In one aspect, the invention features a pharmaceutical composition including an siRNA compound, *e.g.*, a double-stranded siRNA compound, or ssiRNA compound, (*e.g.*, a precursor thereof, *e.g.*, a larger siRNA compound which can be processed into a ssiRNA compound, or a DNA which encodes an siRNA compound, *e.g.*, a double-stranded siRNA compound, or ssiRNA compound, or precursor thereof) in an injectable dosage form. In one embodiment, the injectable dosage form of the pharmaceutical composition includes sterile aqueous solutions or dispersions and sterile powders. In some embodiments the sterile solution can include a diluent such as water; saline solution; fixed oils, polyethylene glycols, glycerin, or propylene glycol.

In one aspect, the invention features a pharmaceutical composition including an siRNA compound, *e.g.*, a double-stranded siRNA compound, or ssiRNA compound, (*e.g.*, a precursor thereof, *e.g.*, a larger siRNA compound which can be processed into a ssiRNA compound, or a DNA which encodes an siRNA compound, *e.g.*, a double-stranded siRNA compound, or ssiRNA compound, or precursor thereof) in oral dosage form. In one embodiment, the oral dosage form is selected from the group consisting of tablets, capsules and gel capsules. In another embodiment, the pharmaceutical composition includes an enteric material that substantially prevents dissolution of the tablets, capsules or gel capsules in a mammalian stomach. In some embodiments the enteric material is a coating. The coating can be acetate phthalate, propylene glycol, sorbitan monoleate, cellulose acetate trimellitate, hydroxy propyl methyl cellulose phthalate or cellulose acetate phthalate. In one embodiment, the oral dosage form of the pharmaceutical composition includes a penetration enhancer, *e.g.*, a penetration enhancer described herein.

In another embodiment, the oral dosage form of the pharmaceutical composition includes an excipient. In one example the excipient is polyethyleneglycol. In another example the excipient is precirol.

In another embodiment, the oral dosage form of the pharmaceutical composition includes a plasticizer. The plasticizer can be diethyl phthalate, triacetin dibutyl sebacate, dibutyl phthalate or triethyl citrate.

X. Methods For Inhibiting Target Gene Expression

Another aspect of the invention relates to a method of reducing the expression of a target gene, *e.g.,* INHBE, ACVR1C, PLIN1, PDE3B, or INHBC, in a cell, comprising contacting the cell with a dsRNA agent of the invention. The methods include contacting the cell with a dsRNA of the disclosure and maintaining the cell for a time sufficient to obtain degradation of the mRNA transcripts of a target gene, thereby inhibiting expression of the target gene in the cell.

Reduction in gene expression can be assessed by any methods known in the art. For example, a reduction in the expression of a target may be determined by determining the mRNA expression level of the target gene using methods routine to one of ordinary skill in the art, *e.g.*, northern blotting, qRT-PCR; by determining the protein level of a target protein using methods routine to one of ordinary skill in the art, such as western blotting, immunological techniques.

In the methods of the disclosure the cell may be contacted *in vitro* or *in vivo*, *i.e.*, the cell may be within a subject. Contacting a cell *in vivo* with the RNAi agent includes contacting a cell or group of cells within a subject, *e.g.*, a human subject, with the RNAi agent. Combinations of *in vitro* and *in vivo* methods of contacting a cell are also possible.

The cell may be an extra-hepatic cell, such as a liver cell or an adipocyte.

A cell suitable for treatment using the methods of the disclosure may be any cell that expresses a target gene. A cell suitable for use in the methods of the disclosure may be a mammalian cell, *e.g.,* a primate cell (such as a human cell or a non-human primate cell, *e.g.,* a monkey cell or a chimpanzee cell), a non-primate cell (such as a rat cell, or a mouse cell. In one embodiment, the cell is a human cell, *e.g.,* a human liver cell or a human kidney cell.

Contacting a cell may be direct or indirect, as discussed above. Furthermore, contacting a cell may be accomplished *via* a targeting ligand, including any ligand described herein or known in the art. In some embodiments, the targeting ligand is a carbohydrate moiety, *e.g.,* a GalNAc ligand, or any other ligand that directs the RNAi agent to a site of interest. In certain embodiments, the RNAi agent does not include a targeting ligand.

The term "inhibiting," as used herein, is used interchangeably with "reducing," "silencing," "downregulating," "suppressing" and other similar terms, and includes any level of inhibition. In certain embodiments, a level of inhibition, *e.g.,* for an RNAi agent of the instant disclosure, can be assessed in cell culture conditions, *e.g.,* wherein cells in cell culture are transfected *via* Lipofectamine™-mediated transfection at a concentration in the vicinity of a cell of 10 nM or less, 1 nM or less, *etc*. Knockdown of a given RNAi agent can be determined *via* comparison of pre-treated

levels in cell culture versus post-treated levels in cell culture, optionally also comparing against cells treated in parallel with a scrambled or other form of control RNAi agent. Knockdown in cell culture of, *e.g.,* 50% or more, can thereby be identified as indicative of "inhibiting" or "reducing", "downregulating" or "suppressing", *etc.* having occurred. It is expressly contemplated that assessment of targeted mRNA or encoded protein levels (and therefore an extent of "inhibiting", *etc.* caused by a RNAi agent of the disclosure) can also be assessed in *in vivo* systems for the RNAi agents of the instant disclosure, under properly controlled conditions as described in the art.

The phrase "inhibiting expression of a target gene" or "inhibiting expression of a target," as used herein, includes inhibition of expression of any target gene (such as, *e.g.,* a mouse target gene, a rat target gene, a monkey target gene, or a human target gene) as well as variants or mutants of a target gene that encode a target protein. Thus, the target gene may be a wild-type target gene, a mutant target gene , or a transgenic target gene in the context of a genetically manipulated cell, group of cells, or organism.

"Inhibiting expression of a target gene" includes any level of inhibition of a target gene, *e.g.,* at least partial suppression of the expression of a target gene, such as an inhibition by at least 20%. In certain embodiments, inhibition is by at least 30%, at least 40%, at least 50%, at least about 60%, at least 70%, at least about 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%; or to below the level of detection of the assay method. In certain method, inhibition is measured at a 10 nM concentration of the siRNA using the luciferase assay provided in Example 1.

The expression of a target gene may be assessed based on the level of any variable associated with target gene expression, *e.g.,* target mRNA level or target protein level.

Inhibition may be assessed by a decrease in an absolute or relative level of one or more of these variables compared with a control level. The control level may be any type of control level that is utilized in the art, *e.g.,* a pre-dose baseline level, or a level determined from a similar subject, cell, or sample that is untreated or treated with a control (such as, *e.g.,* buffer only control or inactive agent control).

In some embodiments of the methods of the disclosure, expression of a target gene is inhibited by at least 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, or 95%, or to below the level of detection of the assay. In certain embodiments, the methods include a clinically relevant inhibition of expression of a target gene, *e.g.* as demonstrated by a clinically relevant outcome after treatment of a subject with an agent to reduce the expression of a target gene.

Inhibition of the expression of a target gene may be manifested by a reduction of the amount of mRNA expressed by a first cell or group of cells (such cells may be present, for example, in a sample derived from a subject) in which a target gene is transcribed and which has or have been treated (*e.g.,* by contacting the cell or cells with a RNAi agent of the disclosure, or by administering a RNAi agent of the disclosure to a subject in which the cells are or were present) such that the expression of a target gene is inhibited, as compared to a second cell or group of cells substantially identical to the first cell or group of cells but which has not or have not been so treated (control cell(s)

not treated with a RNAi agent or not treated with a RNAi agent targeted to the genome of interest). The degree of inhibition may be expressed in terms of:

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

In other embodiments, inhibition of the expression of a target gene may be assessed in terms of a reduction of a parameter that is functionally linked to a target gene expression, *e.g.,* target protein expression. Target gene silencing may be determined in any cell expressing a target gene, either endogenous or heterologous from an expression construct, and by any assay known in the art.

Inhibition of the expression of a target protein may be manifested by a reduction in the level of the target protein that is expressed by a cell or group of cells (*e.g.,* the level of protein expressed in a sample derived from a subject). As explained above, for the assessment of genome suppression, the inhibiton of protein expression levels in a treated cell or group of cells may similarly be expressed as a percentage of the level of protein in a control cell or group of cells.

A control cell or group of cells that may be used to assess the inhibition of the expression of a target gene includes a cell or group of cells that has not yet been contacted with an RNAi agent of the disclosure. For example, the control cell or group of cells may be derived from an individual subject (*e.g.,* a human or animal subject) prior to treatment of the subject with an RNAi agent.

The level of target gene mRNA that is expressed by a cell or group of cells may be determined using any method known in the art for assessing RNA expression. In one embodiment, the level of expression of target gene in a sample is determined by detecting a transcribed polynucleotide, or portion thereof, *e.g.,* mRNA of the target gene. RNA may be extracted from cells using RNA extraction techniques including, for example, using acid phenol/guanidine isothiocyanate extraction (RNAzol B; Biogenesis), RNeasy™ RNA preparation kits (Qiagen®) or PAXgene (PreAnalytix, Switzerland). Typical assay formats utilizing ribonucleic acid hybridization include nuclear run-on assays, RT-PCR, RNase protection assays, northern blotting, *in situ* hybridization, and microarray analysis. Circulating target mRNA may be detected using methods the described in WO2012/177906, the entire contents of which are hereby incorporated herein by reference.

In some embodiments, the level of expression of target gene is determined using a nucleic acid probe. The term "probe", as used herein, refers to any molecule that is capable of selectively binding to a specific target nucleic acid or protein, or fragment thereof. Probes can be synthesized by one of skill in the art, or derived from appropriate biological preparations. Probes may be specifically designed to be labeled. Examples of molecules that can be utilized as probes include, but are not limited to, RNA, DNA, proteins, antibodies, and organic molecules.

Isolated mRNA can be used in hybridization or amplification assays that include, but are not limited to, Southern or northern analyses, polymerase chain reaction (PCR) analyses and probe arrays. One method for the determination of RNA levels involves contacting the isolated RNA with a nucleic acid molecule (probe) that can hybridize to target RNA. In one embodiment, the RNA is immobilized

on a solid surface and contacted with a probe, for example by running the isolated RNA on an agarose gel and transferring the RNA from the gel to a membrane, such as nitrocellulose. In an alternative embodiment, the probe(s) are immobilized on a solid surface and the RNA is contacted with the probe(s), for example, in an Affymetrix® gene chip array. A skilled artisan can readily adapt known RNA detection methods for use in determining the level of target mRNA.

An alternative method for determining the level of expression of target in a sample involves the process of nucleic acid amplification or reverse transcriptase (to prepare cDNA) of for example mRNA in the sample, *e.g.*, by RT-PCR (the experimental embodiment set forth in Mullis, 1987, US Patent No. 4,683,202), ligase chain reaction (Barany (1991) *Proc. Natl. Acad. Sci. USA* 88:189-193), self sustained sequence replication (Guatelli *et al.* (1990) *Proc. Natl. Acad. Sci. USA* 87:1874-1878), transcriptional amplification system (Kwoh *et al.* (1989) *Proc. Natl. Acad. Sci. USA* 86:1173-1177), Q-Beta Replicase (Lizardi *et al.* (1988) *Bio/Technology* 6:1197), rolling circle replication (Lizardi *et al.*, US Patent No. 5,854,033) or any other nucleic acid amplification method, followed by the detection of the amplified molecules using techniques well known to those of skill in the art. These detection schemes are especially useful for the detection of nucleic acid molecules if such molecules are present in very low numbers. In particular aspects of the disclosure, the level of expression of target is determined by quantitative fluorogenic RT-PCR (*i.e.*, the TaqMan™ System), by a Dual-Glo® Luciferase assay, or by other art-recognized method for measurement of target expression or mRNA level.

The expression level of target mRNA may be monitored using a membrane blot (such as used in hybridization analysis such as northern, Southern, dot, and the like), or microwells, sample tubes, gels, beads or fibers (or any solid support comprising bound nucleic acids). See US Patent Nos. 5,770,722, 5,874,219, 5,744,305, 5,677,195 and 5,445,934, which are incorporated herein by reference. The determination of target expression level may also comprise using nucleic acid probes in solution.

In some embodiments, the level of RNA expression is assessed using branched DNA (bDNA) assays or real time PCR (qPCR). The use of this PCR method is described and exemplified in the Examples presented herein. Such methods can also be used for the detection of target nucleic acids.

The level of target protein expression may be determined using any method known in the art for the measurement of protein levels. Such methods include, for example, electrophoresis, capillary electrophoresis, high performance liquid chromatography (HPLC), thin layer chromatography (TLC), hyperdiffusion chromatography, fluid or gel precipitin reactions, absorption spectroscopy, a colorimetric assays, spectrophotometric assays, flow cytometry, immunodiffusion (single or double), immunoelectrophoresis, western blotting, radioimmunoassay (RIA), enzyme-linked immunosorbent assays (ELISAs), immunofluorescent assays, electrochemiluminescence assays, and the like. Such assays can also be used for the detection of proteins indicative of the presence or replication of target proteins.

In some embodiments, the efficacy of the methods of the disclosure in the treatment of a target gene-related disease is assessed by a decrease in target mRNA level (*e.g*, by assessment of a blood target gene level, or otherwise).

In some embodiments, the efficacy of the methods of the disclosure in the treatment of a target gene-related disease is assessed by a decrease in target mRNA level (*e.g*, by assessment of a liver or kidney sample for target level, by biopsy, or otherwise).

In some embodiments of the methods of the disclosure, the RNAi agent is administered to a subject such that the RNAi agent is delivered to a specific site within the subject. The inhibition of expression of target may be assessed using measurements of the level or change in the level of target mRNA or target protein in a sample derived from a specific site within the subject, *e.g.,* liver or kidney cells. In certain embodiments, the methods include a clinically relevant inhibition of expression of target, *e.g.* as demonstrated by a clinically relevant outcome after treatment of a subject with an agent to reduce the expression of target gene.

As used herein, the terms detecting or determining a level of an analyte are understood to mean performing the steps to determine if a material, *e.g.,* protein, RNA, is present. As used herein, methods of detecting or determining include detection or determination of an analyte level that is below the level of detection for the method used.

XI. Prophylactic and Treatment Methods of the Invention

The present invention also provides methods of using an iRNA of the invention or a composition containing an iRNA of the invention to inhibit expression of a metabolic disorder-associated target gene, thereby preventing or treating a metabolic disorder, *e.g.,* metabolic syndrome, a disorder of carbohydrates, *e.g.*, type II diabetes, pre-diabetes, a lipid metabolism disorder, *e.g.*, a hyperlipidemia, hypertension, lipodystrophy; a kidney disease; a cardiovascular disease, a disorder of body weight. In the methods of the invention the cell may be contacted with the siRNA *in vitro* or *in vivo, i.e.,* the cell may be within a subject.

A cell suitable for treatment using the methods of the invention may be any cell that expresses a metabolic disorder-associated target gene, *e.g.,* INHBE, ACVR1C, PLIN1, PDE3B, or INHBC, *e.g.*, an adipocyte cell, or a liver cell. A cell suitable for use in the methods of the invention may be a mammalian cell, *e.g.,* a primate cell (such as a human cell, including human cell in a chimeric non-human animal, or a non-human primate cell, *e.g.*, a monkey cell or a chimpanzee cell), or a non-primate cell. In certain embodiments, the cell is a human cell, *e.g.,* a human liver cell. In the methods of the invention, target gene expression is inhibited in the cell by at least 50, 55, 60, 65, 70, 75, 80, 85, 90, or 95, or to a level below the level of detection of the assay.

The *in vivo* methods of the invention may include administering to a subject 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 the targe gene of the mammal to which the RNAi agent is to be administered. The composition can be administered by any means known in the art including, but not limited to oral, intraperitoneal, or parenteral routes, including intracranial (*e.g.*, intraventricular,

intraparenchymal, and intrathecal), intravenous, intramuscular, subcutaneous, transdermal, airway (aerosol), nasal, rectal, intraocular (*e.g.*, periocular, conjunctival, subtenon, intracameral, intravitreal, intraocular, anterior or posterior juxtascleral, subretinal, subconjunctival, retrobulbar, or intracanalicular injection), intravenous, intramuscular, subcutaneous, transdermal, airway (aerosol), and topical (including buccal and sublingual) administration.

In certain embodiments, the compositions are administered by intravenous infusion or injection. In certain embodiments, the compositions are administered by subcutaneous injection. In certain embodiments, the compositions are administered by intramuscular injection.

The mode of administration may be chosen based upon whether local or systemic treatment is desired and based upon the area to be treated. The route and site of administration may be chosen to enhance targeting.

In one aspect, the present invention also provides methods for inhibiting the expression of a metabolic disorder-associated target gene selected from the group consisting of inhibin subunit beta E (INHBE), activin A receptor type 1C (ACVR1C), perilipin-1 (PLIN1), phosphodiesterase 3B (PDE3B), and inhibin subunit beta C (INHBC) in a mammal. The methods include administering to the mammal a composition comprising a dsRNA that targets a target gene in a cell of the mammal and maintaining the mammal for a time sufficient to obtain degradation of the mRNA transcript of the target gene, thereby inhibiting expression of the target gene in the cell. Reduction in gene expression can be assessed by any methods known in the art and by methods, *e.g.* qRT-PCR, described herein, *e.g.*, in Example 2. Reduction in protein production can be assessed by any methods known it the art, *e.g.* ELISA. In certain embodiments, a puncture liver biopsy sample serves as the tissue material for monitoring the reduction in the target gene or protein expression. In other embodiments, a blood sample serves as the subject sample for monitoring the reduction in the target protein expression.

The present invention further provides methods of treatment in a subject in need thereof, *e.g.*, a subject diagnosed with a a metabolic disorder, *e.g.,* metabolic syndrome, a disorder of carbohydrates, *e.g.*, type II diabetes, pre-diabetes, a lipid metabolism disorder, *e.g.*, a hyperlipidemia, hypertension, lipodystrophy; a kidney disease; a cardiovascular disease, a disorder of body weight.

The present invention further provides methods of prophylaxis in a subject in need thereof. The treatment methods of the invention include administering an iRNA of the invention to a subject, *e.g.*, a subject that would benefit from a reduction of expression of a metabolic disorder-associated target gene selected from the group consisting of inhibin subunit beta E (INHBE), activin A receptor type 1C (ACVR1C), perilipin-1 (PLIN1), phosphodiesterase 3B (PDE3B), and inhibin subunit beta C (INHBC), in a prophylactically effective amount of a dsRNA targeting INHBE, ACVR1C, PLIN1, PDE3B, or INHBC or a pharmaceutical composition comprising a dsRNA targeting INHBE, ACVR1C, PLIN1, PDE3B, or INHBC.

In one aspect, the present invention provides methods of treating a subject having a disorder that would benefit from reduction in expression of a metabolic disorder-associated target gene selected from the group consisting of inhibin subunit beta E (INHBE), activin A receptor type 1C (ACVR1C), perilipin-

1 (PLIN1), phosphodiesterase 3B (PDE3B), and inhibin subunit beta C (INHBC), *e.g.,* a metabolic disorder, *e.g.,* diabetes.

Treatment of a subject that would benefit from a reduction and/or inhibition of INHBE, ACVR1C, PLIN1, PDE3B, or INHBC gene expression includes therapeutic treatment (*e.g.*, a subject is having a metabolic disorder) and prophylactic treatment (*e.g.*, the subject is not having a metablic disorder or a subject may be at risk of developing a metabolic disorder).

Examples of metablic disorders include but are not limited to, metabolic syndrome, a disorder of carbohydrates, *e.g.*, type II diabetes, pre-diabetes, a lipid metabolism disorder, *e.g.*, a hyperlipidemia, hypertension, lipodystrophy; a kidney disease; a cardiovascular disease, a disorder of body weight.

In some embodiments, the metablic disorder is metabolic syndrome.

In some embodiments, the RNAi agent is administered to a subject in an amount effective to inhibit expression of a metabolic disorder-associated target gene selected from the group consisting of inhibin subunit beta E (INHBE), activin A receptor type 1C (ACVR1C), perilipin-1 (PLIN1), phosphodiesterase 3B (PDE3B), and inhibin subunit beta C (INHBC) in a cell within the subject. The amount effective to inhibit target gene expression in a cell within a subject may be assessed using methods discussed above, including methods that involve assessment of the inhibition of target gene mRNA, target gene protein, or related variables, such as insulin resistance, BMI, WHRadj BMI, adipose tissue, *e.g.,* image-based quantification of adipose tissue, *e.g.,* MRI or DEXA for abdominal subcutaneous adipose and visceral adipose tissue quantification.

An iRNA of the invention may be administered as a "free iRNA." A free iRNA is administered in the absence of a pharmaceutical composition. The naked iRNA may be in a suitable buffer solution. The buffer solution may comprise acetate, citrate, prolamine, carbonate, or phosphate, or any combination thereof. In one embodiment, the buffer solution is phosphate buffered saline (PBS). The pH and osmolarity of the buffer solution containing the iRNA can be adjusted such that it is suitable for administering to a subject.

Alternatively, an iRNA of the invention may be administered as a pharmaceutical composition, such as a dsRNA liposomal formulation.

Subjects that would benefit from an inhibition of INHBE, ACVR1C, PLIN1, PDE3B, or INHBC gene expression are subjects susceptible to or diagnosed with a metablic disorder, *e.g.,* metabolic syndrome, a disorder of carbohydrates, *e.g.*, type II diabetes, pre-diabetes, a lipid metabolism disorder, *e.g.*, a hyperlipidemia, hypertension, lipodystrophy; a kidney disease; a cardiovascular disease, a disorder of body weight. In an embodiment, the method includes administering a composition featured herein such that expression of the target gene is decreased, such as for about 1, 2, 3, 4, 5, 6, 1-6, 1-3, or 3-6 months per dose. In certain embodiments, the composition is administered once every 3-6 months.

In one embodiment, the iRNAs useful for the methods and compositions featured herein specifically target RNAs (primary or processed) of the target gene. Compositions and methods for inhibiting the expression of these genes using iRNAs can be prepared and performed as described herein.

Administration of the iRNA according to the methods of the invention may result prevention or treatment of a metablic disorder, *e.g.,* metabolic syndrome, a disorder of carbohydrates, *e.g.*, type II diabetes, pre-diabetes, a lipid metabolism disorder, *e.g.*, a hyperlipidemia, hypertension, lipodystrophy; a kidney disease; a cardiovascular disease, a disorder of body weight. Subjects can be administered a therapeutic amount of iRNA, such as about 0.01 mg/kg to about 200 mg/kg.

In one embodiment, the iRNA is administered subcutaneously, *i.e.*, by subcutaneous injection. One or more injections may be used to deliver the desired dose of iRNA to a subject. The injections may be repeated over a period of time.

The administration may be repeated on a regular basis. In certain embodiments, after an initial treatment regimen, the treatments can be administered on a less frequent basis. A repeat-dose regimen may include administration of a therapeutic amount of iRNA on a regular basis, such as once per month to once a year. In certain embodiments, the iRNA is administered about once per month to about once every three months, or about once every three months to about once every six months.

The invention further provides methods and uses of an iRNA agent or a pharmaceutical composition thereof for treating a subject that would benefit from reduction and/or inhibition of INHBE, ACVR1C, PLIN1, PDE3B, or INHBC gene expression, *e.g.*, a subject having a metabolic disorder, in combination with other pharmaceuticals and/or other therapeutic methods, *e.g.*, with known pharmaceuticals and/or known therapeutic methods, such as, for example, those which are currently employed for treating these disorders.

Accordingly, in some aspects of the invention, the methods which include administration of an iRNA agent of the invention, further include administering to the subject one or more additional therapeutic agents.

For example, in certain embodiments, an iRNA targeting INHBE, ACVR1C, PLIN1, PDE3B, or INHBC is administered in combination with, *e.g.*, an agent useful in treating a metabolic disorder as described herein or otherwise known in the art. For example, additional agents and treatments suitable for treating a subject that would benefit from reducton in INHBE, ACVR1C, PLIN1, PDE3B, or INHBC expression, *e.g.*, a subject having a metabolic disorder, may include agents currently used to treat symptoms of a metabolic disorder.

Examples of the additional therapeutic agents which can be used with an RNAi agent of the invention include, but are not limited to, insulin, a glucagon-like peptide 1 agonist (*e.g.*, exenatide, liraglutide, dulaglutide, semaglutide, and pramlintide, a sulfonylurea (*e.g.*, chlorpropamide, glipizide), a seglitinide (*e.g.*, repaglinide, nateglinidie), biguanides (*e.g.*, metformin), a thiazolidinedione, e.g, rosiglitazone, troglitazone, an alpha-glucosidase inhibitor (*e.g.*, acarbose and meglitol), an SGLT2 inhibitor (*e.g.*, dapagliflozin), a DPP-4 inhibitor (*e.g.*, linagliptin), or an HMG-CoA reductase inhibitor, *e.g.*, statins, such as atorvastatin (Lipitor), fluvastatin (Lescol), lovastatin (Mevacor), lovastatin extended-release (Altoprev), pitavastatin (Livalo), pravastatin (Pravachol), rosuvastatin (Crestor), and simvastatin (Zocor).

The method according to any one of claims 34 to 36, wherein the metabolic disorder is type 2 diabetes, and the therapeutic agent is chosen from metformin, insulin, glyburide, glipizide,

glimepiride, repaglinide, nateglinide, thiazolidinediones, rosiglitazone, pioglitazone, sitagliptin, saxagliptin, linagliptin, exenatide, liraglutide, semaglutide, canagliflozin, dapagliflozin, and empagliflozin, or any combination thereof.

In one embodiment, the metabolic disorder is obesity, and the therapeutic agent is chosen from orlistat, phentermine, topiramate, bupropion, naltrexone, and liraglutide, or any combination thereof.

In one embodiment, the metabolic disorder is elevated triglyceride, and the therapeutic agent is chosen from rosuvastatin, simvastatin, atorvastatin, fenofibrate, gemfibrozil, fenofibric acid, niacin, and an omega-3 fatty acid, or any combination thereof.

In one embodiment, the metabolic disorder is lipodystrophy, and the therapeutic agent is chosen from tesamorelin, metformin, poly-L-lactic acid, calcium hydroxyapatite, polymethylmethacrylate, bovine collagens, human collagens, silicone, and hyaluronic acid, or any combination thereof.

In one embodiment, the metabolic disorder is liver inflammation, and the therapeutic agent is a hepatitis therapeutic or a hepatitis vaccine.

In one embodiment, the metabolic disorder is fatty liver disease include, and the subject is administered bariatric surgery and/or dietary intervention.

In one embodiment, the metabolic disorder is hypercholesterolemia, and the therapeutic agent is chosen from: atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin calcium, simvastatin, cholestyramine, colesevelam, and colestipol, alirocumab, evolocumab, niaspan, niacor, fenofibrate, gemfibrozil, and bempedoic, or any combination thereof.

In one embodiment, the metabolic disorder is an elevated liver enzyme), and the therapeutic agent is chosen from coffee, folic acid, potassium, vitamin B6, a statin, and fiber, or any combination thereof.

In one embodiment, the metabolic disorder is nonalcoholic steatohepatitis (NASH) and the therapeutic agent is obeticholic acid, Selonsertib, Elafibranor, Cenicriviroc, GR_MD_02, MGL_3196, IMM124E, arachidyl amido cholanoic acid, GS0976, Emricasan, Volixibat, NGM282, GS9674, Tropifexor, MN_001, LMB763, Bl_1467335, MSDC_0602, PF_05221304, DF102, Saroglitazar, BMS986036, Lanifibranor, Semaglutide, Nitazoxanide, GRI_0621, EYP001, VK2809, Nalmefene, LIK066, MT_3995, Elobixibat, Namodenoson, Foralumab, SAR425899, Sotagliflozin, EDP_305, Isosabutate, Gemcabene, TERN_101, KBP_042, PF_06865571, DUR928, PF_06835919, NGM313, BMS_986171, Namacizumab, CER_209, ND_L02_s0201, RTU_1096, DRX_065, IONIS_DGAT2Rx, INT_767, NC_001, Seladepar, PXL770, TERN_201, NV556, AZD2693, SP_1373, VK0214, Hepastem, TGFTX4, RLBN1127, GKT_137831, RYI_018, CB4209-CB4211, and JH_0920.

In one embodiment, the therapeutic agent that treats or inhibits the metabolic disorder is a melanocortin 4 receptor (MC4R) agonist.

In one embodiment, the MC4R agonist comprises a protein, a peptide, a nucleic acid molecule, or a small molecule.

In one embodiment, the protein is a peptide analog of MC4R.

In one embodiment, the peptide is setmelanotide.

In one embodiment, the MC4R agonist is a peptide comprising the amino acid sequence His-Phe-Arg-Trp.

In one embodiment, the small molecule is 1,2,3R,4-tetrahydroisoquinoline-3-carboxylic acid.

In one embodiment, the MC4R agonist is ALB-127158(a).

In one embodiment, the cardiovascular disease is high blood pressure, and the therapeutic agent is chosen from chlorthalidone, chlorothiazide, hydrochlorothiazide, indapamide, metolazone, acebutolol, atenolol, betaxolol, bisoprolol fumarate, carteolol hydrochloride, metoprolol tartrate, metoprolol succinate, nadolol, benazepril hydrochloride, captopril, enalapril maleate, fosinopril sodium, lisinopril, moexipril, perindopril, quinapril hydrochloride, ramipril, trandolapril, candesartan, eprosartan mesylate, irbesartan, losartan potassium, telmisartan, valsartan, amlodipine besylate, bepridil, diltiazem hydrochloride, felodipine, isradipine, nicardipine, nifedipine, nisoldipine, verapamil hydrochloride, doxazosin mesylate, prazosin hydrochloride, terazosin hydrochloride, methyldopa, carvedilol labetalol hydrochloride, alpha methyldopa, clonidine hydrochloride, guanabenz acetate, guanfacine hydrochloride, guanadrel, guanethidine monosulfate, reserpine, hydralazine hydrochloride, and minoxidil, or any combination thereof.

In one embodiment, the cardiovascular disease is cardiomyopathy, and the therapeutic agent is an ACE inhibitor, an angiotensin II receptor blocker, a beta blocker, a calcium channel blocker, digoxin, an antiarrhythmic, an aldosterone blocker, a diuretic, an anticoagulant, a blood thinner, and a corticosteroid.

In one embodiment, the cardiovascular disease is heart failure, and the therapeutic agent is an ACE inhibitor, an angiotensin-2 receptor blocker, a beta blocker, a mineralocorticoid receptor antagonist, a diuretic, ivabradine, sacubitril valsartan, hydralazine with nitrate, and digoxin.

The iRNA agent and an additional therapeutic agent and/or treatment may be administered at the same time and/or in the same combination, *e.g.*, parenterally, or the additional therapeutic agent can be administered as part of a separate composition or at separate times and/or by another method known in the art or described herein.

XII. Kits

In certain aspects, the instant disclosure provides kits that include a suitable container containing a pharmaceutical formulation of a siRNA compound, *e.g.*, a double-stranded siRNA compound, or siRNA compound, (*e.g.*, a precursor, *e.g.*, a larger siRNA compound which can be processed into a siRNA compound, or a DNA which encodes an siRNA compound, *e.g.*, a double-stranded siRNA compound, or ssiRNA compound, or precursor thereof).

Such kits include one or more dsRNA agent(s) and instructions for use, *e.g.*, instructions for administering a prophylactically or therapeutically effective amount of a dsRNA agent(s). The dsRNA agent may be in a vial or a pre-filled syringe. The kits may optionally further comprise means for administering the dsRNA agent (*e.g.*, an injection device, such as a pre-filled syringe), or means

for measuring the inhibition of a metabolic disorder-associated target gene, *e.g.,* INHBE, ACVR1C, PLIN1, PDE3B, or INHBC (*e.g.,* means for measuring the inhibition of target gene mRNA, target gene protein, and/or target gebe activity). Such means for measuring the inhibition of target gene may comprise a means for obtaining a sample from a subject, such as, *e.g.*, a plasma sample. The kits of the invention may optionally further comprise means for determining the therapeutically effective or prophylactically effective amount.

In certain embodiments the individual components of the pharmaceutical formulation may be provided in one container, *e.g.,* a vial or a pre-filled syringe. Alternatively, it may be desirable to provide the components of the pharmaceutical formulation separately in two or more containers, *e.g.*, one container for a siRNA compound preparation, and at least another for a carrier compound. The kit may be packaged in a number of different configurations such as one or more containers in a single box. The different components can be combined, *e.g.*, according to instructions provided with the kit. The components can be combined according to a method described herein, *e.g.*, to prepare and administer a pharmaceutical composition. The kit can also include a delivery device.

This invention is further illustrated by the following examples which should not be construed as limiting. The entire contents of all references, patents and published patent applications cited throughout this application, as well as the informal Sequence Listing and Figures, are hereby incorporated herein by reference.

EXAMPLES

Example 1. Identification of Association of INHBE Loss-Of-Function with Waist-To-Hip Ratio in UK Biobank

Abdominal obesity is the most prevalent manifestation of metabolic syndrome (Després J. and Lemieux I. *Nature* 2006; 444:881-887) and is recognized as a contributor to cardiovascular disease and metabolic risk beyond body mass index (BMI) (Neeland IJ *et al. Lancet Diabetes & Endocrinology* 2019; 7(9):715-725). Waist-to-hip ratio adjusted for BMI (WHRadjBMI) reflects abdominal adiposity and correlates with direct imaging of abdominal fat. Mendelian randomization studies have shown a causal relationship between WHRadjBMI and risk of type 2 diabetes and coronary heart disease along with ischemic stroke, glycemic traits and circulating lipids (Emdin CA *et al. JAMA* 2017; 317(6):626-634; Dale CE *et al. Circulation* 2017; 135(24):2373-2388).

Rare genetic variants were tested for association with waist-to-hip ratio adjusted for BMI using exome sequencing data from the UK Biobank (UKBB). UKBB, a large long-term biobank study in the United Kingdom (UK) is investigating the respective contributions of genetic predisposition and environmental exposure (including nutrition, lifestyle, medications etc.) to the development of disease (see, *e.g.*, www.ukbiobank.ac.uk). The study is following about 500,000 volunteers in the UK, enrolled at ages from 40 to 69. Initial enrollment took place over four years from 2006, and the volunteers will be followed for at least 30 years thereafter. A plethora of phenotypic data has been collected including anthropometric measurements such as waist and hip circumference. Recently, the exome sequencing data (or the portion of the genomes composed of exons) from about 450,000 participants in the study has been obtained.

These whole exome sequences were used to identify rare predicted loss-of-function (pLOF) variants (*i.e.*, frameshift, stop gain, splice donor or splice acceptor variants) called as high confidence by LOFTEE. WHR adjBMI were calculated for participants using manual measurements for waist circumference, hip circumference, and body mass index (BMI) which were taken at their UKBB assessment. WHR was calculated as the ratio of these two measurements. Using these data, along with age at recruitment and sex, a linear model was built modeling WHR (WHR ~ Age + Sex + BMI). WHR adjBMI was defined using the residuals from this model.

Gene-based collapsing tests (*i.e.*, burden tests) were used to look for associations between rare (minor allele frequency ≤1%) pLOF variants and WHRadjBMI. Burden testing was performed in the unrelated White population (n=363,973) adjusting for age, sex and genetic ancestry via 12 principal components. INHBE pLOF associated with a 0.22 standard deviation decrease in WHRadjBMI (Table A). INHBE was tested for association with additional quantitative traits and we detected associations with birth weight, WHR (not adjusted for BMI), triglycerides and HDL cholesterol (Table A). INHBE pLOF also has a lower odds ratio for hypertension, coronary heart disease and T2D (Table B)

The most common INHBE pLOF variant in the UKBB exome-sequencing data was a splice acceptor variant (rs150777893) carried by 536 out of 620 pLOF carriers. Tested as a single variant, rs150777893 significantly associated with decreased WHRadj BMI (Table C).

Table A: Association of INHBE pLOF with WHRadj BMI and other traits

	Variant set	pvalue	Effect (SD)	N carrier measured
WaistHipRatioAdjBMI	INHBE pLOF	4.76E-08	-0.22	618
EarlyLife_Birth_weight	INHBE pLOF	7.01E-07	0.26	345
WaistHipRatio	INHBE pLOF	3.45E-05	-0.13	619
Blood_Biochemistry_Triglycerides	INHBE pLOF	0.001	-0.13	594
Blood_Biochemistry_HDL_cholesterol	INHBE pLOF	0.01	0.10	550

Table B: Association of INHBE pLOF with hypertension, heat disease and T2D

phenotype	pvalue	Odds ratio (95% CI)	n carrier cases	n expected
I10_essential_primary_hypertension	0.10	0.86 (0.71, 1.03)	186	202.31
I25_chronic_ischaemic_heart_disease	0.21	0.83 (0.63, 1.11)	56	61.31
E11_non_insulin_dependent_diabetes	0.36	0.87 (0.64, 1.18)	45	50.30

Table C: Association of splice acceptor variant rs150777893 with WHRadjBMI

	chrom	pos	ref	alt	pvalue	Effect (SD)	rsid	gene	consequence	MAF white	N white carriers
WHRAdj BMI	12	57456093	G	C	3.75 E-08	-0.24	rs1507 77893	INHB E	splice acceptor variant	0.07 %	539

Example 2. iRNA Synthesis

Source of reagents

Where the source of a reagent is not specifically given herein, such reagent can be obtained from any supplier of reagents for molecular biology at a quality/purity standard for application in molecular biology.

siRNA Design

siRNAs targeting the inhibin subunit beta E gene (INHBE, human: NCBI refseqID NM_031479.5, NCBI Gene ID: 83729) were designed using custom R and Python scripts. The human NM_031479.5 mRNA has a length of 2460 bases.

Detailed lists of the unmodified INHBE sense and antisense strand nucleotide sequences are shown in Table 2.

Detailed lists of the modified INHBE sense and antisense strand nucleotide sequences are shown in Table 3.

siRNAs targeting the activin A receptor type 1C (ACVR1C) gene (ACVR1C, human: NCBI refseqID NM_145259.3, NCBI Gene ID: 130399) were designed using custom R and Python scripts. The human NM_145259.3 mRNA has a length of 8853 bases.

Detailed lists of the unmodified sense and antisense strand sequences of ACVR1C dsRNA agents comprising an unsaturated C22 hydrocarbon chain conjugated to position 6 on the sense strand, counting from the 5'-end of the sense strand are shown in Table 4.

Detailed lists of the modified sense and antisense strand sequences of ACVR1C dsRNA agents comprising an unsaturated C22 hydrocarbon chain conjugated to position 6 on the sense strand, counting from the 5'-end of the sense strand are shown in Table 5.

Detailed lists of the unmodified sense and antisense strand sequences of ACVR1C dsRNA agents comprising a GalNAc derivative targeting ligand are shown in Table 6.

Detailed lists of the modified sense and antisense strand sequences of ACVR1C dsRNA agents comprising a GalNAc derivative targeting ligand are shown in Table 7.

siRNAs targeting the perilipin-1 (PLIN1) gene (PLIN1, human: NCBI refseqID NM_002666.5, NCBI Gene ID: 5346) were designed using custom R and Python scripts. The human NM_002666.5 mRNA has a length of 2916 bases.

Detailed lists of the unmodified sense and antisense strand sequences of PLIN1 dsRNA agents comprising an unsaturated C22 hydrocarbon chain conjugated to position 6 on the sense strand, counting from the 5'-end of the sense strand are shown in Table 8.

Detailed lists of the modified sense and antisense strand sequences of PLIN1 dsRNA agents comprising an unsaturated C22 hydrocarbon chain conjugated to position 6 on the sense strand, counting from the 5'-end of the sense strand are shown in Table 9.

Detailed lists of the unmodified sense and antisense strand sequences of PLIN1 dsRNA agents comprising a GalNAc derivative targeting ligand are shown in Table 10.

Detailed lists of the modified sense and antisense strand sequences of PLIN1 dsRNA agents comprising a GalNAc derivative targeting ligand are shown in Table 11.

siRNAs targeting the phosphodiesterase 3B (PDE3B) gene (PDE3B, human: NCBI refseqID NM_000922.4, NCBI Gene ID: 5140) were designed using custom R and Python scripts. The human NM_000922.4 mRNA has a length of 5995 bases.

Detailed lists of the unmodified sense and antisense strand sequences of PDE3B dsRNA agents comprising an unsaturated C22 hydrocarbon chain conjugated to position 6 on the sense strand, counting from the 5'-end of the sense strand are shown in Table 12.

Detailed lists of the modified sense and antisense strand sequences of PDE3B dsRNA agents comprising an unsaturated C22 hydrocarbon chain conjugated to position 6 on the sense strand, counting from the 5'-end of the sense strand are shown in Table 13.

Detailed lists of the unmodified sense and antisense strand sequences of PDE3B dsRNA agents comprising a GalNAc derivative targeting ligand are shown in Table 14.

Detailed lists of the modified sense and antisense strand sequences of PDE3B dsRNA agents comprising a GalNAc derivative targeting ligand are shown in Table 15.

siRNAs targeting the inhibin subunit beta C (INHBC) gene (INHBC, human: NCBI refseqID NM_005538.4, NCBI Gene ID: 3626) were designed using custom R and Python scripts. The human NM_005538.4, mRNA has a length of 3202 bases.

Detailed lists of the unmodified sense and antisense strand sequences of INHBC dsRNA agents comprising a GalNAc derivative targeting ligand are shown in Table 16.

Detailed lists of the modified sense and antisense strand sequences of INHBC dsRNA agents comprising a GalNAc derivative targeting ligand are shown in Table 17.

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-959917 is equivalent to AD-959917.1.

siRNA Synthesis

siRNAs were designed, synthesized, and prepared using methods known in the art.

Briefly, siRNA sequences were synthesized on a 1 µmol scale using a Mermade 192 synthesizer (BioAutomation) with phosphoramidite chemistry on solid supports. The solid support was controlled pore glass (500-1000 Å) loaded with a custom GalNAc ligand (3'-GalNAc conjugates), universal solid support (AM Chemicals), or the first nucleotide of interest. Ancillary synthesis reagents and standard 2-cyanoethyl phosphoramidite monomers (2'-deoxy-2'-fluoro, 2'-O-methyl, RNA, DNA) were obtained from Thermo-Fisher (Milwaukee, WI), Hongene (China), or Chemgenes (Wilmington, MA, USA). Additional phosphoramidite monomers were procured from commercial suppliers, prepared in-house, or procured using custom synthesis from various CMOs. Phosphoramidites were prepared at a concentration of 100 mM in either acetonitrile or 9:1 acetonitrile:DMF and were coupled using 5-Ethylthio-1H-tetrazole (ETT, 0.25 M in acetonitrile) with a reaction time of 400 s. Phosphorothioate linkages were generated using a 100 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 (9:1 v/v). Oxidation time was 5 minutes. All sequences were synthesized with final removal of the DMT group ("DMT-Off").

Upon completion of the solid phase synthesis, solid-supported oligoribonucleotides were treated with 300 µL of Methylamine (40% aqueous) at room temperature in 96 well plates for approximately 2 hours to afford cleavage from the solid support and subsequent removal of all additional base-labile protecting groups. For sequences containing any natural ribonucleotide linkages (2'-OH) protected with a tert-butyl dimethyl silyl (TBDMS) group, a second deprotection step was performed using TEA.3HF (triethylamine trihydrofluoride). To each oligonucleotide solution in aqueous methylamine was added 200 µL of dimethyl sulfoxide (DMSO) and 300 µL TEA.3HF and the solution was incubated for approximately 30 mins at 60 °C. After incubation, the plate was allowed to come to room temperature and crude oligonucleotides were precipitated by the addition of 1 mL of 9:1 acetontrile:ethanol or 1:1 ethanol:isopropanol. The plates were then centrifuged at 4 °C

for 45 mins and the supernatant carefully decanted with the aid of a multichannel pipette. The oligonucleotide pellet was resuspended in 20 mM NaOAc and subsequently desalted using a HiTrap size exclusion column (5 mL, GE Healthcare) on an Agilent LC system equipped with an autosampler, UV detector, conductivity meter, and fraction collector. Desalted samples were collected in 96 well plates and then analyzed by LC-MS and UV spectrometry to confirm identity and quantify the amount of material, respectively.

Duplexing of single strands was performed on a Tecan liquid handling robot. Sense and antisense single strands were combined in an equimolar ratio to a final concentration of 10 µM in 1x PBS in 96 well plates, the plate sealed, incubated at 100 °C for 10 minutes, and subsequently allowed to return slowly to room temperature over a period of 2-3 hours. The concentration and identity of each duplex was confirmed and then subsequently utilized for *in vitro* screening assays.

Example 3. *In vitro* screening methods

Cell culture and 96-well transfections

Hep3b cells (ATCC, Manassas, VA) 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 7.5 µl of Opti-MEM plus 0.3 µl of Lipofectamine RNAiMax per well (Invitrogen, Carlsbad CA. cat # 13778-150) to 2.5 µl of each siRNA duplex to an individual well in a 384-well plate. The mixture was then incubated at room temperature for 15 minutes. Forty µl of complete growth media without antibiotic containing ~1.5 x10^4 cells were then added to the siRNA mixture. Cells were incubated for 24 hours prior to RNA purification. Single dose experiments were performed at 10 nM, and 1 nM final duplex concentration.

Total RNA isolation using DYNABEADS mRNA Isolation Kit (Invitrogen™, part #: 610-12)

Cells were lysed in 75µl of Lysis/Binding Buffer containing 3 µL of beads per well and 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 90µL) 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, 1µl Random primers, 0.5µl Reverse Transcriptase, 0.5µl RNase inhibitor and 6.6µl of H_2O per reaction were added per well. Plates were sealed, agitated for 10 minutes on an electrostatic shaker, and then incubated at 37 degrees C for 2 hours. Following this, the plates were agitated at 80 degrees C for 8 minutes.

Real time PCR

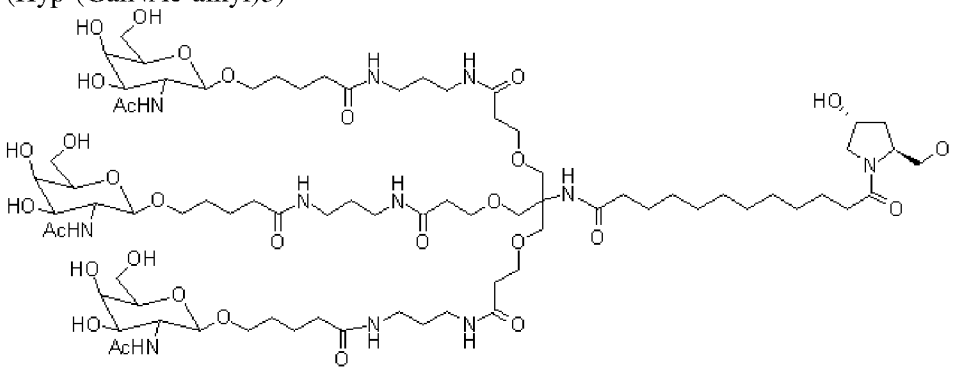
Two microlitre (µl) of cDNA were added to a master mix containing 0.5µl of human GAPDH TaqMan Probe (4326317E), 0.5µl human INHBE, 2µl nuclease-free water and 5µl Lightcycler 480 probe master mix (Roche Cat # 04887301001) per well in a 384 well plates (Roche cat # 04887301001). Real time PCR was done in a LightCycler480 Real Time PCR system (Roche).

To calculate relative fold change, data were analyzed using the ΔΔCt method and normalized to assays performed with cells transfected with 10nM AD-1955, or mock transfected cells. IC_{50}s are calculated using a 4 parameter fit model using XLFit and normalized to cells transfected with AD-1955 or mock-transfected. The sense and antisense sequences of AD-1955 are: sense: cuuAcGcuGAGuAcuucGAdTsdT and antisense UCGAAGuACUcAGCGuAAGdTsdT.

Table 18 shows the results of a single dose screen in Hep3b cells transfected with the indicated agents from Tables 2 and 3.

Table 1. 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; and it is understood that when the nucleotide contains a 2'-fluoro modification, then the fluoro replaces the hydroxy at that position in the parent nucleotide (*i.e.*, it is a 2'-deoxy-2'-fluoronucleotide).

Abbre*via*tion	**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
As	adenosine-3'-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
Cs	cytidine-3'-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
Gs	guanosine-3'-phosphorothioate
T	5'-methyluridine-3'-phosphate
Tf	2'-fluoro-5-methyluridine-3'-phosphate
Tfs	2'-fluoro-5-methyluridine-3'-phosphorothioate
Ts	5-methyluridine-3'-phosphorothioate
U	Uridine-3'-phosphate
Uf	2'-fluorouridine-3'-phosphate
Ufs	2'-fluorouridine -3'-phosphorothioate
Us	uridine -3'-phosphorothioate

Abbre*via*tion	Nucleotide(s)
N	any nucleotide, modified or unmodified
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
s	phosphorothioate linkage
L10	N-(cholesterylcarboxamidocaproyl)-4-hydroxyprolinol (Hyp-C6-Chol)
L96	N-[tris(GalNAc-alkyl)-amidodecanoyl)]-4-hydroxyprolinol (Hyp-(GalNAc-alkyl)3) 
Y34	2-hydroxymethyl-tetrahydrofurane-4-methoxy-3-phosphate (abasic 2'-OMe furanose)
Y44	inverted abasic DNA (2-hydroxymethyl-tetrahydrofurane-5-phosphate)
(Agn)	Adenosine-glycol nucleic acid (GNA)
(Cgn)	Cytidine-glycol nucleic acid (GNA)
(Ggn)	Guanosine-glycol nucleic acid (GNA)
(Tgn)	Thymidine-glycol nucleic acid (GNA) S-Isomer
P	Phosphate
VP	Vinyl-phosphonate
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`-deoxythimidine -3`-phosphate
dTs	2`-deoxythimidine-3`-phosphorothioate
dU	2`-deoxyuridine
dUs	2`-deoxyuridine-3`-phosphorothioate
(C2p)	cytidine-2`-phosphate
(G2p)	guanosine-2`-phosphate
(U2p)	uridine-2`-phosphate
(A2p)	adenosine-2`-phosphate
(Chd)	2'-O-hexadecyl-cytidine-3'-phosphate
(Ahd)	2'-O-hexadecyl-adenosine-3'-phosphate
(Ghd)	2'-O-hexadecyl-guanosine-3'-phosphate

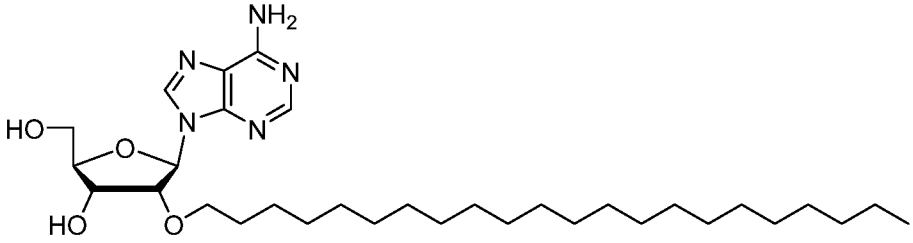
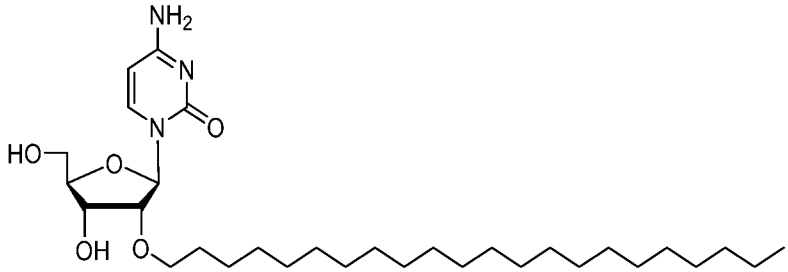
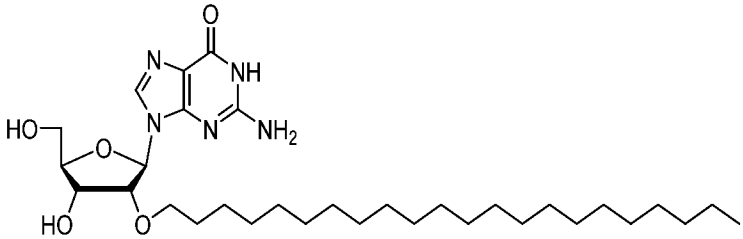
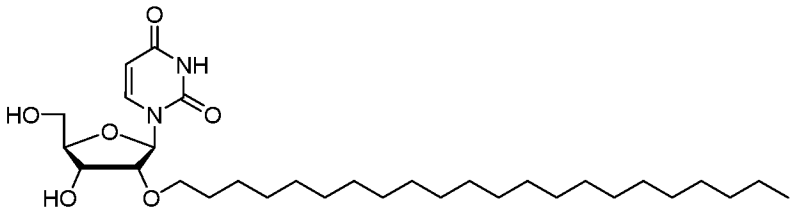
Abbreviation	Nucleotide(s)
(Uhd)	2'-O-hexadecyl-uridine-3'-phosphate
Ada	 (2*R*,3*S*,4*S*,5*R*)-5-(6-amino-9*H*-purin-9-yl)-4-(docosyloxy)-2-(hydroxymethyl)tetrahydrofuran-3-ol
Cda	 4-amino-1-((2*R*,3*R*,4*R*,5*R*)-3-(docosyloxy)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)pyrimidin-2(1*H*)-one
Gda	 2-amino-9-((2*R*,3*S*,4*S*,5*R*)-3-(docosyloxy)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-1,9-dihydro-6*H*-purin-6-one
Uda	 1-((2*R*,3*R*,4*R*,5*R*)-3-(docosyloxy)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione

Table 2. Unmodified Sense and Antisense Strand Sequences of INHBE dsRNA Agents

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in INHBE mRNA NM_031479.5	Antisense Sequence 5' to 3'	SEQ ID NO:
AD-1656008	UAGCCAGACAUGAGCUGUGAU		1-23	AUCACAGCUCAUGUCUGGCUACU	
AD-1656026	GAGGGUCAAGCACAGCUAUCU		19-41	AGAUAGCUGUGCUUGACCCUCAC	
AD-1656043	AUCCAUCAGAUGAUCUACUUU		36-58	AAAGUAGAUCAUCUGAUGGAUAG	
AD-1656054	GAUCUACUUUCAGCCUUCCUU		47-69	AAGGAAGGCUGAAAGUAGAUCAU	
AD-1656074	GAGUCCCAGACAAUAGAAGAU		67-89	AUCUUCUAUUGUCUGGGACUCAG	
AD-1656086	AUAGAAGACAGGUGGCUGUAU		79-101	AUACAGCCACCUGUCUUCUAUUG	
AD-1656097	GUGGCUGUACCCUUGGCCAAU		90-112	AUUGGCCAAGGGUACAGCCACCU	
AD-1656108	CUUGGCCAAGGGUAGGUGUGU		101-123	ACACACCUACCCUUGGCCAAGGG	
AD-1656125	GUGGCAGUGGUGUCUGCUGUU		118-140	AACAGCAGACACCACUGCCACAC	
AD-1656139	UGCUGUCACUGUGCCCUCAUU		132-154	AAUGAGGGCACAGUGACAGCAGA	
AD-1656146	AGCAAUCAGACUCAACAGACU		160-182	AGUCUGUUGAGUCUGAUUGCUGG	
AD-1656164	ACGGAGCAACUGCCAUCCGAU		178-200	AUCGGAUGGCAGUUGCUCCGUCU	
AD-1656185	GCUCCUGAACCAGGGCCAUUU		199-221	AAAUGGCCCUGGUUCAGGAGCCU	
AD-1656196	AGGGCCAUUCACCAGGAGCAU		210-232	AUGCUCCUGGUGAAUGGCCCUGG	
AD-1656220	GCUCCCUGAUGUCCAGCUCUU		234-256	AAGAGCUGGACAUCAGGGAGCCG	
AD-1656233	CAGCUCUGGCUGGUGCUGCUU		247-269	AAGCAGCACCAGCCAGAGCUGGA	
AD-1656254	UGGGCACUGGUGCGAGCACAU		268-290	AUGUGCUCGCACCAGUGCCCACA	
AD-1656260	AGGGUCUGUGUGUCCCUCCUU		294-316	AAGGAGGGACACACAGACCCUGU	
AD-1656265	CAAGCAGAACGAGCUCUGGUU		337-359	AACCAGAGCUCGUUCUGCUUGGG	
AD-1656280	CUGGUGCUGGAGCUAGCCAAU		352-374	AUUGGCUAGCUCCAGCACCAGAG	
AD-1656292	CUAGCCAAGCAGCAAAUCCUU		364-386	AAGGAUUUGCUGCUUGGCUAGCU	
AD-1656307	AUCCUGGAUGGGUUGCACCUU		379-401	AAGGUGCAACCCAUCCAGGAUUU	
AD-1656319	UUGCACCUGACCAGUCGUCCU		391-413	AGGACGACUGGUCAGGUGCAACC	
AD-1656333	UCGUCCCAGAAUAACUCAUCU		405-427	AGAUGAGUUAUUCUGGGACGACU	

AD-1656360	CCCUCCGGAGACUACAGCCAU		452-474	AUGGCUGUAGUCUCCGGAGGGCU	
AD-1656372	UACAGCCAGGGAGUGUGGCUU		464-486	AAGCCACACUCCCUGGCUGUAGU	
AD-1656383	AGUGUGGCUCCAGGGAAUGGU		475-497	ACCAUUCCCUGGAGCCACACUCC	
AD-1656392	CAUCAGCUUUGCUACUGUCAU		504-526	AUGACAGUAGCAAAGCUGAUGAC	
AD-1656406	CUGUCACAGACUCCACUUCAU		518-540	AUGAAGUGGAGUCUGUGACAGUA	
AD-1656417	UCCACUUCAGCCUACAGCUCU		529-551	AGAGCUGUAGGCUGAAGUGGAGU	
AD-1656437	CCUGCUCACUUUUUCACCUGUU		549-571	AACAGGUGAAAAAGUGAGCAGGGA	
AD-1656449	UCACCUGUCCACUCCUCGGUU		561-583	AACCGAGGAGUGGACAGGUGAAA	
AD-1656468	UCCCACCACCUGUACCAUGCU		580-602	AGCAUGGUACAGGUGGUGGGACC	
AD-1656480	UACCAUGCCCGCCUGUGGCUU		592-614	AAGCCACAGGCGGGCAUGGUACA	
AD-1656492	CCCUUCCUGGCACUCUUUGCU		626-648	AGCAAAGAGUGCCAGGAAGGGUG	
AD-1656504	CUCUUUGCUUGAGGAUCUUCU		638-660	AGAAGAUCCUCAAGCAAAGAGUG	
AD-1656535	ACUCUCCUGGCUGAGCACCAU		694-716	AUGGUGCUCAGCCAGGAGAGUGC	
AD-1656547	GAGCACCACAUCACCAACCUU		706-728	AAGGUUGGUGAUGUGGUGCUCAG	
AD-1656559	ACCAACCUGGGCUGGCAUACU		718-740	AGUAUGCCAGCCCAGGUUGGUGA	
AD-1656570	CUGGCAUACCUUAACUCUGCU		729-751	AGCAGAGUUAAGGUAUGCCAGCC	
AD-1656587	UGCCCUCUAGUGGCUUGAGGU		746-768	ACCUCAAGCCACUAGAGGGCAGA	
AD-1656591	AGAAGUCUGGUGUCCUGAAAU		770-792	AUUUCAGGACACCAGACUUCUCA	
AD-1656602	GUCCUGAAACUGCAACUAGAU		781-803	AUCUAGUUGCAGUUUCAGGACAC	
AD-1656622	ACAGCACAGUUACUGGACAAU		821-843	AUUGUCCAGUAACUGUGGCUGUUG	
AD-1656634	CUGGACAACCGAGGCGGCUCU		833-855	AGAGCCGCCUCGGUUGUCCAGUA	
AD-1656647	GCGGCUCUUGGACACAGCAGU		846-868	ACUGCUGUGUCCAAGAGCCGCCU	
AD-1656667	GACACCAGCAGCCCUUCCUAU		866-888	AUAGGAAGGGCUGCUGGUGUCCU	
AD-1656679	CCUUCCUAGAGCUUAAGAUCU		878-900	AGAUCUUAAGCUCUAGGAAGGGC	
AD-1656690	CUUAAGAUCCGAGCCAAUGAU		889-911	AUCAUUGGCUCGGAUCUUAAGCU	
AD-1656701	AGCCAAUGAGCCUGGAGCAGU		900-922	ACUGCUCCAGGCUCAUUGGCUCG	
AD-1656716	AGGCGAGACCAUUACGUAGAU		973-995	AUCUACGUAAUGGUCUCGCCUGC	
AD-1656728	UACGUAGACUUCCAGGAACUU		985-1007	AAGUUCCUGGAAGUCUACGUAAU	
AD-1656740	CAGGAACUGGGAUGGCGGGAU		997-1019	AUCCCGCCAUCCCAGUUCCUGGA	

AD-1656754	GCGGGACUGGAUACUGCAGCU		1011-1033	AGCUGCAGUAUCCAGUCCCGCCA	
AD-1656762	UACCAGCUGAAUUACUGCAGU		1039-1061	ACUGCAGUAAUUCAGCUGGUACC	
AD-1656775	ACUGCAGUGGGGCAGUGCCCUU		1052-1074	AAGGGCACUGCCCACUGCAGUAA	
AD-1656792	CAGGCAUUGCUGCCUCUUUCU		1091-1113	AGAAAGAGGCAGCAAUGCCUGGG	
AD-1656808	UUUCCAUUCUGCCGUCUUCAU		1107-1129	AUGAAGACGGCAGAAUGGAAAGA	
AD-1656820	CGUCUUCAGCCUCCUCAAAGU		1119-1141	ACUUUGAGGAGGCUGAAGACGGC	
AD-1656832	CCUCAAAGCCAACAAUCCUUU		1131-1153	AAAGGAUUGUUGGCUUUGAGGAG	
AD-1656849	CUUGGCCUGCCAGUACCUCCU		1148-1170	AGGAGGUACUGGCAGGCCAAGGA	
AD-1656862	UACCUCCUGUUGUGUCCCUAU		1161-1183	AUAGGGACACAACAGGAGGUACU	
AD-1656873	GUGUCCCUACUGCCCGAAGGU		1172-1194	ACCUUCGGGCAGUAGGGACACAA	
AD-1656876	CUCUCUCCCUCUACCUGGAU		1195-1217	AUCCAGGUAGAGGAGAGAGAGGG	
AD-1656888	UACCUGGAUCAUAAUGGCAAU		1207-1229	AUUGCCAUUAUGAUCCAGGUAGA	
AD-1656900	AAUGGCAAUGUGGUCAAGACU		1219-1241	AGUCUUGACCACAUUGCCAUUAU	
AD-1656915	AAGACGGAUGUGCCAGAUAUU		1234-1256	AAUAUCUGGCACAUCCGUCUUGA	
AD-1656926	GCCAGAUAUGGUGGUGGAGGU		1245-1267	ACCUCCACCACCAUAUCUGGCAC	
AD-1656942	GAGGCCUGUGGCUGCAGCUAU		1261-1283	AUAGCUGCAGCCACAGGCCUCCA	
AD-1656954	UGCAGCUAGCAAGAGGACCUU		1273-1295	AAGGUCCUCUUGCUAGCUGCAGC	
AD-1656958	CUUUGGAGUGAAGAGACCAAU		1297-1319	AUUGGUCUCUUCACUCCAAAGCC	
AD-1656969	AGAGACCAAGAUGAAGUUUCU		1308-1330	AGAAACUUCAUCUUGGUCUCUUC	
AD-1656996	CAGGGCAUCUGUGACUGGAGU		1335-1357	ACUCCAGUCACAGAUGCCCUGUG	
AD-1657013	GAGGCAUCAGAUUCCUGAUCU		1352-1374	AGAUCAGGAAUCUGAUGCCUCCA	
AD-1657022	ACCCAACAACCACCUGGCAAU		1381-1403	AUUGCCAGGUGGUUGUUGGGUUG	
AD-1657037	GGCAAUAUGACUCACUUGACU		1396-1418	AGUCAAGUGAGUCAUAUUGCCAG	
AD-1657045	GACCCAAAUGGGCACUUUCUU		1424-1446	AAGAAAGUGCCCAUUUGGGUCCC	
AD-1657058	ACUUUCUUGUCUGAGACUCUU		1437-1459	AAGAGUCUCAGACAAGAAAGUGC	
AD-1657069	UGAGACUCUGGCUUAUUCCAU		1448-1470	AUGGAAUAAGCCAGAGUCUCAGA	
AD-1657085	UCCAGGUUGGCUGAUGUGUUU		1464-1486	AAACACAUCAGCCAACCUGGAAU	
AD-1657099	UGUGUUGGGAGAUGGGUAAAU		1478-1500	AUUUACCCAUCUCCCAACACAUC	
AD-1657113	GGUAAAGCGUUUCUUCUAAAU		1492-1514	AUUUAGAAGAAACGCUUUACCCA	

AD-1657119	UACCCAGAAAGCAUGAUUUCU		1518-1540	AGAAAUCAUGCUUUCUGGGUAGA	
AD-1657133	GAUUUCCUGCCCUAAGUCCUU		1532-1554	AAGGACUUAGGGCAGGAAAUCAU	
AD-1657147	AGUCCUGUGAGAAGAUGUCAU		1546-1568	AUGACAUCUUCUCACAGGACUUA	
AD-1657164	UCAGGGACUAGGGAGGGAGGU		1563-1585	ACCUCCCUCCCUAGUCCCUGACA	
AD-1657185	AAUUACUUAGCCUCUCCCAAU		1600-1622	AUUGGGAGAGGCUAAGUAAUUUU	
AD-1657202	CAAGAUGAGAAAGUCCUCAAU		1617-1639	AUUGAGGACUUUCUCAUCUUGGG	
AD-1657211	GGAGGAAGCAGAUAGAUGGUU		1646-1668	AACCAUCUAUCUGCUUCCUCCUC	
AD-1657234	GCAGGCUUGAAGCAGGGUAAU		1669-1691	AUUACCCUGCUUCAAGCCUGCUG	
AD-1657245	GCAGGGUAAGCAGGCUGGCCU		1680-1702	AGGCCAGCCUGCUUACCCUGCUU	
AD-1657261	GGCCCAGGGUAAGGGCUGUUU		1696-1718	AAACAGCCCUUACCCUGGGCCAG	
AD-1657274	GGCUGUUGAGGUACCUUAAGU		1709-1731	ACUUAAGGUACCUCAACAGCCCU	
AD-1657286	ACCUUAAGGGAAGGUCAAGAU		1721-1743	AUCUUGACCUUCCCUUAAGGUAC	
AD-1657299	GUCAAGAGGGAGAUGGGCAAU		1734-1756	AUUGCCCAUCUCCCUCUUGACCU	
AD-1657322	GCUGAGGGAGGAUGCUUAGGU		1757-1779	ACCUAAGCAUCCUCCCUCAGCGC	
AD-1657324	AGAAACAGGAGUCAGGAAAAU		1785-1807	AUUUUCCUGACUCCUGUUUCUGG	
AD-1657335	UCAGGAAAAUGAGGCACUAAU		1796-1818	AUUAGUGCCUCAUUUUCCUGACU	
AD-1657347	GGCACUAAGCCUAAGAAGUUU		1808-1830	AAACUUCUUAGGCUUAGUGCCUC	
AD-1657359	AAGAAGUUCCCUGGUUUUUCU		1820-1842	AGAAAAACCAGGGAACUUCUUAG	
AD-1657374	CACUGGGAGACAAGCAUUUAU		1855-1877	AUAAAUGCUUGUCUCCCAGUGGG	
AD-1657385	AAGCAUUUAUACUUUCUUUCU		1866-1888	AGAAAGAAAGUAUAAAUGCUUGU	
AD-1657395	UUUUGAGAUCGAGUCUCGCUU		1899-1921	AAGCGAGACUCGAUCUCAAAAAA	
AD-1657410	UCUCGCUCUGUCACCAGGCUU		1912-1934	AAGCCUGGUGACAGAGCGAGACU	
AD-1657431	AGUGCAGUGACACGAUCUUGU		1934-1956	ACAAGAUCGUGUCACUGCACUCC	
AD-1657446	GCUCACUGCAACCUCCGUCUU		1954-1976	AAGACGGAGGUUGCAGUGAGCCA	
AD-1657457	CCUCCGUCUCCUGGGUUCAAU		1965-1987	AUUGAACCCAGGAGACGGAGGUU	
AD-1657463	UUCUGCCUCAGCCUCCCGAGU		1992-2014	ACUCGGGAGGCUGAGGCAGAAGA	
AD-1657475	UGGGUUCAAGUGAUUCUUCUU		1976-1998	AAGAAGAAUCACUUGAACCCAGG	
AD-1657503	GAGCAGCUGGGAUUACAGGCU		2009-2031	AGCCUGUAAUCCCAGCUGCUCGG	
AD-1657520	CGCCCACUAAUUUUUGUAUUU		2028-2050	AAAUACAAAAAAUUAGUGGGCGCC	

AD-1657529	UGUAUUCUUAGUAGAAACGAU		2042-2064	AUCGUUUCUACUAAGAAUACAAA	
AD-1657540	UAGAAACGAGGUUUCAACAUU		2053-2075	AAUGUUGAAACCUCGUUUCUACU	
AD-1657552	UUCAACAUGUUGGCCAGGAUU		2065-2087	AAUCCUGGCCAACAUGUUGAAAC	
AD-1657564	CCAGGAUGGUCUCAAUCUCUU		2078-2100	AAGAGAUUGAGACCAUCCUGGCC	
AD-1657575	UCAAUCUCUUGACCUCUUGAU		2089-2111	AUCAAGAGGUCAAGAGAUUGAGA	
AD-1657586	ACCUCUUGAUCCACCCGACUU		2100-2122	AAGUCGGGUGGAUCAAGAGGUCA	
AD-1657600	CCGACUUGGCCUCCCGAAGUU		2114-2136	AACUUCGGGAGGCCAAGUCGGGU	
AD-1657615	GAAGUGAUGAGAUUAUAGGCU		2129-2151	AGCCUAUAAUCUCAUCACUUCGG	
AD-1657641	CCUGGCUUAUACUUUCUUAAU		2162-2184	AUUAAGAAAGUAUAAGCCAGGCG	
AD-1657653	GAGAAAGAAAAUCAACAAAUU		2189-2211	AAUUUGUUGAUUUUCUUUCUCCU	
AD-1657674	UGAGUCAUAAAGAAGGGUUAU		2210-2232	AUAACCCUUCUUUAUGACUCACA	
AD-1657687	AGGGUUAGGGUGAUGGUCCAU		2223-2245	AUGGACCAUCACCCUAACCCUUC	
AD-1657704	CCAGAGCAACAGUUCUUCAAU		2240-2262	AUUGAAGAACUGUUGCUCUGGAC	
AD-1657716	UUCUUCAAGUGUACUCUGUAU		2252-2274	AUACAGAGUACACUUGAAGAACU	
AD-1657727	UACUCUGUAGGCUUCUGGGAU		2263-2285	AUCCCAGAAGCCUACAGAGUACA	
AD-1657741	CUGGGAGGUCCCUUUUCAGGU		2277-2299	ACCUGAAAAGGGACCUCCCAGAA	
AD-1657744	GUCCACAAAGUCAAAGCUAUU		2300-2322	AAUAGCUUUGACUUUGUGGACAC	
AD-1657760	CUAACAUGUUAUUUGCCUUUU		2333-2355	AAAAGGCAAAUAACAUGUUAGUA	
AD-1657776	CUUUUGAAUUCUCAUUAUCUU		2349-2371	AAGAUAAUGAGAAUUCAAAAGGC	
AD-1657793	GUAUUGUGGAGUUUUCCAGAU		2376-2398	AUCUGGAAAACUCCACAAUACAA	
AD-1657811	GAGGCCGUGUGACAUGUGAUU		2394-2416	AAUCACAUGUCACACGGCCUCUG	
AD-1657822	ACAUGUGAUUACAUCAUCUUU		2405-2427	AAAGAUGAUGUAAUCACAUGUCA	
AD-1657834	AUCAUCUUUCUGACAUCAUUU		2417-2439	AAAUGAUGUCAGAAAGAUGAUGU	
AD-1657845	GACAUCAUUGUUAAUGGAAUU		2428-2450	AAUUCCAUUAACAAUGAUGUCAG	

Table 3. Modified Sense and Antisense Strand Sequences of INHBE dsRNA Agents

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA target sequence	SEQ ID NO:

AD-1656008	usasgccaGfaCfAfUfgagcugugauL96		asUfscacAfgCfUfcaugUfcUfggcuascsu		AGTAGCCAGACATGAGCTGTGAG	
AD-1656026	gsasggguCfaAfGfCfacagcuaucuL96		asGfsauaGfcUfGfugcuUfgAfcccucsasc		GTGAGGGTCAAGCACAGCTATCC	
AD-1656043	asusccauCfaGfAfUfgaucuacuuuL96		asAfsaguAfgAfUfcaucUfgAfuggausasg		CTATCCATCAGATGATCTACTTT	
AD-1656054	gsasucuaCfuUfUfCfagccuuccuuL96		asAfsggaAfgGfCfugaaAfgUfagaucsasu		ATGATCTACTTTCAGCCTTCCTG	
AD-1656074	gsasguccCfaGfAfCfaauagaagauL96		asUfscuuCfuAfUfugucUfgGfgacucsasg		CTGAGTCCCAGACAATAGAAGAC	
AD-1656086	asusagaaGfaCfAfGfguggcuguauL96		asUfsacaGfcCfAfccugUfcUfucuaususg		CAATAGAAGACAGGTGGCTGTAC	
AD-1656097	gsusggcuGfuAfCfCfcuuggccaauL96		asUfsuggCfcAfAfggguAfcAfgccacscsu		AGGTGGCTGTACCCTTGGCCAAG	
AD-1656108	csusuggcCfaAfGfGfguaggugugguL96		asCfsacaCfcUfAfcccuUfgGfccaagsgsg		CCCTTGGCCAAGGGTAGGTGTGG	
AD-1656125	gsusggcaGfuGfGfUfgucugcuguuL96		asAfscagCfaGfAfcaccAfcUfgccacsasc		GTGTGGCAGTGGTGTCTGCTGTC	
AD-1656139	usgscuguCfaCfUfGfugcccucauuL96		asAfsugaGfgGfCfacagUfgAfcagcasgsa		TCTGCTGTCACTGTGCCCTCATT	
AD-1656146	asgscaauCfaGfAfCfucaacagacuL96		asGfsucuGfuUfGfagucUfgAfuugcusgsg		CCAGCAATCAGACTCAACAGACG	
AD-1656164	ascsggagCfaAfCfUfgccauccgauL96		asUfscggAfuGfGfcaguUfgCfuccguscsu		AGACGGAGCAACTGCCATCCGAG	
AD-1656185	gscsuccuGfaAfCfCfagggccauuuL96		asAfsaugGfcCfCfugguUfcAfggagcscsu		AGGCTCCTGAACCAGGGCCATTC	
AD-1656196	asgsggccAfuUfCfAfccaggagcauL96		asUfsgcuCfcUfGfgugaAfuGfgcccusgsg		CCAGGGCCATTCACCAGGAGCAT	
AD-1656220	gscsucccUfgAfUfGfuccagcucuuL96		asAfsgagCfuGfGfacauCfaGfggagcscsg		CGGCTCCCTGATGTCCAGCTCTG	
AD-1656233	csasgcucUfgGfCfUfggugcugcuuL96		asAfsgcaGfcAfCfcagcCfaGfagcugsgsa		TCCAGCTCTGGCTGGTGCTGCTG	
AD-1656254	usgsggcaCfuGfGfUfgcgagcacauL96		asUfsgugCfuCfGfcaccAfgUfgcccascsa		TGTGGGCACTGGTGCGAGCACAG	
AD-1656260	asgsggucUfgUfGfUfgucccuccuuL96		asAfsggaGfgGfAfcacaCfaGfacccusgsu		ACAGGGTCTGTGTGTCCCTCCTG	
AD-1656265	csasagcaGfaAfCfGfagcucugguuL96		asAfsccaGfaGfCfucguUfcUfgcuugsgsg		CCCAAGCAGAACGAGCTCTGGTG	
AD-1656280	csusggugCfuGfGfAfgcuagccaauL96		asUfsuggCfuAfGfcuccAfgCfaccagsasg		CTCTGGTGCTGGAGCTAGCCAAG	
AD-1656292	csusagccAfaGfCfAfgcaaauccuuL96		asAfsggaUfuUfGfcugcUfuGfgcuagscsu		AGCTAGCCAAGCAGCAAATCCTG	
AD-1656307	asusccugGfaUfGfGfguugcaccuuL96		asAfsgguGfcAfAfcccaUfcCfaggaususu		AAATCCTGGATGGGTTGCACCTG	
AD-1656319	ususgcacCfuGfAfCfcagucguccuL96		asGfsgacGfaCfUfggucAfgGfugcaascsc		GGTTGCACCTGACCAGTCGTCCC	
AD-1656333	uscsguccCfaGfAfAfuaacucaucuL96		asGfsaugAfgUfUfauucUfgGfgacgascsu		AGTCGTCCCAGAATAACTCATCC	
AD-1656360	cscscuccGfgAfGfAfcuacagccauL96		asUfsggcUfgUfAfgucuCfcGfgagggscsu		AGCCCTCCGGAGACTACAGCCAG	
AD-1656372	usascagcCfaGfGfGfaguguggcuuL96		asAfsgccAfcAfCfucccUfgGfcuguasgsu		ACTACAGCCAGGGAGTGTGGCTC	
AD-1656383	asgsugugGfcUfCfCfagggaaugguL96		asCfscauUfcCfCfuggaGfcCfacacuscsc		GGAGTGTGGCTCCAGGGAATGGG	
AD-1656392	csasucagCfuUfUfGfcuacugucauL96		asUfsgacAfgUfAfgcaaAfgCfugaugsasc		GTCATCAGCTTTGCTACTGTCAC	
AD-1656406	csusgucaCfaGfAfCfuccacuucauL96		asUfsgaaGfuGfGfagucUfgUfgacagsusa		TACTGTCACAGACTCCACTTCAG	

AD-1656417	uscscacuUfcAfGfCfcuacagcucuL96		asGfsagcUfgUfAfggcuGfaAfguggasgsu		ACTCCACTTCAGCCTACAGCTCC	
AD-1656437	cscsugcuCfaCfUfUfuucaccuguuL96		asAfscagGfuGfAfaaagUfgAfgcaggsgsa		TCCCTGCTCACTTTTCACCTGTC	
AD-1656449	uscsaccuGfuCfCfAfcuccucgguuL96		asAfsccgAfgGfAfguggAfcAfgugasasa		TTTCACCTGTCCACTCCTCGGTC	
AD-1656468	uscsccacCfaCfCfUfguaccaugcuL96		asGfscauGfgUfAfcaggUfgGfugggascsc		GGTCCCACCACCTGTACCATGCC	
AD-1656480	usasccauGfcCfCfCfGfccuguggcuuL96		asAfsgccAfcAfGfgcggGfcAfugguascsa		TGTACCATGCCCGCCTGTGGCTG	
AD-1656492	cscscuucCfuGfGfCfacucuuugcuL96		asGfscaaAfgAfGfugccAfgGfaagggsusg		CACCCTTCCTGGCACTCTTTGCT	
AD-1656504	csuscuuuGfcUfUfUfGfaggaucuucuL96		asGfsaagAfuCfCfucaaGfcAfaagagsusg		CACTCTTTGCTTGAGGATCTTCC	
AD-1656535	ascsucucCfuGfGfCfUfgagcaccauuL96		asUfsggaGfcUfCfagccAfgGfagagusgsc		GCACTCTCCTGGCTGAGCACCAC	
AD-1656547	gsasgcacCfaCfAfUfcaccaaccuuL96		asAfsggaUfgGfUfUfgaugUfgGfugcucsasg		CTGAGCACCACATCACCAACCTG	
AD-1656559	ascscaacCfuGfGfGfcuggcauacuL96		asGfsuauGfcCfAfgcccAfgGfuuggusgsa		TCACCAACCTGGGCTGGCATACC	
AD-1656570	csusggcaUfaCfCfUfuaacucugcuL96		asGfscagAfgUfUfaaggUfaUfgccagcscsc		GGCTGGCATACCTTAACTCTGCC	
AD-1656587	usgscccuCfuAfGfUfggcuugagguL96		asCfscucAfaGfCfcacuAfgAfgggcasgsa		TCTGCCCTCTAGTGGCTTGAGGG	
AD-1656591	asgsaaguCfuGfGfUfguccugaaauL96		asUfsuucAfgGfAfcaccAfgAfcuucuscsa		TGAGAAGTCTGGTGTCCTGAAAC	
AD-1656602	gsusccugAfaAfCfUfgcaacuagauL96		asUfscuaGfuUfGfcaguUfuCfaggacsasc		GTGTCCTGAAACTGCAACTAGAC	
AD-1656622	ascsagcaCfaGfUfUfUfacuggacaauL96		asUfsuguCfcAfGfuaacUfgUfgcugususg		CAACAGCACAGTTACTGGACAAC	
AD-1656634	csusggacAfaCfCfGfagcggcucuL96		asGfsagcCfgCfCfucggUfuGfuccagsusa		TACTGGACAACCGAGGCGGCTCT	
AD-1656647	gscsggcuCfuUfGfGfacacagcaguL96		asCfsugcUfgUfGfuccaAfgAfgccgcscsu		AGGCGGCTCTTGGACACAGCAGG	
AD-1656667	gsascaccAfgCfAfGfcccuuccuauL96		asUfsaggAfaGfGfgcugCfuGfgugucscsu		AGGACACCAGCAGCCCTTCCTAG	
AD-1656679	cscsuuccUfaGfAfGfcuuaagaucuL96		asGfsaucUfuAfAfgcucUfaGfgaaggsgsc		GCCCTTCCTAGAGCTTAAGATCC	
AD-1656690	csusuaagAfuCfCfGfagccaaugauL96		asUfscauUfgGfCfucggAfuCfuuaagscsu		AGCTTAAGATCCGAGCCAATGAG	
AD-1656701	asgsccaaUfgAfGfCfcuggagcaguL96		asCfsugcUfcCfAfggcuCfaUfuggcuscsg		CGAGCCAATGAGCCTGGAGCAGG	
AD-1656716	asgsgcgaGfaCfCfAfuuacguagauL96		asUfscuaCfgUfAfauggUfcUfcgccusgsc		GCAGGCGAGACCATTACGTAGAC	
AD-1656728	usascguaGfaCfUfUfUfccaggaacuuL96		asAfsguuCfcUfGfgaagUfcUfacguasasu		ATTACGTAGACTTCCAGGAACTG	
AD-1656740	csasggaaCfuGfGfGfauggcgggguL96		asUfscccGfcCfAfucccAfgUfuccugsgsa		TCCAGGAACTGGGATGGCGGGAC	
AD-1656754	gscsgggaCfuGfGfAfuacugcagcuL96		asGfscugCfaGfUfauccAfgUfcccgcscsa		TGGCGGGACTGGATACTGCAGCC	
AD-1656762	usasccagCfuGfAfAfuuacugcaguL96		asCfsugcAfgUfAfauucAfgCfugguascsc		GGTACCAGCTGAATTACTGCAGT	
AD-1656775	ascsugcaGfuGfGfGfcagugcccuuL96		asAfsgggCfaCfUfgcccAfcUfgcagusasa		TTACTGCAGTGGGCAGTGCCCTC	
AD-1656792	csasggcaUfuGfCfUfgccucuuuucuL96		asGfsaaaGfaGfGfcagcAfaUfgccugsgsg		CCCAGGCATTGCTGCCTCTTTCC	
AD-1656808	ususuccaUfuCfUfGfccgucuucauL96		asUfsgaaGfaCfGfgcagAfaUfggaaasgsa		TCTTTCCATTCTGCCGTCTTCAG	

AD-1656820	csgsucuuCfaGfCfCfuccucaaaguL96		asCfsuuuGfaGfGfaggcUfgAfagacgsgsc		GCCGTCTTCAGCCTCCTCAAAGC	
AD-1656832	cscsucaaAfgCfCfAfacaauccuuuL96		asAfsaggAfuUfGfuuggCfuUfugaggsasg		CTCCTCAAAGCCAACAATCCTTG	
AD-1656849	csusuggcCfuGfCfCfaguaccuccuL96		asGfsgagGfuAfCfuggcAfgGfccaagsgsa		TCCTTGGCCTGCCAGTACCTCCT	
AD-1656862	usasccucCfuGfUfUfgugucccuauL96		asUfsaggGfaCfAfcaacAfgGfagguascsu		AGTACCTCCTGTTGTGTCCCTAC	
AD-1656873	gsusguccCfuAfCfUfgcccgaagguL96		asCfscuuCfgGfGfcaguAfgGfgacacsasa		TTGTGTCCCTACTGCCCGAAGGC	
AD-1656876	csuscucuCfuCfCfUfcuaccuggauL96		asUfsccaGfgUfAfgaggAfgAfgagagsgsg		CCCTCTCTCTCCTCTACCTGGAT	
AD-1656888	usasccugGfaUfCfAfuaauggcaauL96		asUfsugcCfaUfUfaugaUfcCfagguasgsa		TCTACCTGGATCATAATGGCAAT	
AD-1656900	asasuggcAfaUfGfUfggucaagacuL96		asGfsucuUfgAfCfcacaUfuGfccauusasu		ATAATGGCAATGTGGTCAAGACG	
AD-1656915	asasgacgGfaUfGfUfgccagauauuL96		asAfsuauCfuGfGfcacaUfcCfgucuusgsa		TCAAGACGGATGTGCCAGATATG	
AD-1656926	gscscagaUfaUfGfGfugguggagguL96		asCfscucCfaCfCfaccaUfaUfcuggcsasc		GTGCCAGATATGGTGGTGGAGGC	
AD-1656942	gsasggccUfgUfGfGfcugcagcuauL96		asUfsagcUfgCfAfgccaCfaGfgccucscsa		TGGAGGCCTGTGGCTGCAGCTAG	
AD-1656954	usgscagcUfaGfCfAfagaggaccuuL96		asAfsgguCfcUfCfuugcUfaGfcugcasgsc		GCTGCAGCTAGCAAGAGGACCTG	
AD-1656958	csusuuggAfgUfGfAfagagaccaauL96		asUfsuggUfcUfCfuucaCfuCfcaaagscsc		GGCTTTGGAGTGAAGAGACCAAG	
AD-1656969	asgsagacCfaAfGfAfugaaguuucuL96		asGfsaaaCfuUfCfaucuUfgGfucucususc		GAAGAGACCAAGATGAAGTTTCC	
AD-1656996	csasgggcAfuCfUfGfugacuggaguL96		asCfsuccAfgUfCfacagAfuGfcccugsusg		CACAGGGCATCTGTGACTGGAGG	
AD-1657013	gsasggcaUfcAfGfAfuuccugaucuL96		asGfsaucAfgGfAfaucuGfaUfgccucscsa		TGGAGGCATCAGATTCCTGATCC	
AD-1657022	ascsccaaCfaAfCfCfaccuggcaauL96		asUfsugcCfaGfGfugguUfgUfugggususg		CAACCCAACAACCACCTGGCAAT	
AD-1657037	gsgscaauAfuGfAfCfucacuugacuL96		asGfsucaAfgUfGfagucAfuAfuugccsasg		CTGGCAATATGACTCACTTGACC	
AD-1657045	gsascccaAfaUfGfGfgcacuuucuuL96		asAfsgaaAfgUfGfcccaUfuUfgggucscsc		GGGACCCAAATGGGCACTTTCTT	
AD-1657058	ascsuuucUfuGfUfCfugagacucuuL96		asAfsgagUfcUfCfagacAfaGfaaagusgsc		GCACTTTCTTGTCTGAGACTCTG	
AD-1657069	usgsagacUfcUfGfGfcuuauuccauL96		asUfsggaAfuAfAfgccaGfaGfucucasgsa		TCTGAGACTCTGGCTTATTCCAG	
AD-1657085	uscscaggUfuGfGfCfugauguguuuL96		asAfsacaCfaUfCfagccAfaCfcuggasasu		ATTCCAGGTTGGCTGATGTGTTG	
AD-1657099	usgsuguuGfgGfAfGfauggguaaauL96		asUfsuuaCfcCfAfucucCfcAfacacasusc		GATGTGTTGGGAGATGGGTAAAG	
AD-1657113	gsgsuaaaGfcGfUfUfucuucuaaauL96		asUfsuuaGfaAfGfaaacGfcUfuuaccscsa		TGGGTAAAGCGTTTCTTCTAAAG	
AD-1657119	usascccaGfaAfAfGfcaugauuucuL96		asGfsaaaUfcAfUfgcuuUfcUfggguasgsa		TCTACCCAGAAAGCATGATTTCC	
AD-1657133	gsasuuucCfuGfCfCfcuaaguccuuL96		asAfsggaCfuUfAfgggcAfgGfaaaucsasu		ATGATTTCCTGCCCTAAGTCCTG	
AD-1657147	asgsuccuGfuGfAfGfaagaugucauL96		asUfsgacAfuCfUfucucAfcAfggacususa		TAAGTCCTGTGAGAAGATGTCAG	
AD-1657164	uscsagggAfcUfAfGfggagggagguL96		asCfscucCfcUfCfccuaGfuCfccugascsa		TGTCAGGGACTAGGGAGGGAGGG	
AD-1657185	asasuuacUfuAfGfCfcucucccaauL96		asUfsuggGfaGfAfggcuAfaGfuaauususu		AAAATTACTTAGCCTCTCCCAAG	

AD-1657202	csasagauGfaGfAfAfaguccucaauL96		asUfsugaGfgAfCfuuucUfcAfucuugsgsg		CCCAAGATGAGAAAGTCCTCAAG	
AD-1657211	gsgsaggaAfgCfAfGfauagaugguuL96		asAfsccaUfcUfAfucugCfuUfccuccsusc		GAGGAGGAAGCAGATAGATGGTC	
AD-1657234	gscsaggcUfuGfAfAfgcaggguaauL96		asUfsuacCfcUfGfcuucAfaGfccugcsusg		CAGCAGGCTTGAAGCAGGGTAAG	
AD-1657245	gscsagggUfaAfGfCfaggcuggccuL96		asGfsgccAfgCfCfugcuUfaCfccugcsusu		AAGCAGGGTAAGCAGGCTGGCCC	
AD-1657261	gsgscccaGfgGfUfAfagggcuguuuL96		asAfsacaGfcCfCfuuacCfcUfgggccsasg		CTGGCCCAGGGTAAGGGCTGTTG	
AD-1657274	gsgscuguUfgAfGfGfuaccuuaaguL96		asCfsuuaAfgGfUfaccuCfaAfcagccscsu		AGGGCTGTTGAGGTACCTTAAGG	
AD-1657286	ascscuuaAfgGfGfAfaggucaagauL96		asUfscuuGfaCfCfuuccCfuUfaaggusasc		GTACCTTAAGGGAAGGTCAAGAG	
AD-1657299	gsuscaagAfgGfGfAfgaugggcaauL96		asUfsugcCfcAfUfcuccCfuCfuugacscsu		AGGTCAAGAGGGAGATGGGCAAG	
AD-1657322	gscsugagGfgAfGfGfaugcuuagguL96		asCfscuaAfgCfAfuccuCfcCfucagcsgsc		GCGCTGAGGGAGGATGCTTAGGG	
AD-1657324	asgsaaacAfgGfAfGfucaggaaaauL96		asUfsuuuCfcUfGfacucCfuGfuuucusgsg		CCAGAAACAGGAGTCAGGAAAAT	
AD-1657335	uscsaggaAfaAfUfGfaggcacuaauL96		asUfsuagUfgCfCfucauUfuUfccugascsu		AGTCAGGAAAATGAGGCACTAAG	
AD-1657347	gsgscacuAfaGfCfCfuaagaaguuuL96		asAfsacuUfcUfUfaggcUfuAfgugccsusc		GAGGCACTAAGCCTAAGAAGTTC	
AD-1657359	asasgaagUfuCfCfCfugguuuuucuL96		asGfsaaaAfaCfCfagggAfaCfuucuusasg		CTAAGAAGTTCCCTGGTTTTTCC	
AD-1657374	csascuggGfaGfAfCfaagcauuuauL96		asUfsaaaUfgCfUfugucUfcCfcagugsgsg		CCCACTGGGAGACAAGCATTTAT	
AD-1657385	asasgcauUfuAfUfAfcuuucuuucuL96		asGfsaaaGfaAfAfguauAfaAfugcuusgsu		ACAAGCATTTATACTTTCTTTCT	
AD-1657395	ususuugaGfaUfCfGfagucucgcuuL96		asAfsgcgAfgAfCfucgaUfcUfcaaaasasa		TTTTTTGAGATCGAGTCTCGCTC	
AD-1657410	uscsucgcUfcUfGfUfcaccaggcuuL96		asAfsgccUfgGfUfgacaGfaGfcgagascsu		AGTCTCGCTCTGTCACCAGGCTG	
AD-1657431	asgsugcaGfuGfAfCfacgaucuuguL96		asCfsaagAfuCfGfugucAfcUfgcacuscsc		GGAGTGCAGTGACACGATCTTGG	
AD-1657446	gscsucacUfgCfAfAfccuccgucuuL96		asAfsgacGfgAfGfguugCfaGfugagcscsa		TGGCTCACTGCAACCTCCGTCTC	
AD-1657457	cscsuccgUfcUfCfCfuggguucaauL96		asUfsugaAfcCfCfaggaGfaCfggaggsusu		AACCTCCGTCTCCTGGGTTCAAG	
AD-1657463	ususcugcCfuCfAfGfccucccgaguL96		asCfsucgGfgAfGfgcugAfgGfcagaasgsa		TCTTCTGCCTCAGCCTCCCGAGC	
AD-1657475	usgsgguuCfaAfGfUfgauucuucuuL96		asAfsgaaGfaAfUfcacuUfgAfacccasgsg		CCTGGGTTCAAGTGATTCTTCTG	
AD-1657503	gsasgcagCfuGfGfGfauuacaggcuL96		asGfsccuGfuAfAfucccAfgCfugcucsgsg		CCGAGCAGCTGGGATTACAGGCG	
AD-1657520	csgscccaCfuAfAfUfuuuguauuuL96		asAfsauaCfaAfAfaauuAfgUfgggcgcsc		GGCGCCCACTAATTTTTGTATTC	
AD-1657529	usgsuauuCfuUfAfGfuagaaacgauL96		asUfscguUfuCfUfacuaAfgAfauacasasa		TTTGTATTCTTAGTAGAAACGAG	
AD-1657540	usasgaaaCfgAfGfGfuuucaacauuL96		asAfsuguUfgAfAfaccuCfgUfuucuascsu		AGTAGAAACGAGGTTTCAACATG	
AD-1657552	ususcaacAfuGfUfUfggccaggauuL96		asAfsuccUfgGfCfcaacAfuGfuugaasasc		GTTTCAACATGTTGGCCAGGATG	
AD-1657564	cscsaggaUfgGfUfCfucaaucucuuL96		asAfsgagAfuUfGfagacCfaUfccuggcsc		GGCCAGGATGGTCTCAATCTCTT	
AD-1657575	uscsaaucUfcUfUfGfaccucuugauL96		asUfscaaGfaGfGfucaaGfaGfauugasgsa		TCTCAATCTCTTGACCTCTTGAT	

AD-1657586	ascscucuUfgAfUfCfcacccgacuuL96		asAfsgucGfgGfUfggauCfaAfgaggucscsa		TGACCTCTTGATCCACCCGACTT	
AD-1657600	cscsgacuUfgGfCfCfucccgaaguuL96		asAfscuuCfgGfGfaggcCfaAfgucggsgsu		ACCCGACTTGGCCTCCCGAAGTG	
AD-1657615	gsasagugAfuGfAfGfauuauaggcuL96		asGfsccuAfuAfAfucucAfuCfacuucsgsg		CCGAAGTGATGAGATTATAGGCG	
AD-1657641	cscsuggcUfuAfUfAfcuuucuuaauL96		asUfsuaaGfaAfAfguauAfaGfccaggscsg		CGCCTGGCTTATACTTTCTTAAT	
AD-1657653	gsasgaaaGfaAfAfAfucaacaaauuL96		asAfsuuuGfuUfGfauuuUfcUfuucucscsu		AGGAGAAAGAAAATCAACAAATG	
AD-1657674	usgsagucAfuAfAfAfgaaggguuauL96		asUfsaacCfcUfUfcuuuAfuGfacucascsa		TGTGAGTCATAAAGAAGGGTTAG	
AD-1657687	asgsgguuAfgGfGfUfgaugguccauL96		asUfsggaCfcAfUfcaccCfuAfacccususc		GAAGGGTTAGGGTGATGGTCCAG	
AD-1657704	cscsagagCfaAfCfAfguucuucaauL96		asUfsugaAfgAfAfcuguUfgCfucuggsasc		GTCCAGAGCAACAGTTCTTCAAG	
AD-1657716	ususcuucAfaGfUfGfuacucuguauL96		asUfsacaGfaGfUfacacUfuGfaagaascsu		AGTTCTTCAAGTGTACTCTGTAG	
AD-1657727	usascucuGfuAfGfGfcuucugggauL96		asUfscccAfgAfAfgccuAfcAfgaguascsa		TGTACTCTGTAGGCTTCTGGGAG	
AD-1657741	csusgggaGfgUfCfCfcuuuucagguL96		asCfscugAfaAfAfgggaCfcUfcccagsasa		TTCTGGGAGGTCCCTTTTCAGGG	
AD-1657744	gsusccacAfaAfGfUfcaaagcuauuL96		asAfsuagCfuUfUfgacuUfuGfuggacsasc		GTGTCCACAAAGTCAAAGCTATT	
AD-1657760	csusaacaUfgUfUfAfuuugccuuuuL96		asAfsaagGfcAfAfauaaCfaUfguuagsusa		TACTAACATGTTATTTGCCTTTT	
AD-1657776	csusuuugAfaUfUfCfucauuaucuuL96		asAfsgauAfaUfGfagaaUfuCfaaaagsgsc		GCCTTTTGAATTCTCATTATCTT	
AD-1657793	gsusauugUfgGfAfGfuuuuccagauL96		asUfscugGfaAfAfacucCfaCfaauacsasa		TTGTATTGTGGAGTTTTCCAGAG	
AD-1657811	gsasggccGfuGfUfGfacaugugauuL96		asAfsucaCfaUfGfucacAfcGfgccucsusg		CAGAGGCCGTGTGACATGTGATT	
AD-1657822	ascsauguGfaUfUfAfcaucaucuuuL96		asAfsagaUfgAfUfguaaUfcAfcauguscsa		TGACATGTGATTACATCATCTTT	
AD-1657834	asuscaucUfuUfCfUfgacaucauuuL96		asAfsaugAfuGfUfcagaAfaGfaugausgsu		ACATCATCTTTCTGACATCATTG	
AD-1657845	gsascaucAfuUfGfUfuaauggaauuL96		asAfsuucCfaUfUfaacaAfuGfaugucsasg		CTGACATCATTGTTAATGGAATG	

Table 4. Unmodified Sense and Antisense Strand Sequences of ACVR1C dsRNA Agents Comprising anUnsaturated C22 Hydrocarbon Chain Conjugated to Position 6 on the Sense Strand, Counting from the 5'-end of the Sense Strand

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3
AD-1735861	UUUUUUCAAACUCCAUUCCUA		3085-3105	UAGGAAUGGAGUUUGAAAAAAGA		3083-3105
AD-1735862	ACUUUCAUCUGUCUUCAGAUA		8677-8697	UAUCUGAAGACAGAUGAAAGUUA		8675-8697
AD-1735863	CCUCAUAACUUCUCCAGUAAA		6745-6765	UUUACUGGAGAAGUUAUGAGGUG		6743-6765

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3
AD-1735864	CUCACUAUCUUUCAACAUUAA		5871-5891	UUAAUGUUGAAAGAUAGUGAGGG		5869-5891
AD-1735865	CUCGUUAAUGCUCUCAUCCAA		3562-3582	UUGGAUGAGAGCAUUAACGAGUA		3560-3582
AD-1735866	GUUCUUCAUAAUCCACUACUA		2292-2312	UAGUAGUGGAUUAUGAAGAACAG		2290-2312
AD-1735867	GUUGACUUUCAUCCAAUCUCUA		1876-1896	UAGAGAUUGGAUGAAGUCAACUC		1874-1896
AD-1735868	CUACACAAUGAACUUCUUAAA		6692-6712	UUUAAGAAGUUCAUUGUGUAGAA		6690-6712
AD-1735869	CACAUCUAGAAUUCUUAAUUA		4835-4855	UAAUUAAGAAUUCUAGAUGUGAC		4833-4855
AD-1735870	AAAUCUCUCAUAGCUUUCUUA		1725-1745	UAAGAAAGCUAUGAGAGAUUUCU		1723-1745
AD-1735871	CCUACUAUUGUAGAAUUACUA		5093-5113	UAGUAAUUCUACAAUAGUAGGUG		5091-5113
AD-1735872	AUCUUCUUUUAGUGCAUUAAA		6589-6609	UUUAAUGCACUAAAAGAAGAUGA		6587-6609
AD-1735873	CUCAUGUACUCUUCUGAUUCA		7977-7997	UGAAUCAGAAGAGUACAUGAGCU		7975-7997
AD-1735874	UUUCUCUUUGUACCUUGGAAA		6449-6469	UUUCCAAGGUACAAAGAGAAAGA		6447-6469
AD-1735875	UGGCUUAUACAUCUUCAGAAA		7515-7535	UUUCUGAAGAUGUAUAAGCCAGA		7513-7535
AD-1735876	CAAAACAAAACUACUCCUAUA		5120-5140	UAUAGGAGUAGUUUUGUUUUGUU		5118-5140
AD-1735877	ACUAGCAGAACUCUUAUGAAA		6055-6075	UUUCAUAAGAGUUCUGCUAGUAA		6053-6075
AD-1735878	CCAAGUCACUCUAUAAUUCCA		6635-6655	UGGAAUUAUAGAGUGACUUGGGA		6633-6655
AD-1735879	UCCAUUUUUCUUGUCAUUAUA		4114-4134	UAUAAUGACAAGAAAAAUGGAGA		4112-4134
AD-1735880	CAACACCUCAACUCAUCUUUA		1923-1943	UAAAGAUGAGUUGAGGUGUUGCU		1921-1943
AD-1735881	ACUCUGAAAGAUCUGAUUUAA		716-736	UUAAAUCAGAUCUUUCAGAGUUU		714-736
AD-1735882	CUAGUUCUUUUUCCGCAAUGAA		7946-7966	UUCAUUGCGGAAAAGAACUAGAA		7944-7966
AD-1735883	CUUUCACUCUGAAGAAAUCCA		4189-4209	UGGAUUUCUUCAGAGUGAAAGUU		4187-4209
AD-1735884	UCUAACUUUUCUCUCUUUCUA		6525-6545	UAGAAAGAGAGAAAAGUUAGAUA		6523-6545
AD-1735885	UCUCAACUUUGUGUCAAAGAA		1667-1687	UUCUUUGACACAAAGUUGAGAUA		1665-1687
AD-1735886	CUUCAAUAAUCAUUCCUUUAA		5445-5465	UUAAAGGAAUGAUUAUUGAAGAC		5443-5465
AD-1735887	UAACUGCUCUUCGUAUUAAGA		1638-1658	UCUUAAUACGAAGAGCAGUUAGG		1636-1658
AD-1735888	UCUUCUGUCAUAGUUCCAACA		438-458	UGUUGGAACUAUGACAGAAGACU		436-458
AD-1735889	AUCUCAGAACCAUAUCUGUUA		2584-2604	UAACAGAUAUGGUUCUGAGAUUU		2582-2604

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3
AD-1735890	UGAAUCUAUCUUCAUUUUACA		3483-3503	UGUAAAAUGAAGAUAGAUUCAGU		3481-3503
AD-1735891	ACCACUAAACUUGUUCCUUUA		2326-2346	UAAAGGAACAAGUUUAGUGGUUC		2324-2346
AD-1735892	AGUGUUCUUUACUCCUUACAA		4578-4598	UUGUAAGGAGUAAAGAACACUGA		4576-4598
AD-1735893	CUUUACUCUUAACAGGAUUAA		4367-4387	UUAAUCCUGUUAAGAGUAAAGGA		4365-4387
AD-1735894	UAUACCUAAGAACAUAUUACA		8153-8173	UGUAAUAUGUUCUUAGGUAUAAG		8151-8173
AD-1735895	CUUCUACUGAGAUGAUCCAAA		3114-3134	UUUGGAUCAUCUCAGUAGAAGAA		3112-3134
AD-1735896	CUGUAUUUUCUCAUAGAGUAA		3420-3440	UUACUCUAUGAGAAAAUACAGAA		3418-3440
AD-1735897	ACUUUUCUCUUUCAGUUGUAA		7116-7136	UUACAACUGAAAGAGAAAAGUAU		7114-7136
AD-1735898	AUUAAUUUCUAGUCUGUGAAA		8493-8513	UUUCACAGACUAGAAAUUAAUGA		8491-8513
AD-1735899	CUCUGUAUAAGAGGUUUCACA		6726-6746	UGUGAAACCUCUUAUACAGAGAA		6724-6746
AD-1735900	GACUUUCAAAGUACUAAUACA		8098-8118	UGUAUUAGUACUUUGAAAGUCAA		8096-8118
AD-1735901	UUUGCCAUUAUACAAAGUUUA		5262-5282	UAAACUUUGUAUAAUGGCAAACA		5260-5282
AD-1735902	GAACACUAUCGACAUACCUCA		1276-1296	UGAGGUAUGUCGAUAGUGUUCAG		1274-1296
AD-1735903	UAGAAUGACAUUUACUAAUAA		7818-7838	UUAUUAGUAAAUGUCAUUCUACG		7816-7838
AD-1735904	AAGCUACUUAGAAAUGUUUAA		5491-5511	UUAAACAUUUCUAAGUAGCUUGU		5489-5511
AD-1735905	CCUUAGUACUCUCAGAGAUUA		5968-5988	UAAUCUCUGAGAGUACUAAGGGA		5966-5988
AD-1735906	UGAAUGCACACUAACGUAAUA		6163-6183	UAUUACGUUAGUGUGCAUUCAAG		6161-6183
AD-1735907	AAGCCUAAUGAUGAUAAUUAA		1695-1715	UUAAUUAUCAUCAUUAGGCUUUG		1693-1715
AD-1735908	AAACUUUUUACUAUCCCAUAA		3341-3361	UUAUGGGAUAGUAAAAAGUUUCC		3339-3361
AD-1735909	CUAGCUGAUACUCUUAAGUAA		8268-8288	UUACUUAAGAGUAUCAGCUAGCU		8266-8288
AD-1735910	AGCAUGAAAAGAUAACUCUAA		1837-1857	UUAGAGUUAUCUUUUCAUGCUGC		1835-1857
AD-1735911	UAAGCCAUUAUGCUAUUAGUA		7017-7037	UACUAAUAGCAUAAUGGCUUAGU		7015-7037
AD-1735912	UCUAGCUUUUAGCUAACAUAA		6850-6870	UUAUGUUAGCUAAAAGCUAGAAU		6848-6870
AD-1735913	GUGUGAUUCUUCAAACUUCAA		316-336	UUGAAGUUUGAAGAAUCACACAA		314-336
AD-1735914	UCUCCAGACCUAACAGUUUUA		7247-7267	UAAAACUGUUAGGUCUGGAGAGA		7245-7267
AD-1735915	CUUUUUUUCAUCUAGCCUUGA		5808-5828	UCAAGGCUAGAUGAAAAAAAAGAA		5806-5828

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3
AD-1735916	CAAAAUAAUUCUUGACAUCUA		7552-7572	UAGAUGUCAAGAAUUAUUUUGAC		7550-7572
AD-1735917	GCAUCACUUUCUGAAAAUAAA		4690-4710	UUUAUUUUCAGAAAGUGAUGCUG		4688-4710
AD-1735918	UCUUUUGUGAAACAUACUAUA		5563-5583	UAUAGUAUGUUUCACAAAAGAUG		5561-5583
AD-1735919	CUAUUUCUUCCAUAGGCUAAA		7841-7861	UUUAGCCUAUGGAAGAAAUAGAA		7839-7861
AD-1735920	CUUCAAUGAAGUGUUAACAAA		2839-2859	UUUGUUAACACUUCAUUGAAGAG		2837-2859
AD-1735921	UUUGCCUUCAUUCUACUUUCA		2952-2972	UGAAAGUAGAAUGAAGGCAAAAC		2950-2972
AD-1735922	AGGUUUUUAAAUGUCCUAAAA		8035-8055	UUUUAGGACAUUUAAAAACCUGA		8033-8055
AD-1735923	GAAUAUCUUUGAGUCCUUCAA		1360-1380	UUGAAGGACUCAAAGAUAUUCAC		1358-1380
AD-1735924	GAACACUUCCAAAGAUUAAUA		2666-2686	UAUUAAUCUUUGGAAGUGUUCAG		2664-2686
AD-1735925	CUAAAUUUUGUCUAACAAAUA		7791-7811	UAUUUGUUAGACAAAAUUUAGGC		7789-7811
AD-1735926	GUAAACAACUUAAAAAUUGCUA		5284-5304	UAGCAAUUUUAAGUUGUUUACUC		5282-5304
AD-1735927	AAAAUAAUUUACUCACUCAGA		6233-6253	UCUGAGUGAGUAAAUUAUUUUAG		6231-6253
AD-1735928	GACAUCUAUUCUGUUGGUCUA		1388-1408	UAGACCAACAGAAUAGAUGUCAG		1386-1408
AD-1735929	UAACUGAGUAGUCUUAUAUUA		4267-4287	UAAUAUAAGACUACUCAGUUAGG		4265-4287
AD-1735930	UCUGGAAUUUAGCCUUCUAAA		5936-5956	UUUAGAAGGCUAAAUUCCAGACG		5934-5956
AD-1735931	ACAUGCCUUGAACUCUUGAAA		8207-8227	UUUCAAGAGUUCAAGGCAUGUUU		8205-8227
AD-1735932	AUCAAGCACUUCUUGCACUUA		8782-8802	UAAGUGCAAGAAGUGCUUGAUUU		8780-8802
AD-1735933	CUUGCUUUUCAUCUUUAUACA		4915-4935	UGUAUAAAGAUGAAAAGCAAGUG		4913-4935
AD-1735934	UUUUCUCCCUAUGUAAUAUCA		2493-2513	UGAUAUUACAUAGGGAGAAAAGC		2491-2513
AD-1735935	UGCUUUCUUCUAUGUCUAAAA		4802-4822	UUUUAGACAUAGAAGAAAGCAUA		4800-4822
AD-1735936	ACCUGCUUAGCAAAUCGUCUA		5224-5244	UAGACGAUUUGCUAAGCAGGUUC		5222-5244
AD-1735937	AUAUUCCUCUACCCUUUCACA		2895-2915	UGUGAAAGGGUAGAGGAAUAUCU		2893-2915
AD-1735938	UCCCACUUUUCUUUGGGUUUA		6208-6228	UAAACCCAAAGAAAAGUGGGAUU		6206-6228
AD-1735939	AGGCUUCUUGUAUAUACUUAA		4442-4462	UUAAGUAUAUACAAGAAGCCUGC		4440-4462
AD-1735940	AAACUUGAUCUGUGUUUCAGA		8017-8037	UCUGAAACACAGAUCAAGUUUGA		8015-8037
AD-1735941	UUUGCUUUAAUGCUAAAUUCA		6885-6905	UGAAUUUAGCAUUAAAGCAAAAG		6883-6905

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3
AD-1735942	AGACUAGCUGUUAUUUGUAUA		6830-6850	UAUACAAAUAACAGCUAGUCUUU		6828-6850
AD-1735943	UUCCUACUUUCCCUUGAAUAA		2469-2489	UUAUUCAAGGGAAAGUAGGAAGC		2467-2489
AD-1735944	CAGAACUGAAUGCUCAAGUCA		420-440	UGACUUGAGCAUUCAGUUCUGGA		418-440
AD-1735945	UCUUGUUACUAAUUUCUCAUA		3945-3965	UAUGAGAAAUUAGUAACAAGAAC		3943-3965
AD-1735946	CUCAGUGAUAGCCUUUAUACA		8586-8606	UGUAUAAAGGCUAUCACUGAGUU		8584-8606
AD-1735947	UUUUAUGCUCCUAAAACAUCA		3065-3085	UGAUGUUUUAGGAGCAUAAAAGA		3063-3085
AD-1735948	UUCUCCUUAGGUUAUGUUCAA		4551-4571	UUGAACAUAACCUAAGGAGAAUU		4549-4571
AD-1735949	AUUGCUCAUCGAGACAUAAAA		1175-1195	UUUUAUGUCUCGAUGAGCAAUAG		1173-1195
AD-1735950	CCUUUGUACAUACACACUUAA		2746-2766	UUAAGUGUGUAUGUACAAAGGAA		2744-2766
AD-1735951	UUGAACCAAGAGCACAUGAAA		2025-2045	UUUCAUGUGCUCUUGGUUCAAGU		2023-2045
AD-1735952	UCAGGGAUUUUAAAGUCUAAA		3668-3688	UUUAGACUUUAAAAUCCCUGAGG		3666-3688
AD-1735953	UACUUGCUUAUAAAGUGAUAA		3153-3173	UUAUCACUUUAUAAGCAAGUACC		3151-3173
AD-1735954	AUGCAUCUAAACCUACCUUGA		6145-6165	UCAAGGUAGGUUUAGAUGCAUGC		6143-6165
AD-1735955	UUGGGAAAACACUAUUAUGAA		4629-4649	UUCAUAAUAGUGUUUUCCCAAGU		4627-4649
AD-1735956	AAACUCCAAAGAGAAAUGAAA		8456-8476	UUUCAUUUCUCUUUGGAGUUUGA		8454-8476
AD-1735957	AUGGGCAUUUUUCAAAACAUA		5758-5778	UAUGUUUUGAAAAAUGCCCAUAU		5756-5778
AD-1735958	AUAAUGGAACUUGGACUCAAA		996-1016	UUUGAGUCCAAGUUCCAUUAUCU		994-1016
AD-1735959	UGUGUAGAUGACGAAACCAAA		6008-6028	UUUGGUUUCGUCAUCUACACAAA		6006-6028
AD-1735960	UUCUACCUCAAAGAUAAGACA		1790-1810	UGUCUUAUCUUUGAGGUAGAACA		1788-1810
AD-1735961	AGAAGGCAUAUUUGAGUUAUUA		2536-2556	UAAUAACUCAAUAUGCCUUCUAA		2534-2556
AD-1735962	AUGGAGUUUUUCUGCUAUUUA		5629-5649	UAAAUAGCAGAAAAACUCCAUGU		5627-5649
AD-1735963	UCAGUUUCUCAUUAGUUUGUA		6558-6578	UACAAACUAAUGAGAAACUGAGG		6556-6578
AD-1735964	CUGCAUAUAUAAGAACGAAAA		3976-3996	UUUUCGUUCUUAUAUAUGCAGAA		3974-3996
AD-1735965	UGAGCCAAAAUAUUAAAUUCA		7927-7947	UGAAUUUAAUAUUUUGGCUCAGA		7925-7947
AD-1735966	AGAAUGAUAUUUCCUGUUUUA		4035-4055	UAAAACAGGAAAUAUCAUUCUUG		4033-4055
AD-1735967	GUGCUCUAUAUAAAUCUUCCA		7385-7405	UGGAAGAUUUAUAUAGAGCACAA		7383-7405

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3
AD-1735968	UUUACAGAGAAGCAUCUUAUA		7468-7488	UAUAAGAUGCUUCUCUGUAAAAU		7466-7488
AD-1735969	GUCUUGAGUUCUGCAUGACAA		3761-3781	UUGUCAUGCAGAACUCAAGACAU		3759-3781
AD-1735970	CUUCAAAUCUAUAAUUUUACA		3017-3037	UGUAAAAUUAUAGAUUUGAAGGG		3015-3037
AD-1735971	GAAGCAUAUAGAACUCUAUUA		8810-8830	UAAUAGAGUUCUAUAUGCUUCAC		8808-8830
AD-1735972	GAGCUGCUUCUAAAUAAACAAA		5678-5698	UUUGUUAUUUAGAAGCAGCUCUC		5676-5698
AD-1735973	UGACUGUAUUUCCUGAUCAUA		7197-7217	UAUGAUCAGGAAAUACAGUCACA		7195-7217
AD-1735974	GUUCUGAAGGAUAUACUUCUA		3402-3422	UAGAAGUAUAUCCUUCAGAACGC		3400-3422
AD-1735975	GUGAAGCAUGAUUCAAUACUA		1256-1276	UAGUAUUGAAUCAUGCUUCACAG		1254-1276
AD-1735976	AAUGCUGCUUCACAGAUUUUA		474-494	UAAAAUCUGUGAAGCAGCAUUCG		472-494
AD-1735977	UGUGGGUUAUGUUAAUCUGAA		7283-7303	UUCAGAUUAACAUAACCCACAGU		7281-7303
AD-1735978	GAGUACAGAAGAAUGCUCAUA		2926-2946	UAUGAGCAUUCUUCUGUACUCAC		2924-2946
AD-1735979	CUGUAUUUCAUCCUAGAUUUA		7162-7182	UAAAUCUAGGAUGAAAUACAGCU		7160-7182
AD-1735980	AAUCUGGUAAAUGCUGGAAAA		695-715	UUUUCCAGCAUUUACCAGAUUGC		693-715
AD-1735981	UGCUCAGAUUACCUGAUCGUA		3293-3313	UACGAUCAGGUAAUCUGAGCAAU		3291-3313
AD-1735982	GACAGCUAUGGAGUUUGCGUA		3531-3551	UACGCAAACUCCAUAGCUGUCAG		3529-3551
AD-1735983	UAGAACAUGCUCACUUACAAA		4391-4411	UUUGUAAGUGAGCAUGUUCUAUA		4389-4411
AD-1735984	AUUAUGCUUCAUUUCACUAUA		3450-3470	UAUAGUGAAAUGAAGCAUAAUCA		3448-3470
AD-1735985	CAACAGCAAGUCAUAAAAGUA		8624-8644	UACUUUUAUGACUUGCUGUUGGU		8622-8644
AD-1735986	UUGUCUGAAAAUGUCUUUAAA		2702-2722	UUUAAAGACAUUUUCAGACAAUG		2700-2722
AD-1735987	UGUUGGUUCAAAGGACAAUUA		774-794	UAAUUGUCCUUUGAACCAACAGA		772-794
AD-1735988	UCUAAACUUUAAUAUAUCGAA		2190-2210	UUCGAUAUAUUAAAGUUUAGAGC		2188-2210
AD-1735989	AAGUGAAACAUGACUGUCGUA		4875-4895	UACGACAGUCAUGUUUCACUUAA		4873-4895
AD-1735990	AUCGUCCAUACAGUUUUCAUA		7719-7739	UAUGAAAACUGUAUGGACGAUAU		7717-7739
AD-1735991	CUUCAGGAAAUAGUAGGAAAA		809-829	UUUUCCUACUAUUUCCUGAAGCA		807-829
AD-1735992	CACCCUUUCUGUAAGGACUGA		6426-6446	UCAGUCCUUACAGAAAGGGUGGG		6424-6446
AD-1735993	AAAGAGAUACCUGACAUCCUA		2354-2374	UAGGAUGUCAGGUAUCUCUUUUG		2352-2374

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3
AD-1735994	AUGAGCAUUAAUGUUUUCUGA		2647-2667	UCAGAAAACAUUAAUGCUCAUUA		2645-2667
AD-1735995	UGACAUUUUUUCUCAUAGAAA		2603-2623	UUUCUAUGAGAAAAAAUGUCAAC		2601-2623
AD-1735996	CAGAGAUUAAAUGACUACUAA		6032-6052	UUAGUAGUCAUUUAAUCUCUGAU		6030-6052
AD-1735997	GCUGUCAAAUGUUAUAUUGUA		4463-4483	UACAAUAUAACAUUUGACAGCAU		4461-4483
AD-1735998	AAUAUAAUACUACAGCAAAAA		7041-7061	UUUUUGCUGUAGUAUUAUAUUCC		7039-7061
AD-1735999	GGUGUCUAAAUAUAAUUUCAA		4153-4173	UUGAAAUUAUAUUUAGACACCCU		4151-4173
AD-1736000	CUCUUUAUACAAAAUGAGAGA		7903-7923	UCUCUCAUUUUGUAUAAAGAGAA		7901-7923
AD-1736001	GCAGUACCAAAUGAAUAAAAA		5410-5430	UUUUUAUUCAUUUGGUACUGCUA		5408-5430
AD-1736002	UUGUUGGUACACAAGGUAAAA		1149-1169	UUUUACCUUGUGUACCAACAAUC		1147-1169
AD-1736003	CUCUUAUUUAACUUAACCGUA		5917-5937	UACGGUUAAGUUAAAUAAGAGUU		5915-5937
AD-1736004	UGCUUGAUGAUACAAUGAAUA		1338-1358	UAUUCAUUGUAUCAUCAAGCAUU		1336-1358
AD-1736005	AACUGGGAAAGACAAUUUGAA		6920-6940	UUCAAAUUGUCUUUCCCAGUUAC		6918-6940
AD-1736006	CUCCUUAUAUGACUAUUUGAA		1048-1068	UUCAAAUAGUCAUAUAAGGAGCC		1046-1068
AD-1736007	AGUCAUGCUAACCAAUGGAAA		367-387	UUUCCAUUGGUUAGCAUGACUGA		365-387
AD-1736008	CCUGAAGUCACACAGCUAAUA		2391-2411	UAUUAGCUGUGUGACUUCAGGAC		2389-2411
AD-1736009	UUGCUGCUGACAACAAAGAUA		978-998	UAUCUUUGUUGUCAGCAGCAAUG		976-998
AD-1736010	UACUGACUUUGCCUGUAAAGA		7757-7777	UCUUUACAGGCAAAGUCAGUAAU		7755-7777
AD-1736011	AAUCCCUAUUUUAAAAAUUCCA		7070-7090	UGGAAUUUUAAAAAUAGGGAUUGU		7068-7090
AD-1736012	GUGCCUUAGGAGAUUACCCUA		7330-7350	UAGGGUAAUCUCCUAAGGCACUC		7328-7350
AD-1736013	GACAAUCUAAAAUAUAUCAUCA		3857-3877	UGAUGAUAUAUUUAGAUUGUCUG		3855-3877
AD-1736014	UGUGAUAAUGAACACCGUAAA		2438-2458	UUUACGGUGUUCAUUAUCACAAG		2436-2458
AD-1736015	UCACCGUUGUAAAGACUUUUA		8242-8262	UAAAAGUCUUUACAACGGUGAUU		8240-8262
AD-1736016	UUAGAGAAGCUUCCUGACAUA		6402-6422	UAUGUCAGGAAGCUUCUCUAAUC		6400-6422
AD-1736017	AACAGUAAAGAAAUGCUACUA		3252-3272	UAGUAGCAUUUCUUUACUGUUAU		3250-3272
AD-1736018	UAUGUUCUGACUUGAGAGUUA		4855-4875	UAACUCUCAAGUCAGAACAUAAA		4853-4875
AD-1736019	UUAGAGCAUGCUAUCUUUAGA		2109-2129	UCUAAAGAUAGCAUGCUCUAAUU		2107-2129

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3
AD-1736020	UAGUCUUUGAUUGAAAUAAGA		5314-5334	UCUUAUUUCAAUCAAAGACUAUG		5312-5334
AD-1736021	UUGGUAAACGAGAUUUAACAA		3038-3058	UUGUUAAAUCUCGUUUACCAAAG		3036-3058
AD-1736022	GUCUGAAAAUUGCUUUCAUUA		3798-3818	UAAUGAAAGCAAUUUUCAGACCU		3796-3818
AD-1736023	AUGAACUUGUUGCCUUGUAAA		4741-4761	UUUACAAGGCAACAAGUUCAUGC		4739-4761
AD-1736024	GGGCAAUAAACUGUAUCAAAA		8379-8399	UUUUGAUACAGUUUAUUGCCCAA		8377-8399
AD-1736025	ACAUGUUAGCAUAUAAUGUAA		3175-3195	UUACAUUAUAUGCUAACAUGUAC		3173-3195
AD-1736026	UGUGAGAGUAUAGAAUUUCUA		6367-6387	UAGAAAUUCUAUACUCUCACAGU		6365-6387
AD-1736027	AUCCUUCAUUUGGCACUAUAA		6764-6784	UUAUAGUGCCAAAUGAAGGAUUA		6762-6784
AD-1736028	ACAUUUAGAAAGUAGCUUUAA		3824-3844	UUAAAGCUACUUUCUAAAUGUGU		3822-3844
AD-1736029	AACUGUUCUAUAAAGCAAAGA		3364-3384	UCUUUGCUUUAUAGAACAGUUAA		3362-3384
AD-1736030	CCUCCAGAGAUGAAAGAUCUA		894-914	UAGAUCUUUCAUCUCUGGAGGAG		892-914
AD-1736031	UUGUUUAACUAUGACUCCUAA		4249-4269	UUAGGAGUCAUAGUUAAACAACA		4247-4269
AD-1736032	CUGUUUGACAAUGCUUUGUUA		5585-5605	UAACAAAGCAUUGUCAAACAGAA		5583-5605
AD-1736033	UGUCCUAAAAGAAAUUUUUCA		7227-7247	UGAAAAAUUUCUUUUAGGACAAC		7225-7247
AD-1736034	ACAGAUUGAACAAAGAACUUA		7572-7592	UAAGUUCUUUGUUCAAUCUGUAG		7570-7592
AD-1736035	GUUUAACCUGUCCAAACUUCA		6673-6693	UGAAGUUUGGACAGGUUAAACGA		6671-6693
AD-1736036	CAAAAUGUUUAACUUUACCAA		8606-8626	UUGGUAAAGUUAAACAUUUUGGU		8604-8626
AD-1736037	UCCCAUUGUGUAAUAUUUAUA		4494-4514	UAUAAAUAUUACACAAUGGGACU		4492-4514
AD-1736038	GUUGGGUAAAUAUGCUUAUUA		4065-4085	UAAUAAGCAUAUUUACCCAACAU		4063-4085
AD-1736039	CAGGGUUGUCUUUGAGUCUGA		5187-5207	UCAGACUCAAAGACAACCCUGAG		5185-5207
AD-1736040	GCUAAAAUCCCAACUGCAAUUA		7425-7445	UAAUUGCAGUUGGAUUUUAGCCC		7423-7445
AD-1736041	CAGGACUGAAGUGUGUAUGUA		291-311	UACAUACACACUUCAGUCCUGGC		289-311
AD-1736042	GAGUACCAAUUGCCUUAUUAA		1457-1477	UUAAUAAGGCAAUUGGUACUCCU		1455-1477
AD-1736043	AAGUGCCUAUGUGAAGUGAUA		3886-3906	UAUCACUUCACAUAGGCACUUUU		3884-3906
AD-1736044	UAACAAUAAUAGAACUGCCAA		7092-7112	UUGGCAGUUCUAUUAUUGUUAGG		7090-7112
AD-1736045	GCUGUUCCAUACCAUUGCUUA		6978-6998	UAAGCAAUGGUAUGGAACAGCAG		6976-6998

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3
AD-1736046	UAGACUGGAGAAGAUUAUUCA		7997-8017	UGAAUAAUCUUCUCCAGUCUAGA		7995-8017
AD-1736047	UUCCAACAGCAUCACCAAAUA		516-536	UAUUUGGUGAUGCUGUUGGAAGG		514-536
AD-1736048	UAAUUGGUACAGAUUCUGUUA		4779-4799	UAACAGAAUCUGUACCAAUUACA		4777-4799
AD-1736049	GAGAAACAUUAUUUGUUGUCA		4710-4730	UGACAACAAAUAAUGUUUCUCUU		4708-4730
AD-1736050	CGCUCUCAAUUGCUAGUGGUA		1107-1127	UACCACUAGCAAUUGAGAGCGCC		1105-1127
AD-1736051	CGGUAUCAGAAACAGCAAAUA		2873-2893	UAUUUGCUGUUUCUGAUACCGUC		2871-2893
AD-1736052	CCCAGACAUAAUUUUAUAUUA		7449-7469	UAAUAUAAAAUUAUGUCUGGGAG		7447-7469
AD-1736053	UAGUACAUUUUGAGGUAUUUA		4215-4235	UAAAUACCUCAAAAUGUACUAAC		4213-4235
AD-1736054	AAAUGCUAUUGAUAACAGUAA		3211-3231	UUACUGUUAUCAAUAGCAUUUAC		3209-3231
AD-1736055	UAGCUGAAUUUGGGACUAUGA		6490-6510	UCAUAGUCCCAAAUUCAGCUAUC		6488-6510
AD-1736056	AUUGUGGUUUUCAAAGAUAUA		5535-5555	UAUAUCUUUGAAAACCACAAUGG		5533-5555
AD-1736057	CCUGGUUGCAGUAUCUGAAAA		4985-5005	UUUUCAGAUACUGCAACCAGGUU		4983-5005
AD-1736058	UAGAAUGGUUGUUGAGCUAAA		6297-6317	UUUAGCUCAACAACCAUUCUACA		6295-6317
AD-1736059	CUGGCCAUCAUUAUUACUGUA		560-580	UACAGUAAUAAUGAUGGCCAGCU		558-580
AD-1736060	UUGACAGAUAAAAAUACGAAGA		3735-3755	UCUUCGUAUUUUAUCUGUCAAUU		3733-3755
AD-1736061	UCACAAACACACAUCAUUACAAA		5473-5493	UUUGUAAUGAUGUGUUUGUGAAU		5471-5493
AD-1736062	CCAUGAUUGUAUGAAAAUAGA		4962-4982	UCUAUUUUCAUACAAUCAUGGAA		4960-4982
AD-1736063	CACAGAGUAAAUGAAUAUUUAA		2978-2998	UUAAAUAUUCAUUACUCUGUGUC		2976-2998
AD-1736064	AGCUGCUUAGUGGGAAGAUGUA		2222-2242	UACAUCUUCCACUAAGCAGCUCC		2220-2242
AD-1736065	UAGCUCUGUGUGCUGAUACCA		5606-5626	UGGUAUCAGCACACAGAGCUAGA		5604-5626
AD-1736066	CAUUCGAGAGAAUAUGAGCUA		7144-7164	UAGCUCAUAUUCUCUCGAAUGUA		7142-7164
AD-1736067	AUGCAUUUUCUGAAAAUGUAA		8734-8754	UUACAUUUUCAGAAAAUGCAUAC		8732-8754
AD-1736068	GUUUCGACCAAGUAUCCCAAA		1537-1557	UUUGGGAUACUUGGUCGAAACUU		1535-1557
AD-1736069	UCUUGCUUGCCACAAUAUCGA		3610-3630	UCGAUAUUGUGGCAAGCAAGAUA		3608-3630
AD-1736070	GGGUACAAGAGGGAAUACAAA		3629-3649	UUUGUAUUCCCUCUUGUACCCGA		3627-3649
AD-1736071	GGUGAUCAAAUCCUGUGUCUA		394-414	UAGACACAGGAUUUGAUCACCUG		392-414

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3
AD-1736072	CAGUGGGUUUCUAGGAUAGGA		3779-3799	UCCUAUCCUAGAAACCCACUGUC		3777-3799
AD-1736073	AACUAAGUAUUUUUAAGGACA		7869-7889	UGUCCUUAAAAAUACUUAGUUAC		7867-7889
AD-1736074	CAUAAUGUGAUUGUUAAAUUA		6951-6971	UAAUUUAACAAUCACACAUUAUGGG		6949-6971
AD-1736075	GAGAAGAAUUAAGAAAACUCA		2820-2840	UGAGUUUUCUUAAUUCUUCUCAA		2818-2840
AD-1736076	GAAGAGAAAUUGAUUGUUUAA		7635-7655	UUAAACAAUCAAUUUCUCUUCUC		7633-7655
AD-1736077	AGUGUGAAACUUGUGCCAUAA		1218-1238	UUAUGGCACAAGUUUCACACUUU		1216-1238
AD-1736078	CUGAGACACUGAGAAAAUGUCA		2372-2392	UGACAUUUCUCAGUGUCUCAGGA		2370-2392
AD-1736079	UGGCUUAUAUGUGUUUAAAGA		7488-7508	UCUUUAAACACAUAUAAGCCAAU		7486-7508
AD-1736080	UGCAUUUUGACAUUGCAAAAA		8188-8208	UUUUUGCAAUGUCAAAAUGCAAU		8186-8208
AD-1736081	UUAGGUUAGAAGUUCCAGAAA		5053-5073	UUUCUGGAACUUCUAACCUAAUG		5051-5073
AD-1736082	UGCGACAUGAAAACAUCCUUA		951-971	UAAGGAUGUUUUCAUGUCGCAGC		949-971
AD-1736083	GAGAGGAUUUUUUACCAUCUA		4095-4115	UAGAUGGUAAAAAAUCCUCUCUU		4093-4115
AD-1736084	GAAGGUGAAGAGAAUUUCAAA		8438-8458	UUUGAAAUUCUCUUCACCUUCCA		8436-8458
AD-1736085	UGGUAUCUGAAUAUCAUGAAA		1023-1043	UUUCAUGAUAUUCAGAUACCAGC		1021-1043
AD-1736086	UGUUGGUUUAAUUUUUUCAACA		7658-7678	UGUUGAAAAAUUAAACCAACAUG		7656-7678
AD-1736087	UAGUUGUAAUUUAAAUGUGGA		8419-8439	UCCACAUUUAAAUUACAACUACU		8417-8439
AD-1736088	GUGAAUGUUUUUGCCAUUUUA		1763-1783	UAAAAUGGCAAAAACAUUCACAU		1761-1783
AD-1736089	CAGAGAUGAUUUUUCUUUUAA		6800-6820	UUAAAAGAAAAAUCAUCUCUGCC		6798-6820
AD-1736090	AGAAAAUUAGAUUCAGAUCUA		8058-8078	UAGAUCUGAAUCUAAUUUUUCUGU		8056-8078
AD-1736091	ACUGGAAAAUUAAGAAAGUAA		5390-5410	UUACUUUUCUUAAUUUUUCCAGUGG		5388-5410
AD-1736092	UAAAGUGGGAAAGAUAAUAAA		8762-8782	UUUAUUAUCUUUUCCCACUUUACA		8760-8782
AD-1736093	CUAGGCUAAGAAAGAGUUGUA		6278-6298	UACAACUCUUUCUUAGCCUAGUU		6276-6298
AD-1736094	GCUGAUAAAAUUAAAUGGAUAA		6335-6355	UUAUCCAUUAAUUUUAUCAGCAC		6333-6355
AD-1736095	CCUGUAUUUCUUUAGUUGUCA		6653-6673	UGACAACUAAAGAAAUACAGGAA		6651-6673
AD-1736096	UUUGUUUUGCUUUUGACAAAA		6996-7016	UUUUGUCAAAAGCAAAACAAAGC		6994-7016
AD-1736097	UGGCUGUGAAAAUAUUCUCCA		876-896	UGGAGAAUAUUUUCACAGCCACA		874-896

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3
AD-1736098	ACUAUUUUAGGCAUAGCACUA		4897-4917	UAGUGCUAUGCCUAAAAUAGUGC		4895-4917
AD-1736099	UUUCAGUACUGUAUAAAGUGA		4651-4671	UCACUUUAUACAGUACUGAAAAU		4649-4671
AD-1736100	GUGAUGCAAUCUAUGUUUCCA		2129-2149	UGGAAACAUAGAUUGCAUCACCU		2127-2149
AD-1736101	UGUUUGGCAGAUCUCAUCAAA		6613-6633	UUUGAUGAGAUCUGCCAAACAUU		6611-6633
AD-1736102	AAGGUUGUUUGUGACCAGAAA		1517-1537	UUUCUGGUCACAAACAACCUUUC		1515-1537
AD-1736103	GGAAGGAAAUAUUUUGAGAAA		2794-2814	UUUCUCAAAAUAUUUCCUUCCUU		2792-2814
AD-1736104	UUUUGGUAGCGUGACUCUUCA		8132-8152	UGAAGAGUCACGCUACCAAAAGA		8130-8152
AD-1736105	UGAACAGGAAAAGAUGUAAAA		2045-2065	UUUUACAUCUUUUCCUGUUCAUU		2043-2065
AD-1736106	GGGAACCAAGAGGUAUAUGGA		1309-1329	UCCAUAUACCUCUUGGUUCCCAC		1307-1329
AD-1736107	UGGCACUAGGUCCAAAUCUUA		2419-2439	UAAGAUUUGGACCUAGUGCCAGU		2417-2439
AD-1736108	CACACCUUCAUAUGGAGAUUA		1131-1151	UAAUCUCCAUAUGAAGGUGUGCC		1129-1151
AD-1736109	CUGGUUUACUGGGAAAUAGCA		1406-1426	UGCUAUUUCCCAGUAAACCAGAC		1404-1426
AD-1736110	GCCCAAAGGAAUGUAUAUAAA		8316-8336	UUUAUAUACAUUCCUUUGGGCCU		8314-8336
AD-1736111	UUAACUGCAAGAGUUUACUGA		7265-7285	UCAGUAAACUCUUGCAGUUAAAA		7263-7285
AD-1736112	GAACCACUCUCUGAGUGCAAA		677-697	UUUGCACUCAGAGAGUGGUUCCU		675-697
AD-1736113	UUAUCUUUUCAUCCUGGCAUA		7607-7627	UAUGCCAGGAUGAAAAGAUAAAG		7605-7627
AD-1736114	GUGAGUGUUGGUAUGCCAACA		1605-1625	UGUUGGCAUACCAACACUCACGC		1603-1625
AD-1736115	AGAAUGUAUUUGGCUAAAUAA		5338-5358	UUAUUUAGCCAAAUACAUUCUCA		5336-5358
AD-1736116	GAACCCUUUUAUUAAGAGGAA		3317-3337	UUCCUCUUAAUAAAAGGGUUCCA		3315-3337
AD-1736117	CUCCUGUCCAUAGCUGCGAUA		590-610	UAUCGCAGCUAUGGACAGGAGGC		588-610
AD-1736118	ACUGAGUUGAAAUAAGGAAGA		3501-3521	UCUUCCUUAUUUCAACUCAGUAA		3499-3521
AD-1736119	CUGCCAAACAGAAGGAGCAUA		337-357	UAUGCUCCUUCUGUUUGGCAGGU		335-357
AD-1736120	GGCAAAGUUGUGAAGCACUCA		1563-1583	UGAGUGCUUCACAACUUUGCCAC		1561-1583
AD-1736121	AUAGGAUGAUGAAGUUUAGAA		4413-4433	UUCUAAACUUCAUCAUCCUAUUU		4411-4433
AD-1736122	AUUCGUAUCUUAAAAUGGCAA		5513-5533	UUGCCAUUUUAAGAUACGAAUAC		5511-5533
AD-1736123	CACAGCUUGGGUAAUAGCGUA		3384-3404	UACGCUAUUACCCAAGCUGUGCU		3382-3404

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3
AD-1736124	UUUGCAACAACAUAACACUGA		492-512	UCAGUGUUAUGUUGUUGCAAAAA		490-512
AD-1736125	UGCCACCAUGUGACUUAUUGA		5153-5173	UCAAUAAGUCACAUGGUGGCAAA		5151-5173
AD-1736126	UCGAUAGAGGAAAUGAGAAAA		1499-1519	UUUUCUCAUUUCCUCUAUCGAGG		1497-1519
AD-1736127	UUUUUAAGUUAGCAGGACUUA		2152-2172	UAAGUCCUGCUAACUUAAAAAGG		2150-2172
AD-1736128	UGUAAAUAAUUAUCUGCCUAA		8696-8716	UUAGGCAGAUAAUUAUUUACAUC		8694-8716
AD-1736129	UGGUUGUACGUGCCUCAAAUA		4010-4030	UAUUUGAGGCACGUACAACCAUA		4008-4030

Table 5. Modified Sense and Antisense Strand Sequences of ACVR1C dsRNA Agents Comprising anUnsaturated C22 Hydrocarbon Chain Conjugated to Position 6 on the Sense Strand, Counting from the 5'-end of the Sense Strand

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1735861	usususuu(Uda)CfaAfAfCfuccauucc susa		VPusAfsggaAfuGfGfaguuUfgAfaaaaasgsa		UCUUUUUUCAAACUCCAUUCCUU	
AD-1735862	ascsuuu(Cda)AfuCfUfGfucuucaga susa		VPusAfsucuGfaAfGfacagAfuGfaaagususa		UAACUUUCAUCUGUCUUCAGAUG	
AD-1735863	cscsuca(Uda)AfaCfUfUfcuccaguas asa		VPusUfsuacUfgGfAfgaagUfuAfugaggsusg		CACCUCAUAACUUCUCCAGUAAU	
AD-1735864	csuscac(Uda)AfuCfUfUfucaacauu sasa		VPusUfsaauGfuUfGfaaagAfuAfgugagsgsg		CCCUCACUAUCUUUCAACAUUAU	
AD-1735865	csuscgu(Uda)AfaUfGfCfucucaucc sasa		VPusUfsggaUfgAfGfagcaUfuAfacgagsusa		UACUCGUUAAUGCUCUCAUCCAC	
AD-1735866	gsusucu(Uda)CfaUfAfAfuccacuac susa		VPusAfsguaGfuGfGfauuaUfgAfagaacsasg		CUGUUCUUCAUAAUCCACUACUG	
AD-1735867	gsusuga(Cda)UfuCfAfUfccaaucuc susa		VPusAfsgagAfuUfGfgaugAfaGfucaacsusc		GAGUUGACUUCAUCCAAUCUCUA	
AD-1735868	csusaca(Cda)AfaUfGfAfacuucuua sasa		VPusUfsuaaGfaAfGfuucaUfuGfuguagsasa		UUCUACACAAUGAACUUCUUAAC	
AD-1735869	csascau(Cda)UfaGfAfAfuucuuaau susa		VPusAfsauuAfaGfAfauucUfaGfaugugsasc		GUCACAUCUAGAAUUCUUAAUUU	

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1735870	asasauc(Uda)CfuCfAfUfagcuuucu susa		VPusAfsagaAfaGfCfuaugAfgAfgauuuscsu		AGAAAUCUCUCAUAGCUUUCUUU	
AD-1735871	cscsuac(Uda)AfuUfGfUfagaauuac susa		VPusAfsguaAfuUfCfuacaAfuAfguaggsusg		CACCUACUAUUGUAGAAUUACUA	
AD-1735872	asuscuu(Cda)UfuUfUfAfgugcauua sasa		VPusUfsuaaUfgCfAfcuaaAfaGfaagausgsa		UCAUCUUCUUUUAGUGCAUUAAA	
AD-1735873	csuscau(Gda)UfaCfUfCfuucugauu scsa		VPusGfsaauCfaGfAfagagUfaCfaugagscsu		AGCUCAUGUACUCUUCUGAUUCU	
AD-1735874	ususucu(Cda)UfuUfGfUfaccuugga sasa		VPusUfsuccAfaGfGfuacaAfaGfagaaasgsa		UCUUUCUCUUUGUACCUUGGAAU	
AD-1735875	usgsgcu(Uda)AfuAfCfAfucuucaga sasa		VPusUfsucuGfaAfGfauguAfuAfagccasgsa		UCUGGCUUAUACAUCUUCAGAAA	
AD-1735876	csasaaa(Cda)AfaAfAfCfuacuccuas usa		VPusAfsuagGfaGfUfaguuUfuGfuuuugsusu		AACAAAACAAAACUACUCCUAUU	
AD-1735877	ascsuag(Cda)AfgAfAfCfucuuauga sasa		VPusUfsucaUfaAfGfaguuCfuGfcuagusasa		UUACUAGCAGAACUCUUAUGAAA	
AD-1735878	cscsaag(Uda)CfaCfUfCfuauaauucs csa		VPusGfsgaaUfuAfUfagagUfgAfcuuggsgsa		UCCCAAGUCACUCUAUAAUUCCU	
AD-1735879	uscscau(Uda)UfuUfCfUfugucauua susa		VPusAfsuaaUfgAfCfaagaAfaAfauggasgsa		UCUCCAUUUUUCUUGUCAUUAUG	
AD-1735880	csasaca(Cda)CfuCfAfAfcucaucuus usa		VPusAfsaagAfuGfAfguugAfgGfuguugscsu		AGCAACACCUCAACUCAUCUUUU	
AD-1735881	ascsucu(Gda)AfaAfGfAfucugauuu sasa		VPusUfsaaaUfcAfGfaucuUfuCfagagususu		AAACUCUGAAAGAUCUGAUUUAU	
AD-1735882	csusagu(Uda)CfuUfUfUfccgcaaug sasa		VPusUfscauUfgCfGfgaaaAfgAfacuagsasa		UUCUAGUUCUUUUCCGCAAUGAC	
AD-1735883	csusuuc(Ada)CfuCfUfGfaagaaauc scsa		VPusGfsgauUfuCfUfucagAfgUfgaaagsusu		AACUUUCACUCUGAAGAAAUCCG	
AD-1735884	uscsuaa(Cda)UfuUfUfCfucucuuuc susa		VPusAfsgaaAfgAfGfagaaAfaGfuuagasusa		UAUCUAACUUUUCUCUCUUUCUC	
AD-1735885	uscsuca(Ada)CfuUfUfGfugucaaag sasa		VPusUfscuuUfgAfCfacaaAfgUfugagasusa		UAUCUCAACUUUGUGUCAAAGAA	
AD-1735886	csusuca(Ada)UfaAfUfCfauuccuuu sasa		VPusUfsaaaGfgAfAfugauUfaUfugaagsasc		GUCUUCAAUAAUCAUUCCUUUAA	
AD-1735887	usasacu(Gda)CfuCfUfUfcguauuaa		VPusCfsuuaAfuAfCfgaagAfgCfaguuasgsg		CCUAACUGCUCUUCGUAUUAAGA	

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
	sgsa					
AD-1735888	uscsuuc(Uda)GfuCfAfUfaguuccaa scsa		VPusGfsuugGfaAfCfuaugAfcAfgaagascsu		AGUCUUCUGUCAUAGUUCCAACA	
AD-1735889	asuscuc(Ada)GfaAfCfCfauaucugu susa		VPusAfsacaGfaUfAfuggUfcUfgagaususu		AAAUCUCAGAACCAUAUCUGUUG	
AD-1735890	usgsaau(Cda)UfaUfCfUfucauuuua scsa		VPusGfsuaaAfaUfGfaagaUfaGfauucasgsu		ACUGAAUCUAUCUUCAUUUUACU	
AD-1735891	ascscac(Uda)AfaAfCfUfuguuccuu susa		VPusAfsaagGfaAfCfaaguUfuAfguggususc		GAACCACUAAACUUGUUCCUUUC	
AD-1735892	asgsugu(Uda)CfuUfUfAfcuccuuac sasa		VPusUfsguaAfgGfAfguaaAfgAfacacusgsa		UCAGUGUUCUUUACUCCUUACAG	
AD-1735893	csusuua(Cda)UfcUfUfAfacaggauu sasa		VPusUfsaauCfcUfGfuuaaGfaGfuaaagsgsa		UCCUUUACUCUUAACAGGAUUAU	
AD-1735894	usasuac(Cda)UfaAfGfAfacauauua scsa		VPusGfsuaaUfaUfGfuucuUfaGfguauasasg		CUUAUACCUAAGAACAUAUUACA	
AD-1735895	csususcu(Ada)CfuGfAfGfaugaucca sasa		VPusUfsuggAfuCfAfucucAfgUfagaagsasa		UUCUUCUACUGAGAUGAUCCAAG	
AD-1735896	csusgua(Uda)UfuUfCfUfcauagagu sasa		VPusUfsacuCfuAfUfgagaAfaAfuacagsasa		UUCUGUAUUUUCUCAUAGAGUAC	
AD-1735897	ascsuuuu(Uda)CfuCfUfUfucaguugu sasa		VPusUfsacaAfcUfGfaaagAfgAfaaagusasu		AUACUUUUCUCUUUCAGUUGUAG	
AD-1735898	asusuaa(Uda)UfuCfUfAfgucuguga sasa		VPusUfsucaCfaGfAfcuagAfaAfuuaausgsa		UCAUUAAUUUCUAGUCUGUGAAA	
AD-1735899	csuscug(Uda)AfuAfAfGfagguuuca scsa		VPusGfsugaAfaCfCfucuuAfuAfcagagsasa		UUCUCUGUAUAAGAGGUUUCACC	
AD-1735900	gsascuu(Uda)CfaAfAfGfuacuaaua scsa		VPusGfsuauUfaGfUfacuuUfgAfaagucsasa		UUGACUUUCAAAGUACUAAUACU	
AD-1735901	ususugc(Cda)AfuUfAfUfacaaaguu susa		VPusAfsaacUfuUfGfuauaAfuGfgcaaascsa		UGUUUGCCAUUAUACAAAGUUUG	
AD-1735902	gsasaca(Cda)UfaUfCfGfacauaccus csa		VPusGfsaggUfaUfGfucgaUfaGfuguucsasg		CUGAACACUAUCGACAUACCUCA	
AD-1735903	usasgaa(Uda)GfaCfAfUfuuacuaau sasa		VPusUfsauuAfgUfAfaaugUfcAfuucuascsg		CGUAGAAUGACAUUUACUAAUAU	
AD-1735904	asasgcu(Ada)CfuUfAfGfaaauguuu sasa		VPusUfsaaaCfaUfUfucuaAfgUfagcuusgsu		ACAAGCUACUUAGAAAUGUUUAG	

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1735905	cscsuua(Gda)UfaCfUfCfucagagau susa		VPusAfsaucUfcUfGfagagUfaCfuaaggsgsa		UCCCUUAGUACUCUCAGAGAUUA	
AD-1735906	usgsaau(Gda)CfaCfAfCfuaacguaas usa		VPusAfsuuaCfgUfUfagugUfgCfauucasasg		CUUGAAUGCACACUAACGUAAUG	
AD-1735907	asasgcc(Uda)AfaUfGfAfugauaauu sasa		VPusUfsaauUfaUfCfaucaUfuAfggcuususg		CAAAGCCUAAUGAUGAUAAUUAU	
AD-1735908	asasacu(Uda)UfuUfAfCfuaucccau sasa		VPusUfsaugGfgAfUfaguaAfaAfaguuuscsc		GGAAACUUUUUACUAUCCCAUAU	
AD-1735909	csusagc(Uda)GfaUfAfCfucuuaagu sasa		VPusUfsacuUfaAfGfaguaUfcAfgcuagscsu		AGCUAGCUGAUACUCUUAAGUAU	
AD-1735910	asgscau(Gda)AfaAfAfGfauaacucu sasa		VPusUfsagaGfuUfAfucuuUfuCfaugcusgsc		GCAGCAUGAAAAGAUAACUCUAA	
AD-1735911	usasagc(Cda)AfuUfAfUfgcuauuag susa		VPusAfscuaAfuAfGfcauaAfuGfgcuuasgsu		ACUAAGCCAUUAUGCUAUUAGUU	
AD-1735912	uscsuag(Cda)UfuUfUfAfgcuaacau sasa		VPusUfsaugUfuAfGfcuaaAfaGfcuagasasu		AUUCUAGCUUUUAGCUAACAUAU	
AD-1735913	gsusgug(Ada)UfuCfUfUfcaaacuuc sasa		VPusUfsgaaGfuUfUfgaagAfaUfcacacsasa		UUGUGUGAUUCUUCAAACUUCAC	
AD-1735914	uscsucc(Ada)GfaCfCfUfaacaguuu susa		VPusAfsaaaCfuGfUfuaggUfcUfggagasgsa		UCUCUCCAGACCUAACAGUUUUA	
AD-1735915	csusuuu(Uda)UfuCfAfUfcuagccuu sgsa		VPusCfsaagGfcUfAfgaugAfaAfaaaagsasa		UUCUUUUUUUCAUCUAGCCUUGC	
AD-1735916	csasaaaa(Uda)AfaUfUfCfuugacaucs usa		VPusAfsgauGfuCfAfagaaUfuAfuuuugsasc		GUCAAAAUAAUUCUUGACAUCUA	
AD-1735917	gscsauc(Ada)CfuUfUfCfugaaaaua sasa		VPusUfsuauUfuUfCfagaaAfgUfgaugcsusg		CAGCAUCACUUUCUGAAAAUAAG	
AD-1735918	uscsuuuu(Uda)GfuGfAfAfacauacua susa		VPusAfsuagUfaUfGfuuucAfcAfaaagasusg		CAUCUUUUGUGAAACAUACUAUU	
AD-1735919	csusauu(Uda)CfuUfCfCfauaggcua sasa		VPusUfsuagCfcUfAfuggaAfgAfaauagsasa		UUCUAUUUCUUCCAUAGGCUAAA	
AD-1735920	csusuca(Ada)UfgAfAfGfuguuaaca sasa		VPusUfsuguUfaAfCfacuuCfaUfugaagsasg		CUCUUCAAUGAAGUGUUAACAAC	
AD-1735921	ususugc(Cda)UfuCfAfUfucuacuuu scsa		VPusGfsaaaGfuAfGfaaugAfaGfgcaaasasc		GUUUUGCCUUCAUUCUACUUUCU	
AD-1735922	asgsguu(Uda)UfuAfAfAfuguccuaa		VPusUfsuuaGfgAfCfauuuAfaAfaaccusgsa		UCAGGUUUUUAAAUGUCCUAAAA	

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
	sasa					
AD-1735923	gsasaua(Uda)CfuUfUfGfaguccuuc sasa		VPusUfsgaaGfgAfCfucaaAfgAfuauucsasc		GUGAAUAUCUUUGAGUCCUUCAA	
AD-1735924	gsasaca(Cda)UfuCfCfAfaagauuaas usa		VPusAfsuuaAfuCfUfuuggAfaGfuguucsasg		CUGAACACUUCCAAAGAUUAAUC	
AD-1735925	csusaaa(Uda)UfuUfGfUfcuaacaaas usa		VPusAfsuuuGfuUfAfgacaAfaAfuuuagsgsc		GCCUAAAUUUUGUCUAACAAAUG	
AD-1735926	gsusaaa(Cda)AfaCfUfUfaaaauugcs usa		VPusAfsgcaAfuUfUfuaagUfuGfuuuacsusc		GAGUAAACAACUUAAAAUUGCUU	
AD-1735927	asasaau(Ada)AfuUfUfAfcucacuca sgsa		VPusCfsugaGfuGfAfguaaAfuUfauuuusasg		CUAAAAUAAUUUACUCACUCAGA	
AD-1735928	gsascau(Cda)UfaUfUfCfuguugguc susa		VPusAfsgacCfaAfCfagaaUfaGfaugucsasg		CUGACAUCUAUUCUGUUGGUCUG	
AD-1735929	usasacu(Gda)AfgUfAfGfucuuauau susa		VPusAfsauaUfaAfGfacuaCfuCfaguuasgsg		CCUAACUGAGUAGUCUUAUAUUU	
AD-1735930	uscsugg(Ada)AfuUfUfAfgccuucua sasa		VPusUfsuagAfaGfGfcuaaAfuUfccagascsg		CGUCUGGAAUUUAGCCUUCUAAU	
AD-1735931	ascsaug(Cda)CfuUfGfAfacucuuga sasa		VPusUfsucaAfgAfGfuucaAfgGfcaugususu		AAACAUGCCUUGAACUCUUGAAC	
AD-1735932	asuscaa(Gda)CfaCfUfUfcuugcacus usa		VPusAfsaguGfcAfAfgaagUfgCfuugaususu		AAAUCAAGCACUUCUUGCACUUG	
AD-1735933	csusugc(Uda)UfuUfCfAfucuuuaua scsa		VPusGfsuauAfaAfGfaugaAfaAfgcaagsusg		CACUUGCUUUUCAUCUUUAUACU	
AD-1735934	ususuuc(Uda)CfcCfUfAfuguaauau scsa		VPusGfsauaUfuAfCfauagGfgAfgaaaasgsc		GCUUUUCUCCCUAUGUAAUAUCU	
AD-1735935	usgscuu(Uda)CfuUfCfUfaugucuaa sasa		VPusUfsuuaGfaCfAfuagaAfgAfaagcasusa		UAUGCUUUCUUCUAUGUCUAAAA	
AD-1735936	ascscug(Cda)UfuAfGfCfaaaucguc susa		VPusAfsgacGfaUfUfugcuAfaGfcaggususc		GAACCUGCUUAGCAAAUCGUCUG	
AD-1735937	asusauu(Cda)CfuCfUfAfcccuuuca scsa		VPusGfsugaAfaGfGfguagAfgGfaauauscsu		AGAUAUUCCUCUACCCUUUCACA	
AD-1735938	uscscca(Cda)UfuUfUfCfuuuggguu susa		VPusAfsaacCfcAfAfagaaAfaGfugggasusu		AAUCCCACUUUUCUUUGGGUUUC	
AD-1735939	asgsgcu(Uda)CfuUfGfUfauauacuu sasa		VPusUfsaagUfaUfAfuacaAfgAfagccusgsc		GCAGGCUUCUUGUAUAUACUUAU	

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1735940	asasacu(Uda)GfaUfCfUfguguuuca sgsa		VPusCfsugaAfaCfAfcagaUfcAfaguuusgsa		UCAAACUUGAUCUGUGUUUCAGG	
AD-1735941	ususugc(Uda)UfuAfAfUfgcuaaauu scsa		VPusGfsaauUfuAfGfcauuAfaAfgcaaasasg		CUUUUGCUUUAAUGCUAAAUUCC	
AD-1735942	asgsacu(Ada)GfcUfGfUfuauuugua susa		VPusAfsuacAfaAfUfaacaGfcUfagucususu		AAAGACUAGCUGUUAUUUGUAUU	
AD-1735943	ususccu(Ada)CfuUfUfCfccuugaau sasa		VPusUfsauuCfaAfGfggaaAfgUfaggaasgsc		GCUUCCUACUUUCCCUUGAAUAG	
AD-1735944	csasgaa(Cda)UfgAfAfUfgcucaagu scsa		VPusGfsacuUfgAfGfcauuCfaGfuucugsgsa		UCCAGAACUGAAUGCUCAAGUCU	
AD-1735945	uscsuug(Uda)UfaCfUfAfauuucuca susa		VPusAfsugaGfaAfAfuuagUfaAfcaagasasc		GUUCUUGUUACUAAUUUCUCAUA	
AD-1735946	csuscag(Uda)GfaUfAfGfccuuuaua scsa		VPusGfsuauAfaAfGfgcuaUfcAfcugagsusu		AACUCAGUGAUAGCCUUUAUACC	
AD-1735947	ususuua(Uda)GfcUfCfCfcuaaaacau scsa		VPusGfsaugUfuUfUfaggaGfcAfuaaaasgsa		UCUUUUAUGCUCCUAAAACAUCU	
AD-1735948	ususcuc(Cda)UfuAfGfGfuuauguuc sasa		VPusUfsgaaCfaUfAfaccuAfaGfgagaasusu		AAUUCUCCUUAGGUUAUGUUCAG	
AD-1735949	asusugc(Uda)CfaUfCfCfgfagacauuas asa		VPusUfsuuaUfgUfCfucgaUfgAfgcaausasg		CUAUUGCUCAUCGAGACAUAAAA	
AD-1735950	cscsuuuu(Gda)UfaCfAfUfacacacuu sasa		VPusUfsaagUfgUfGfuaugUfaCfaaaggsasa		UUCCUUUGUACAUACACACUUAG	
AD-1735951	ususgaa(Cda)CfaAfGfAfgcacauga sasa		VPusUfsucaUfgUfGfcucuUfgGfuucaasgsu		ACUUGAACCAAGAGCACAUGAAU	
AD-1735952	uscsagg(Gda)AfuUfUfUfUfaaagucua sasa		VPusUfsuagAfcUfUfUfuaaaAfuCfccugasgsg		CCUCAGGGAUUUUAAAGUCUAAU	
AD-1735953	usascuu(Gda)CfuUfAfUfaaagugau sasa		VPusUfsaucAfcUfUfUfauaAfgCfaaguascsc		GGUACUUGCUUAUAAAGUGAUAG	
AD-1735954	asusgca(Uda)CfuAfAfAfAfccuaccuu sgsa		VPusCfsaagGfuAfGfguuuAfgAfugcausgsc		GCAUGCAUCUAAACCUACCUUGA	
AD-1735955	ususgggg(Ada)AfaAfCfAfcuauuaug sasa		VPusUfscauAfaUfAfguguUfuUfcccaasgsu		ACUUGGGAAAACACUAUUAUGAA	
AD-1735956	asasacu(Cda)CfaAfAfGfagaaaugas asa		VPusUfsucaUfuUfUfCfucuuUfgGfaguuusgsa		UCAAACUCCAAAGAGAAAUGAAU	
AD-1735957	asusggg(Cda)AfuUfUfUfUfucaaaaca		VPusAfsuguUfuUfUfGfaaaaAfuGfcccausasu		AUAUGGGCAUUUUUUCAAAACAUU	

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
	susa					
AD-1735958	asusaau(Gda)GfaAfCfUfuggacuca sasa		VPusUfsugaGfuCfCfaaguUfcCfauuauscsu		AGAUAAUGGAACUUGGACUCAAC	
AD-1735959	usgsugu(Ada)GfaUfGfAfcgaaacca sasa		VPusUfsuggUfuUfCfgucaUfcUfacacasasa		UUUGUGUAGAUGACGAAACCAAG	
AD-1735960	ususcua(Cda)CfuCfAfAfagauaaga scsa		VPusGfsucuUfaUfCfuuugAfgGfuagaascsa		UGUUCUACCUCAAAGAUAAGACA	
AD-1735961	asgsaag(Gda)CfaUfAfUfugaguuau susa		VPusAfsauaAfcUfCfaauaUfgCfcuucusasa		UUAGAAGGCAUAUUGAGUUAUUU	
AD-1735962	asusgga(Gda)UfuUfUfUfcugcuauu susa		VPusAfsaauAfgCfAfgaaaAfaCfuccausgsu		ACAUGGAGUUUUUCUGCUAUUUU	
AD-1735963	uscsagu(Uda)UfcUfCfAfuuaguuug susa		VPusAfscaaAfcUfAfaugaGfaAfacugasgsg		CCUCAGUUUCUCAUUAGUUUGUC	
AD-1735964	csusgca(Uda)AfuAfUfAfagaacgaa sasa		VPusUfsuucGfuUfCfuuauAfuAfugcagsasa		UUCUGCAUAUAUAAGAACGAAAU	
AD-1735965	usgsagc(Cda)AfaAfAfUfauuaaauu scsa		VPusGfsaauUfuAfAfuauuUfuGfgcucasgsa		UCUGAGCCAAAAUAUUAAAUUCU	
AD-1735966	asgsaau(Gda)AfuAfUfUfuccuguuu susa		VPusAfsaaaCfaGfGfaaauAfuCfauucususg		CAAGAAUGAUAUUUUCCUGUUUUA	
AD-1735967	gsusgcu(Cda)UfaUfAfUfaaaucuuc scsa		VPusGfsgaaGfaUfUfuauaUfaGfagcacsasa		UUGUGCUCUAUAUAAAUCUUCCC	
AD-1735968	ususuac(Ada)GfaGfAfAfgcaucuua susa		VPusAfsuaaGfaUfGfcuucUfcUfguaaasasu		AUUUUACAGAGAAGCAUCUUAUU	
AD-1735969	gsuscuu(Gda)AfgUfUfCfugcaugac sasa		VPusUfsgucAfuGfCfagaaCfuCfaagacsasu		AUGUCUUGAGUUCUGCAUGACAG	
AD-1735970	csusuca(Ada)AfuCfUfAfuaauuuua scsa		VPusGfsuaaAfaUfUfauagAfuUfugaagsgsg		CCCUUCAAAUCUAUAAUUUUACU	
AD-1735971	gsasagc(Ada)UfaUfAfGfaacucuau susa		VPusAfsauaGfaGfUfucuaUfaUfgcuucsasc		GUGAAGCAUAUAGAACUCUAUUU	
AD-1735972	gsasgcu(Gda)CfuUfCfUfaaauaacas asa		VPusUfsuguUfaUfUfuagaAfgCfagcucsusc		GAGAGCUGCUUCUAAAUAACAAA	
AD-1735973	usgsacu(Gda)UfaUfUfUfccugauca susa		VPusAfsugaUfcAfGfgaaaUfaCfagucascsa		UGUGACUGUAUUUCCUGAUCAUU	
AD-1735974	gsusucu(Gda)AfaGfGfAfuauacuuc susa		VPusAfsgaaGfuAfUfauccUfuCfagaacsgsc		GCGUUCUGAAGGAUAUACUUCUG	

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1735975	gsusgaa(Gda)CfaUfGfAfuucaauac susa		VPusAfsguaUfuGfAfaucaUfgCfuucacsasg		CUGUGAAGCAUGAUUCAAUACUG	
AD-1735976	asasugc(Uda)GfcUfUfCfacagauuu susa		VPusAfsaaaUfcUfGfugaaGfcAfgcauuscsg		CGAAUGCUGCUUCACAGAUUUUU	
AD-1735977	usgsugg(Gda)UfuAfUfGfuuaaucu gsasa		VPusUfscagAfuUfAfacauAfaCfccacasgsu		ACUGUGGGUUAUGUUAAUCUGAA	
AD-1735978	gsasgua(Cda)AfgAfAfGfaaugcuca susa		VPusAfsugaGfcAfUfucuuCfuGfuacucsasc		GUGAGUACAGAAGAAUGCUCAUG	
AD-1735979	csusgua(Uda)UfuCfAfUfccuagauu susa		VPusAfsaauCfuAfGfgaugAfaAfuacagscsu		AGCUGUAUUUCAUCCUAGAUUUU	
AD-1735980	asasucu(Gda)GfuAfAfAfugcuggaa sasa		VPusUfsuucCfaGfCfauuuAfcCfagauusgsc		GCAAUCUGGUAAAUGCUGGAAAA	
AD-1735981	usgscuc(Ada)GfaUfUfAfccugaucg susa		VPusAfscgaUfcAfGfguaaUfcUfgagcasasu		AUUGCUCAGAUUACCUGAUCGUG	
AD-1735982	gsascag(Cda)UfaUfGfGfaguuugcg susa		VPusAfscgcAfaAfCfuccaUfaGfcugucsasg		CUGACAGCUAUGGAGUUUGCGUG	
AD-1735983	usasgaa(Cda)AfuGfCfUfcacuuacas asa		VPusUfsuguAfaGfUfgagcAfuGfuucuasusa		UAUAGAACAUGCUCACUUACAAA	
AD-1735984	asusuau(Gda)CfuUfCfAfuuucacua susa		VPusAfsuagUfgAfAfaugaAfgCfauaauscsa		UGAUUAUGCUUCAUUUCACUAUG	
AD-1735985	csasaca(Gda)CfaAfGfUfcauaaaags usa		VPusAfscuuUfuAfUfgacuUfgCfuguugsgsu		ACCAACAGCAAGUCAUAAAAGUA	
AD-1735986	ususguc(Uda)GfaAfAfAfugucuuua sasa		VPusUfsuaaAfgAfCfauuuUfcAfgacaasusg		CAUUGUCUGAAAAUGUCUUUAAG	
AD-1735987	usgsuug(Gda)UfuCfAfAfaggacaau susa		VPusAfsauuGfuCfCfuuugAfaCfcaacasgsa		UCUGUUGGUUCAAAGGACAAUUG	
AD-1735988	uscsuaa(Ada)CfuUfUfAfauauaucg sasa		VPusUfscgaUfaUfAfuuaaAfgUfuuagasgsc		GCUCUAAACUUUAAUAUAUCGAA	
AD-1735989	asasgug(Ada)AfaCfAfUfgacugucg susa		VPusAfscgaCfaGfUfcaugUfuUfcacuusasa		UUAAGUGAAACAUGACUGUCGUG	
AD-1735990	asuscgu(Cda)CfaUfAfCfaguuuuca susa		VPusAfsugaAfaAfCfuguaUfgGfacgausasu		AUAUCGUCCAUACAGUUUUCAUU	
AD-1735991	csusuca(Gda)GfaAfAfUfaguaggaa sasa		VPusUfsuucCfuAfCfuauuUfcCfugaagscsa		UGCUUCAGGAAAUAGUAGGAAAA	
AD-1735992	csasccc(Uda)UfuCfUfGfuaaggacu		VPusCfsaguCfcUfUfacagAfaAfgggugsgsg		CCCACCCUUUCUGUAAGGACUGU	

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
	sgsa					
AD-1735993	asasaga(Gda)AfuAfCfCfugacauccs usa		VPusAfsggaUfgUfCfagguAfuCfucuuususg		CAAAAGAGAUACCUGACAUCCUG	
AD-1735994	asusgag(Cda)AfuUfAfAfuguuuucu sgsa		VPusCfsagaAfaAfCfauuaAfuGfcucaususa		UAAUGAGCAUUAAUGUUUUCUGA	
AD-1735995	usgsaca(Uda)UfuUfUfUfcucauaga sasa		VPusUfsucuAfuGfAfgaaaAfaAfugucasasc		GUUGACAUUUUUUCUCAUAGAAA	
AD-1735996	csasgag(Ada)UfuAfAfAfugacuacu sasa		VPusUfsaguAfgUfCfauuuAfaUfcucugsasu		AUCAGAGAUUAAAUGACUACUAG	
AD-1735997	gscsugu(Cda)AfaAfUfGfuuauauug susa		VPusAfscaaUfaUfAfacauUfuGfacagcsasu		AUGCUGUCAAAUGUUAUAUUGUU	
AD-1735998	asasuau(Ada)AfuAfCfUfacagcaaas asa		VPusUfsuuuGfcUfGfuaguAfuUfauauuscsc		GGAAUAUAAUACUACAGCAAAAU	
AD-1735999	gsgsugu(Cda)UfaAfAfUfauaauuuc sasa		VPusUfsgaaAfuUfAfuauuUfaGfacaccscsu		AGGGUGUCUAAAUAUAAUUUCAU	
AD-1736000	csuscuu(Uda)AfuAfCfAfaaaugaga sgsa		VPusCfsucuCfaUfUfuuguAfuAfaagagsasa		UUCUCUUUAUACAAAAUGAGAGU	
AD-1736001	gscsagu(Ada)CfcAfAfAfugaauaaa sasa		VPusUfsuuuAfuUfCfauuuGfgUfacugcsusa		UAGCAGUACCAAAUGAAUAAAAG	
AD-1736002	ususguu(Gda)GfuAfCfAfcaagguaa sasa		VPusUfsuuaCfcUfUfguguAfcCfaacaasusc		GAUUGUUGGUACACAAGGUAAAC	
AD-1736003	csuscuu(Ada)UfuUfAfAfcuuaaccg susa		VPusAfscggUfuAfAfguuaAfaUfaagagsusu		AACUCUUAUUUAACUUAACCGUC	
AD-1736004	usgscuu(Gda)AfuGfAfUfacaaugaa susa		VPusAfsuucAfuUfGfuaucAfuCfaagcasusu		AAUGCUUGAUGAUACAAUGAAUG	
AD-1736005	asascug(Gda)GfaAfAfGfacaauuug sasa		VPusUfscaaAfuUfGfucuuUfcCfcaguusasc		GUAACUGGGAAAGACAAUUUGAA	
AD-1736006	csusccu(Uda)AfuAfUfGfacuauuug sasa		VPusUfscaaAfuAfGfucauAfuAfaggagscsc		GGCUCCUUAUAUGACUAUUUGAA	
AD-1736007	asgsuca(Uda)GfcUfAfAfccaaugga sasa		VPusUfsuccAfuUfGfguuaGfcAfugacusgsa		UCAGUCAUGCUAACCAAUGGAAA	
AD-1736008	cscsuga(Ada)GfuCfAfCfacagcuaas usa		VPusAfsuuaGfcUfGfugugAfcUfucaggsasc		GUCCUGAAGUCACACAGCUAAUG	
AD-1736009	ususgcu(Gda)CfuGfAfCfaacaaaga susa		VPusAfsucuUfuGfUfugucAfgCfagcaasusg		CAUUGCUGCUGACAACAAAGAUA	

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1736010	usascug(Ada)CfuUfUfGfccuguaaasgsa		VPusCfsuuuAfcAfGfgcaaAfgUfcaguasasu		AUUACUGACUUUGCCUGUAAAGA	
AD-1736011	asasucc(Cda)UfaUfUfUfUfuaaaauucscsa		VPusGfsgaaUfuUfUfaaaaUfaGfggauusgsu		ACAAUCCCUAUUUUAAAAUUCCC	
AD-1736012	gsusgcc(Uda)UfaGfGfAfgauuacccsusa		VPusAfsgggUfaAfUfcuccUfaAfggcacsusc		GAGUGCCUUAGGAGAUUACCCUU	
AD-1736013	gsascaa(Uda)CfuAfAfAfAfuauaucauscsa		VPusGfsaugAfuAfUfauuuAfgAfuugucsusg		CAGACAAUCUAAAUAUAUCAUCA	
AD-1736014	usgsuga(Uda)AfaUfGfAfacaccguasasa		VPusUfsuacGfgUfGfuucaUfuAfucacasasg		CUUGUGAUAAUGAACACCGUAAG	
AD-1736015	uscsacc(Gda)UfuGfUfAfaagacuuususa		VPusAfsaaaGfuCfUfuuacAfaCfggugasusu		AAUCACCGUUGUAAAGACUUUUU	
AD-1736016	ususaga(Gda)AfaGfCfUfuccugacasusa		VPusAfsuguCfaGfGfaagcUfuCfucuaasusc		GAUUAGAGAAGCUUCCUGACAUC	
AD-1736017	asascag(Uda)AfaAfGfAfaaugcuacsusa		VPusAfsguaGfcAfUfuucuUfuAfcuguusasu		AUAACAGUAAAGAAAUGCUACUU	
AD-1736018	usasugu(Uda)CfuGfAfCfuugagagususa		VPusAfsacuCfuCfAfagucAfgAfacauasasa		UUUAUGUUCUGACUUGAGAGUUA	
AD-1736019	ususaga(Gda)CfaUfGfCfuaucuuuasgsa		VPusCfsuaaAfgAfUfagcaUfgCfucuaasusu		AAUUAGAGCAUGCUAUCUUUAGG	
AD-1736020	usasguc(Uda)UfuGfAfUfugaaauaasgsa		VPusCfsuuaUfuUfCfaaucAfaAfgacuasusg		CAUAGUCUUUGAUUGAAAUAAGU	
AD-1736021	ususggu(Ada)AfaCfGfAfgauuuaacsasa		VPusUfsguuAfaAfUfcucgUfuUfaccaasasg		CUUUGGUAAACGAGAUUUAACAU	
AD-1736022	gsuscug(Ada)AfaAfUfUfUfgcuuucausa		VPusAfsaugAfaAfGfcaauUfuUfcagacscsu		AGGUCUGAAAAUUGCUUUCAUUU	
AD-1736023	asusgaa(Cda)UfuGfUfUfUfgccuugusasa		VPusUfsuacAfaGfGfcaacAfaGfuucausgsc		GCAUGAACUUGUUGCCUUGUAAA	
AD-1736024	gsgsgca(Ada)UfaAfAfCfuguaucaasasa		VPusUfsuugAfuAfCfaguuUfaUfugcccsasa		UUGGGCAAUAAACUGUAUCAAAA	
AD-1736025	ascsaug(Uda)UfaGfCfAfuauaaugusasa		VPusUfsacaUfuAfUfaugeUfaAfcaugusasc		GUACAUGUUAGCAUAUAAUGUAU	
AD-1736026	usgsuga(Gda)AfgUfAfUfagaauuucsusa		VPusAfsgaaAfuUfCfuauaCfuCfucacasgsu		ACUGUGAGAGUAUAGAAUUUCUU	
AD-1736027	asusccu(Uda)CfaUfUfUfggcacuausa		VPusUfsauaGfuGfCfcaaaUfgAfaggaususa		UAAUCCUUCAUUUGGCACUAUAG	

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
	sasa					
AD-1736028	ascsauu(Uda)AfgAfAfAfguagcuuu sasa		VPusUfsaaaGfcUfAfcuuuCfuAfaaugusgsu		ACACAUUUAGAAAGUAGCUUUAU	
AD-1736029	asascug(Uda)UfcUfAfUfaaagcaaas gsa		VPusCfsuuuGfcUfUfuauaGfaAfcaguusasa		UUAACUGUUCUAUAAAGCAAAGC	
AD-1736030	cscsucc(Ada)GfaGfAfUfgaaagauc susa		VPusAfsgauCfuUfUfcaucUfcUfggaggsasg		CUCCUCCAGAGAUGAAAGAUCUU	
AD-1736031	ususguu(Uda)AfaCfUfAfugacuccu sasa		VPusUfsaggAfgUfCfauagUfuAfaacaascsa		UGUUGUUUAACUAUGACUCCUAA	
AD-1736032	csusguu(Uda)GfaCfAfAfugcuuugu susa		VPusAfsacaAfaGfCfauugUfcAfaacagsasa		UUCUGUUUGACAAUGCUUUGUUC	
AD-1736033	usgsucc(Uda)AfaAfAfGfaaauuuuu scsa		VPusGfsaaaAfaUfUfucuuUfuAfggacasasc		GUUGUCCUAAAAGAAAUUUUUCU	
AD-1736034	ascsaga(Uda)UfgAfAfCfaaagaacus usa		VPusAfsaguUfcUfUfuguuCfaAfucugusasg		CUACAGAUUGAACAAAGAACUUA	
AD-1736035	gsusuua(Ada)CfcUfGfUfccaaacuu scsa		VPusGfsaagUfuUfGfgacaGfgUfuaaacsgsa		UCGUUUAACCUGUCCAAACUUCU	
AD-1736036	csasaaa(Uda)GfuUfUfAfacuuuacc sasa		VPusUfsgguAfaAfGfuuaaAfcAfuuuugsgsu		ACCAAAAUGUUUAACUUUACCAA	
AD-1736037	uscscca(Uda)UfgUfGfUfaauauuua susa		VPusAfsuaaAfuAfUfuacaCfaAfugggascsu		AGUCCCAUUGUGUAAUAUUUAUU	
AD-1736038	gsusugg(Gda)UfaAfAfUfaugcuuau susa		VPusAfsauaAfgCfAfuauuUfaCfccaacsasu		AUGUUGGGUAAAUAUGCUUAUUG	
AD-1736039	csasggg(Uda)UfgUfCfUfuugagucu sgsa		VPusCfsagaCfuCfAfaagaCfaAfcccugsasg		CUCAGGGUUGUCUUUGAGUCUGC	
AD-1736040	gscsuaa(Ada)AfuCfCfAfacugcaau susa		VPusAfsauuGfcAfGfuuggAfuUfuuagcscsc		GGGCUAAAAUCCAACUGCAAUUG	
AD-1736041	csasgga(Cda)UfgAfAfGfuguguaug susa		VPusAfscauAfcAfCfacuuCfaGfuccugsgsc		GCCAGGACUGAAGUGUGUAUGUC	
AD-1736042	gsasgua(Cda)CfaAfUfUfgccuuauu sasa		VPusUfsaauAfaGfGfcaauUfgGfuacucscsu		AGGAGUACCAAUUGCCUUAUUAU	
AD-1736043	asasgug(Cda)CfuAfUfGfugaaguga susa		VPusAfsucaCfuUfCfacauAfgGfcacuususu		AAAAGUGCCUAUGUGAAGUGAUU	
AD-1736044	usasaca(Ada)UfaAfUfAfgaacugcc sasa		VPusUfsggcAfgUfUfcuauUfaUfuguuasgsg		CCUAACAAUAAUAGAACUGCCAG	

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1736045	gscsugu(Uda)CfcAfUfAfccauugcu susa		VPusAfsagcAfaUfGfguauGfgAfacagcsasg		CUGCUGUUCCAUACCAUUGCUUU	
AD-1736046	usasgac(Uda)GfgAfGfAfagauuauu scsa		VPusGfsaauAfaUfCfuucuCfcAfgucuasgsa		UCUAGACUGGAGAAGAUUAUUCA	
AD-1736047	ususcca(Ada)CfaGfCfAfucaccaaas usa		VPusAfsuuuGfgUfGfaugcUfgUfuggaasgsg		CCUUCCAACAGCAUCACCAAAUG	
AD-1736048	usasauu(Gda)GfuAfCfAfgauucugu susa		VPusAfsacaGfaAfUfcuguAfcCfaauuascsa		UGUAAUUGGUACAGAUUCUGUUG	
AD-1736049	gsasgaa(Ada)CfaUfUfAfuuguugu scsa		VPusGfsacaAfcAfAfauaaUfgUfuucucsusu		AAGAGAAACAUUAUUUGUUGUCA	
AD-1736050	csgscuc(Uda)CfaAfUfUfgcuagugg susa		VPusAfsccaCfuAfGfcaauUfgAfgagcgscsc		GGCGCUCUCAAUUGCUAGUGGUC	
AD-1736051	csgsgua(Uda)CfaGfAfAfacagcaaas usa		VPusAfsuuuGfcUfGfuuucUfgAfuaccgsusc		GACGGUAUCAGAAACAGCAAAUA	
AD-1736052	cscscag(Ada)CfaUfAfAfuuuuauau susa		VPusAfsauaUfaAfAfauuaUfgUfcugggsasg		CUCCCAGACAUAAUUUUAUAUUU	
AD-1736053	usasgua(Cda)AfuUfUfUfgagguauu susa		VPusAfsaauAfcCfUfcaaaAfuGfuacuasasc		GUUAGUACAUUUUGAGGUAUUUU	
AD-1736054	asasaug(Cda)UfaUfUfGfauaacagu sasa		VPusUfsacuGfuUfAfucaaUfaGfcauuusasc		GUAAAUGCUAUUGAUAACAGUAA	
AD-1736055	usasgcu(Gda)AfaUfUfUfgggacuau sgsa		VPusCfsauaGfuCfCfcaaaUfuCfagcuasusc		GAUAGCUGAAUUUGGGACUAUGU	
AD-1736056	asusugu(Gda)GfuUfUfUfcaaagaua susa		VPusAfsuauCfuUfUfgaaaAfcCfacaausgsg		CCAUUGUGGUUUUCAAAGAUAUU	
AD-1736057	cscsugg(Uda)UfgCfAfGfuaucugaa sasa		VPusUfsuucAfgAfUfacugCfaAfccaggsusu		AACCUGGUUGCAGUAUCUGAAAA	
AD-1736058	usasgaa(Uda)GfgUfUfGfuugagcua sasa		VPusUfsuagCfuCfAfacaaCfcAfuucuascsa		UGUAGAAUGGUUGUUGAGCUAAG	
AD-1736059	csusggc(Cda)AfuCfAfUfuauuacug susa		VPusAfscagUfaAfUfaaugAfuGfgccagscsu		AGCUGGCCAUCAUUAUUACUGUG	
AD-1736060	ususgac(Ada)GfaUfAfAfaauacgaa sgsa		VPusCfsuucGfuAfUfuuuaUfcUfgucaasusu		AAUUGACAGAUAAAAUACGAAGU	
AD-1736061	uscsaca(Ada)AfcAfCfAfucauuacas asa		VPusUfsuguAfaUfGfauguGfuUfugugasasu		AUUCACAAACACAUCAUUACAAG	
AD-1736062	cscsaug(Ada)UfuGfUfAfugaaaaua		VPusCfsuauUfuUfCfauacAfaUfcauggsasa		UUCCAUGAUUGUAUGAAAAUAGU	

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
	sgsa					
AD-1736063	csascag(Ada)GfuAfAfUfgaauauuu sasa		VPusUfsaaaUfaUfUfcauuAfcUfcugugsusc		GACACAGAGUAAUGAAUAUUUAA	
AD-1736064	asgscug(Cda)UfuAfGfUfggaagaug susa		VPusAfscauCfuUfCfcacuAfaGfcagcuscsc		GGAGCUGCUUAGUGGAAGAUGUA	
AD-1736065	usasgcu(Cda)UfgUfGfUfgcugauac scsa		VPusGfsguaUfcAfGfcacaCfaGfagcuasgsa		UCUAGCUCUGUGUGCUGAUACCU	
AD-1736066	csasuuc(Gda)AfgAfGfAfauaugagc susa		VPusAfsgcuCfaUfAfuucuCfuCfgaaugsusa		UACAUUCGAGAGAAUAUGAGCUG	
AD-1736067	asusgca(Uda)UfuUfCfUfgaaaaugu sasa		VPusUfsacaUfuUfUfcagaAfaAfugcausasc		GUAUGCAUUUUCUGAAAAUGUAU	
AD-1736068	gsusuuc(Gda)AfcCfAfAfguauccca sasa		VPusUfsuggGfaUfAfcuugGfuCfgaaacsusu		AAGUUUCGACCAAGUAUCCCAAA	
AD-1736069	uscsuug(Cda)UfuGfCfCfcacaauauc sgsa		VPusCfsgauAfuUfGfuggcAfaGfcaagasusa		UAUCUUGCUUGCCACAAUAUCGG	
AD-1736070	gsgsgua(Cda)AfaGfAfGfggaauaca sasa		VPusUfsuguAfuUfCfccucUfuGfuacccgsga		UCGGGUACAAGAGGGAAUACAAA	
AD-1736071	gsgsuga(Uda)CfaAfAfUfccuguguc susa		VPusAfsgacAfcAfGfgauuUfgAfucaccsusg		CAGGUGAUCAAAUCCUGUGUCUC	
AD-1736072	csasgug(Gda)GfuUfUfCfuaggauag sgsa		VPusCfscuaUfcCfUfagaaAfcCfcacugsusc		GACAGUGGGUUUCUAGGAUAGGU	
AD-1736073	asascua(Ada)GfuAfUfUfuuuaagga scsa		VPusGfsuccUfuAfAfaaauAfcUfuaguusasc		GUAACUAAGUAUUUUUAAGGACA	
AD-1736074	csasuaa(Uda)GfuGfAfUfuguuaaau susa		VPusAfsauuUfaAfCfaaucAfcAfuuaugsgsg		CCCAUAAUGUGAUUGUUAAAUUU	
AD-1736075	gsasgaa(Gda)AfaUfUfUfAfagaaaacu scsa		VPusGfsaguUfuUfCfuuaaUfuCfuucucsasa		UUGAGAAGAAUUAAGAAAACUCU	
AD-1736076	gsasaga(Gda)AfaAfUfUfgauuguuu sasa		VPusUfsaaaCfaAfUfcaauUfuCfucuucsusc		GAGAAGAGAAAUUGAUUGUUUAU	
AD-1736077	asgsugu(Gda)AfaAfCfUfugugccau sasa		VPusUfsaugGfcAfCfaaguUfuCfacacususu		AAAGUGUGAAACUUGUGCCAUAG	
AD-1736078	csusgag(Ada)CfaCfUfGfagaaaugu scsa		VPusGfsacaUfuUfCfucagUfgUfcucagsgsa		UCCUGAGACACUGAGAAAUGUCC	
AD-1736079	usgsgcu(Uda)AfuAfUfGfuguuuaaa sgsa		VPusCfsuuuAfaAfCfacauAfuAfagccasasu		AUUGGCUUAUAUGUGUUUAAAGA	

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1736080	usgscau(Uda)UfuGfAfCfauugcaaa sasa		VPusUfsuuuGfcAfAfugucAfaAfaugcasasu		AUUGCAUUUUGACAUUGCAAAAC	
AD-1736081	ususagg(Uda)UfaGfAfAfguuccaga sasa		VPusUfsucuGfgAfAfcuucUfaAfccuaasusg		CAUUAGGUUAGAAGUUCCAGAAU	
AD-1736082	usgscga(Cda)AfuGfAfAfaacauccu susa		VPusAfsaggAfuGfUfuuucAfuGfucgcasgsc		GCUGCGACAUGAAAACAUCCUUG	
AD-1736083	gsasgag(Gda)AfuUfUfUfuuaccauc susa		VPusAfsgauGfgUfAfaaaaAfuCfcucucsusu		AAGAGAGGAUUUUUUACCAUCUC	
AD-1736084	gsasagg(Uda)GfaAfGfAfgaauuuca sasa		VPusUfsugaAfaUfUfcucuUfcAfccuucscsa		UGGAAGGUGAAGAGAAUUUCAAA	
AD-1736085	usgsgua(Uda)CfuGfAfAfuaucauga sasa		VPusUfsucaUfgAfUfauucAfgAfuaccasgsc		GCUGGUAUCUGAAUAUCAUGAAC	
AD-1736086	usgsuug(Gda)UfuUfAfAfuuuuuca ascsa		VPusGfsuugAfaAfAfauuaAfaCfcaacasusg		CAUGUUGGUUUAAUUUUUCAACC	
AD-1736087	usasguu(Gda)UfaAfUfUfuaaaugug sgsa		VPusCfscacAfuUfUfaaauUfaCfaacuascsu		AGUAGUUGUAAUUUAAAUGUGGA	
AD-1736088	gsusgaa(Uda)GfuUfUfUfugccauuu susa		VPusAfsaaaUfgGfCfaaaaAfcAfuucacsasu		AUGUGAAUGUUUUUGCCAUUUUU	
AD-1736089	csasgag(Ada)UfgAfUfUfuuucuuuu sasa		VPusUfsaaaAfgAfAfaaauCfaUfcucugscsc		GGCAGAGAUGAUUUUUCUUUUAA	
AD-1736090	asgsaaa(Ada)UfuAfGfAfuucagauc susa		VPusAfsgauCfuGfAfaucuAfaUfuuucusgsu		ACAGAAAAUUAGAUUCAGAUCUC	
AD-1736091	ascsugg(Ada)AfaAfUfUfaagaaagu sasa		VPusUfsacuUfuCfUfuaauUfuUfccagusgsg		CCACUGGAAAAUUAAGAAAGUAG	
AD-1736092	usasaag(Uda)GfgGfAfAfagauaaua sasa		VPusUfsuauUfaUfCfuuucCfcAfcuuuascsa		UGUAAAGUGGGAAAGAUAAUAAA	
AD-1736093	csusagg(Cda)UfaAfGfAfaagaguug susa		VPusAfscaaCfuCfUfuucuUfaGfccuagsusu		AACUAGGCUAAGAAAGAGUUGUA	
AD-1736094	gscsuga(Uda)AfaAfAfUfuaauggau sasa		VPusUfsaucCfaUfUfaauuUfuAfucagcsasc		GUGCUGAUAAAAUUAAUGGAUAA	
AD-1736095	cscsugu(Ada)UfuUfCfUfuuaguugu scsa		VPusGfsacaAfcUfAfaagaAfaUfacaggsasa		UUCCUGUAUUUCUUUAGUUGUCG	
AD-1736096	ususugu(Uda)UfuGfCfUfuuugacaa sasa		VPusUfsuugUfcAfAfaagcAfaAfacaaasgsc		GCUUUGUUUUGCUUUUGACAAAC	
AD-1736097	usgsgcu(Gda)UfgAfAfAfauauucuc		VPusGfsgagAfaUfAfuuuuCfaCfagccascsa		UGUGGCUGUGAAAAUAUUCUCCU	

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
	scsa					
AD-1736098	ascsuaau(Uda)UfuAfGfGfcauagcac susa		VPusAfsgugCfuAfUfgccuAfaAfauagusgsc		GCACUAUUUUAGGCAUAGCACUU	
AD-1736099	ususuca(Gda)UfaCfUfGfuauaaagu sgsa		VPusCfsacuUfuAfUfacagUfaCfugaaasasu		AUUUUCAGUACUGUAUAAAGUGG	
AD-1736100	gsusgau(Gda)CfaAfUfCfuauguuuc scsa		VPusGfsgaaAfcAfUfagauUfgCfaucacscsu		AGGUGAUGCAAUCUAUGUUUCCC	
AD-1736101	usgsuuu(Gda)GfcAfGfAfucucauca sasa		VPusUfsugaUfgAfGfaucuGfcCfaaacasusu		AAUGUUUGGCAGAUCUCAUCAAU	
AD-1736102	asasggu(Uda)GfuUfUfGfugaccaga sasa		VPusUfsucuGfgUfCfacaaAfcAfaccuususc		GAAAGGUUGUUUGUGACCAGAAG	
AD-1736103	gsgsaag(Gda)AfaAfUfAfuuuugaga sasa		VPusUfsucuCfaAfAfauauUfuCfcuuccsusu		AAGGAAGGAAAUAUUUUGAGAAU	
AD-1736104	ususuug(Gda)UfaGfCfCfGfugacucuu scsa		VPusGfsaagAfgUfCfacgcUfaCfcaaaasgsa		UCUUUUGGUAGCGUGACUCUUCU	
AD-1736105	usgsaac(Ada)GfgAfAfAfagauguaa sasa		VPusUfsuuaCfaUfCfuuuuCfcUfguucasusu		AAUGAACAGGAAAAGAUGUAAAA	
AD-1736106	gsgsgaa(Cda)CfaAfGfAfgguauaug sgsa		VPusCfscauAfuAfCfcucuUfgGfuucccsasc		GUGGGAACCAAGAGGUAUAUGGC	
AD-1736107	usgsgca(Cda)UfaGfGfUfccaaaucu susa		VPusAfsagaUfuUfGfgaccUfaGfugccasgsu		ACUGGCACUAGGUCCAAAUCUUG	
AD-1736108	csascac(Cda)UfuCfAfUfauggagau susa		VPusAfsaucUfcCfAfuaugAfaGfgugugscsc		GGCACACCUUCAUAUGGAGAUUG	
AD-1736109	csusggu(Uda)UfaCfUfGfggaaauag scsa		VPusGfscuaUfuUfCfccagUfaAfaccagsasc		GUCUGGUUUACUGGGAAAUAGCC	
AD-1736110	gscscca(Ada)AfgGfAfAfuguauauua sasa		VPusUfsuauAfuAfCfauucCfuUfugggcscsu		AGGCCCAAAGGAAUGUAUAUAAG	
AD-1736111	ususaac(Uda)GfcAfAfGfaguuuacu sgsa		VPusCfsaguAfaAfCfucuuGfcAfguuaasasa		UUUUAACUGCAAGAGUUUACUGU	
AD-1736112	gsasacc(Ada)CfuCfUfCfugagugca sasa		VPusUfsugcAfcUfCfagagAfgUfgguucscsu		AGGAACCACUCUCUGAGUGCAAU	
AD-1736113	ususauc(Uda)UfuUfCfAfuccuggca susa		VPusAfsugcCfaGfGfaugaAfaAfgauaasasg		CUUUAUCUUUUCAUCCUGGCAUU	
AD-1736114	gsusgag(Uda)GfuUfGfGfuaugccaa scsa		VPusGfsuugGfcAfUfaccaAfcAfcucacsgsc		GCGUGAGUGUUGGUAUGCCAACG	

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1736115	asgsaau(Gda)UfaUfUfUfggcuaaau sasa		VPusUfsauuUfaGfCfcaaaUfaCfauucuscsa		UGAGAAUGUAUUUGGCUAAAUAA	
AD-1736116	gsasacc(Cda)UfuUfUfAfuuaagagg sasa		VPusUfsccuCfuUfAfauaaAfaGfgguucscsa		UGGAACCCUUUUAUUAAGAGGAG	
AD-1736117	csusccu(Gda)UfcCfAfUfagcugcga susa		VPusAfsucgCfaGfCfuaugGfaCfaggagsgsc		GCCUCCUGUCCAUAGCUGCGAUG	
AD-1736118	ascsuga(Gda)UfuGfAfAfauaaggaa sgsa		VPusCfsuucCfuUfAfuuucAfaCfucagusasa		UUACUGAGUUGAAAUAAGGAAGG	
AD-1736119	csusgcc(Ada)AfaCfAfGfaaggagca susa		VPusAfsugcUfcCfUfucugUfuUfggcagsgsu		ACCUGCCAAACAGAAGGAGCAUG	
AD-1736120	gsgscaa(Ada)GfuUfGfUfgaagcacu scsa		VPusGfsaguGfcUfUfcacaAfcUfuugccsasc		GUGGCAAAGUUGUGAAGCACUCC	
AD-1736121	asusagg(Ada)UfgAfUfGfaaguuuag sasa		VPusUfscuaAfaCfUfucauCfaUfccuaususu		AAAUAGGAUGAUGAAGUUUAGAG	
AD-1736122	asusucg(Uda)AfuCfUfUfaaaauggc sasa		VPusUfsgccAfuUfUfuaagAfuAfcgaausasc		GUAUUCGUAUCUUAAAAUGGCAC	
AD-1736123	csascag(Cda)UfuGfGfGfuaauagcg susa		VPusAfscgcUfaUfUfacccAfaGfcugugscsu		AGCACAGCUUGGGUAAUAGCGUU	
AD-1736124	ususugc(Ada)AfcAfAfCfauaacacu sgsa		VPusCfsaguGfuUfAfuguuGfuUfgcaaasasa		UUUUUGCAACAACAUAACACUGC	
AD-1736125	usgscca(Cda)CfaUfGfUfgacuuauu sgsa		VPusCfsaauAfaGfUfcacaUfgGfuggcasasa		UUUGCCACCAUGUGACUUAUUGG	
AD-1736126	uscsgau(Ada)GfaGfGfAfaaugagaa sasa		VPusUfsuucUfcAfUfuuccUfcUfaucgasgsg		CCUCGAUAGAGGAAAUGAGAAAG	
AD-1736127	ususuuu(Ada)AfgUfUfAfgcaggacu susa		VPusAfsaguCfcUfGfcuaaCfuUfaaaaasgsg		CCUUUUUAAGUUAGCAGGACUUU	
AD-1736128	usgsuaa(Ada)UfaAfUfUfaucugccu sasa		VPusUfsaggCfaGfAfuaauUfaUfuuacasusc		GAUGUAAAUAAUUAUCUGCCUAA	
AD-1736129	usgsguu(Gda)UfaCfGfUfgccucaaa susa		VPusAfsuuuGfaGfGfcacgUfaCfaaccasusa		UAUGGUUGUACGUGCCUCAAAUA	

Table 6. Unmodified Sense and Antisense Strand Sequences of ACVR1C dsRNA Agents Comprising a GalNAc Derivative Targeting Ligand

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3
AD-1736131	UUUUUUCAAACUCCAUUCCUA		3085-3105	UAGGAAUGGAGUUUGAAAAAAGA		3083-3105
AD-1736132	ACUUUCAUCUGUCUUCAGAUA		8677-8697	UAUCUGAAGACAGAUGAAAGUUA		8675-8697
AD-1736133	CCUCAUAACUUUCUCCAGUAAA		6745-6765	UUUACUGGAGAAGUUAUGAGGUG		6743-6765
AD-1736134	CUCACUAUCUUUCAACAUUAA		5871-5891	UUAAUGUUGAAAGAUAGUGAGGG		5869-5891
AD-1736135	CUCGUUAAUGCUCUCAUCCAA		3562-3582	UUGGAUGAGAGCAUUAACGAGUA		3560-3582
AD-1736136	GUUCUUCAUAAUCCACUACUA		2292-2312	UAGUAGUGGAUUAUGAAGAACAG		2290-2312
AD-1736137	GUUGACUUCAUCCAAUCUCUA		1876-1896	UAGAGAUUGGAUGAAGUCAACUC		1874-1896
AD-1736138	CUACACAAUGAACUUCUUAAA		6692-6712	UUUAAGAAGUUCAUUGUGUAGAA		6690-6712
AD-1736139	CACAUCUAGAAUUCUUAAUUA		4835-4855	UAAUUAAGAAUUCUAGAUGUGAC		4833-4855
AD-1736140	AAAUCUCUCAUAGCUUUCUUA		1725-1745	UAAGAAAGCUAUGAGAGAUUUCU		1723-1745
AD-1736141	CCUACUAUUGUAGAAUUACUA		5093-5113	UAGUAAUUCUACAAUAGUAGGUG		5091-5113
AD-1736142	AUCUUCUUUUAGUGCAUUAAA		6589-6609	UUUAAUGCACUAAAAGAAGAUGA		6587-6609
AD-1736143	CUCAUGUACUCUUCUGAUUCA		7977-7997	UGAAUCAGAAGAGUACAUGAGCU		7975-7997
AD-1736144	UUUCUCUUUGUACCUUGGAAA		6449-6469	UUUCCAAGGUACAAAGAGAAAGA		6447-6469
AD-1736145	UGGCUUAUACAUCUUCAGAAA		7515-7535	UUUCUGAAGAUGUAUAAGCCAGA		7513-7535
AD-1736146	CAAAACAAAACUACUCCUAUA		5120-5140	UAUAGGAGUAGUUUUGUUUUGUU		5118-5140
AD-1736147	ACUAGCAGAACUCUUAUGAAA		6055-6075	UUUCAUAAGAGUUCUGCUAGUAA		6053-6075
AD-1736148	CCAAGUCACUCUAUAAUUCCA		6635-6655	UGGAAUUAUAGAGUGACUUGGGA		6633-6655
AD-1736149	UCCAUUUUUCUUGUCAUUAUA		4114-4134	UAUAAUGACAAGAAAAAUGGAGA		4112-4134
AD-1736150	CAACACCUCAACUCAUCUUUA		1923-1943	UAAAGAUGAGUUGAGGUGUUGCU		1921-1943
AD-1736151	ACUCUGAAAGAUCUGAUUUAA		716-736	UUAAAUCAGAUCUUUCAGAGUUU		714-736
AD-1736152	CUAGUUCUUUUUCCGCAAUGAA		7946-7966	UUCAUUGCGGAAAAGAACUAGAA		7944-7966
AD-1736153	CUUUCACUCUGAAGAAAUCCA		4189-4209	UGGAUUUCUUCAGAGUGAAAGUU		4187-4209
AD-1736154	UCUAACUUUUCUCUCUUUCUA		6525-6545	UAGAAAGAGAGAAAAGUUAGAUA		6523-6545
AD-1736155	UCUCAACUUUGUGUCAAAGAA		1667-1687	UUCUUUGACACAAAGUUGAGAUA		1665-1687
AD-1736156	CUUCAAUAAUCAUUCCUUUAA		5445-5465	UUAAAGGAAUGAUUAUUGAAGAC		5443-5465

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3
AD-1736157	UAACUGCUCUUCGUAUUAAGA		1638-1658	UCUUAAUACGAAGAGCAGUUAGG		1636-1658
AD-1736158	UCUUCUGUCAUAGUUCCAACA		438-458	UGUUGGAACUAUGACAGAAGACU		436-458
AD-1736159	AUCUCAGAACCAUAUCUGUUA		2584-2604	UAACAGAUAUGGUUCUGAGAUUU		2582-2604
AD-1736160	UGAAUCUAUCUUCAUUUUACA		3483-3503	UGUAAAAUGAAGAUAGAUUCAGU		3481-3503
AD-1736161	ACCACUAAACUUGUUCCUUUA		2326-2346	UAAAGGAACAAGUUUAGUGGUUC		2324-2346
AD-1736162	AGUGUUCUUUACUCCUUACAA		4578-4598	UUGUAAGGAGUAAAGAACACUGA		4576-4598
AD-1736163	CUUUACUCUUAACAGGAUUAA		4367-4387	UUAAUCCUGUUAAGAGUAAAGGA		4365-4387
AD-1736164	UAUACCUAAGAACAUAUUACA		8153-8173	UGUAAUAUGUUCUUAGGUAUAAG		8151-8173
AD-1736165	CUUCUACUGAGAUGAUCCAAA		3114-3134	UUUGGAUCAUCUCAGUAGAAGAA		3112-3134
AD-1736166	CUGUAUUUUCUCAUAGAGUAA		3420-3440	UUACUCUAUGAGAAAAUACAGAA		3418-3440
AD-1736167	ACUUUUCUCUUUUCAGUUGUAA		7116-7136	UUACAACUGAAAGAGAAAAGUAU		7114-7136
AD-1736168	AUUAAUUUCUAGUCUGUGAAA		8493-8513	UUUCACAGACUAGAAAUUAAUGA		8491-8513
AD-1736169	CUCUGUAUAAGAGGUUUCACA		6726-6746	UGUGAAACCUCUUAUACAGAGAA		6724-6746
AD-1736170	GACUUUCAAAGUACUAAUACA		8098-8118	UGUAUUAGUACUUUGAAAGUCAA		8096-8118
AD-1736171	UUUGCCAUUAUACAAAGUUUA		5262-5282	UAAACUUUGUAUAAUGGCAAACA		5260-5282
AD-1736172	GAACACUAUCGACAUACCUCA		1276-1296	UGAGGUAUGUCGAUAGUGUUCAG		1274-1296
AD-1736173	UAGAAUGACAUUUUACUAAUAA		7818-7838	UUAUUAGUAAAUGUCAUUCUACG		7816-7838
AD-1736174	AAGCUACUUAGAAAUGUUUAA		5491-5511	UUAAACAUUUCUAAGUAGCUUGU		5489-5511
AD-1736175	CCUUAGUACUCUCAGAGAUUA		5968-5988	UAAUCUCUGAGAGUACUAAGGGA		5966-5988
AD-1736176	UGAAUGCACACUAACGUAAUA		6163-6183	UAUUACGUUAGUGUGCAUUCAAG		6161-6183
AD-1736177	AAGCCUAAUGAUGAUAAUUAA		1695-1715	UUAAUUAUCAUCAUUAGGCUUUG		1693-1715
AD-1736178	AAACUUUUUACUAUCCCAUAA		3341-3361	UUAUGGGAUAGUAAAAAGUUUCC		3339-3361
AD-1736179	CUAGCUGAUACUCUUAAGUAA		8268-8288	UUACUUAAGAGUAUCAGCUAGCU		8266-8288
AD-1736180	AGCAUGAAAAGAUAACUCUAA		1837-1857	UUAGAGUUAUCUUUUCAUGCUGC		1835-1857
AD-1736181	UAAGCCAUUAUGCUAUUAGUA		7017-7037	UACUAAUAGCAUAAUGGCUUAGU		7015-7037
AD-1736182	UCUAGCUUUUAGCUAACAUAA		6850-6870	UUAUGUUAGCUAAAAGCUAGAAU		6848-6870

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3
AD-1736183	GUGUGAUUCUUCAAACUUCAA		316-336	UUGAAGUUUGAAGAAUCACACAA		314-336
AD-1736184	UCUCCAGACCUAACAGUUUUA		7247-7267	UAAAACUGUUAGGUCUGGAGAGA		7245-7267
AD-1736185	CUUUUUUUCAUCUAGCCUUGA		5808-5828	UCAAGGCUAGAUGAAAAAAAAGAA		5806-5828
AD-1736186	CAAAAUAAUUCUUGACAUCUA		7552-7572	UAGAUGUCAAGAAUUAUUUUGAC		7550-7572
AD-1736187	GCAUCACUUUUCUGAAAAUAAA		4690-4710	UUUAUUUUCAGAAAGUGAUGCUG		4688-4710
AD-1736188	UCUUUUGUGAAACAUACUAUA		5563-5583	UAUAGUAUGUUUCACAAAAGAUG		5561-5583
AD-1736189	CUAUUUCUUCCAUAGGCUAAA		7841-7861	UUUAGCCUAUGGAAGAAAUAGAA		7839-7861
AD-1736190	CUUCAAUGAAGUGUUAACAAA		2839-2859	UUUGUUAACACUUCAUUGAAGAG		2837-2859
AD-1736191	UUUGCCUUCAUUCUACUUUCA		2952-2972	UGAAAGUAGAAUGAAGGCAAAAC		2950-2972
AD-1736192	AGGUUUUUAAAUGUCCUAAAA		8035-8055	UUUUAGGACAUUUAAAAACCUGA		8033-8055
AD-1736193	GAAUAUCUUUGAGUCCUUCAA		1360-1380	UUGAAGGACUCAAAGAUAUUCAC		1358-1380
AD-1736194	GAACACUUCCAAAGAUUAAUA		2666-2686	UAUUAAUCUUUGGAAGUGUUCAG		2664-2686
AD-1736195	CUAAAUUUUGUCUAACAAAUA		7791-7811	UAUUUGUUAGACAAAAUUUAGGC		7789-7811
AD-1736196	GUAAACAACUUAAAAAUUGCUA		5284-5304	UAGCAAUUUUAAGUUGUUUACUC		5282-5304
AD-1736197	AAAAUAAUUUACUCACUCAGA		6233-6253	UCUGAGUGAGUAAAUUAUUUUAG		6231-6253
AD-1736198	GACAUCUAUUCUGUUGGUCUA		1388-1408	UAGACCAACAGAAUAGAUGUCAG		1386-1408
AD-1736199	UAACUGAGUAGUCUUAUAUUA		4267-4287	UAAUAUAAGACUACUCAGUUAGG		4265-4287
AD-1736200	UCUGGAAUUUAGCCUUCUAAA		5936-5956	UUUAGAAGGCUAAAUUCCAGACG		5934-5956
AD-1736201	ACAUGCCUUGAACUCUUGAAA		8207-8227	UUUCAAGAGUUCAAGGCAUGUUU		8205-8227
AD-1736202	AUCAAGCACUUCUUGCACUUA		8782-8802	UAAGUGCAAGAAGUGCUUGAUUU		8780-8802
AD-1736203	CUUGCUUUUCAUCUUUAUACA		4915-4935	UGUAUAAAGAUGAAAAGCAAGUG		4913-4935
AD-1736204	UUUUCUCCCUAUGUAAUAUCA		2493-2513	UGAUAUUACAUAGGGAGAAAAGC		2491-2513
AD-1736205	UGCUUUCUUCUAUGUCUAAAA		4802-4822	UUUUAGACAUAGAAGAAAGCAUA		4800-4822
AD-1736206	ACCUGCUUAGCAAAUCGUCUA		5224-5244	UAGACGAUUUGCUAAGCAGGUUC		5222-5244
AD-1736207	AUAUUCCUCUACCCUUUCACA		2895-2915	UGUGAAAGGGUAGAGGAAUAUCU		2893-2915
AD-1736208	UCCCACUUUUCUUUGGGUUUA		6208-6228	UAAACCCAAAGAAAAGUGGGAUU		6206-6228

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3
AD-1736209	AGGCUUCUUGUAUAUACUUAA		4442-4462	UUAAGUAUAUACAAGAAGCCUGC		4440-4462
AD-1736210	AAACUUGAUCUGUGUUUCAGA		8017-8037	UCUGAAACACAGAUCAAGUUUGA		8015-8037
AD-1736211	UUUGCUUUAAUGCUAAAUUCA		6885-6905	UGAAUUUAGCAUUAAAGCAAAAG		6883-6905
AD-1736212	AGACUAGCUGUUAUUUGUAUA		6830-6850	UAUACAAAUAACAGCUAGUCUUU		6828-6850
AD-1736213	UUCCUACUUUCCCUUGAAUAA		2469-2489	UUAUUCAAGGGAAAGUAGGAAGC		2467-2489
AD-1736214	CAGAACUGAAUGCUCAAGUCA		420-440	UGACUUGAGCAUUCAGUUCUGGA		418-440
AD-1736215	UCUUGUUACUAAUUUCUCAUA		3945-3965	UAUGAGAAAUUAGUAACAAGAAC		3943-3965
AD-1736216	CUCAGUGAUAGCCUUUAUACA		8586-8606	UGUAUAAAGGCUAUCACUGAGUU		8584-8606
AD-1736217	UUUUAUGCUCCUAAAACAUCA		3065-3085	UGAUGUUUUAGGAGCAUAAAAGA		3063-3085
AD-1736218	UUCUCCUUAGGUUAUGUUCAA		4551-4571	UUGAACAUAACCUAAGGAGAAUU		4549-4571
AD-1736219	AUUGCUCAUCGAGACAUAAAA		1175-1195	UUUUAUGUCUCGAUGAGCAAUAG		1173-1195
AD-1736220	CCUUUGUACAUACACACUUAA		2746-2766	UUAAGUGUGUAUGUACAAAGGAA		2744-2766
AD-1736221	UUGAACCAAGAGCACACAUGAAA		2025-2045	UUUCAUGUGCUCUUGGUUCAAGU		2023-2045
AD-1736222	UCAGGGAUUUUAAAGUCUAAA		3668-3688	UUUAGACUUUAAAAUCCCUGAGG		3666-3688
AD-1736223	UACUUGCUUAUAAAGUGAUAA		3153-3173	UUAUCACUUUAUAAGCAAGUACC		3151-3173
AD-1736224	AUGCAUCUAAACCUACCUUGA		6145-6165	UCAAGGUAGGUUUAGAUGCAUGC		6143-6165
AD-1736225	UUGGGAAAACACUAUUAUGAA		4629-4649	UUCAUAAUAGUGUUUUCCCAAGU		4627-4649
AD-1736226	AAACUCCAAAGAGAAAUGAAA		8456-8476	UUUCAUUUCUCUUUGGAGUUUGA		8454-8476
AD-1736227	AUGGGCAUUUUUUCAAAACAUA		5758-5778	UAUGUUUUUGAAAAAUGCCCAUAU		5756-5778
AD-1736228	AUAAUGGAACUUUGGACUCAAA		996-1016	UUUGAGUCCAAGUUCCAUUAUCU		994-1016
AD-1736229	UGUGUAGAUGACGAAACCAAA		6008-6028	UUUGGUUUUCGUCAUCUACACAAA		6006-6028
AD-1736230	UUCUACCUCAAAGAUAAGACA		1790-1810	UGUCUUAUCUUUGAGGUAGAACA		1788-1810
AD-1736231	AGAAGGCAUAUUGAGUUAUUA		2536-2556	UAAUAACUCAAUAUGCCUUCUAA		2534-2556
AD-1736232	AUGGAGUUUUUCUGCUAUUUA		5629-5649	UAAAUAGCAGAAAAACUCCAUGU		5627-5649
AD-1736233	UCAGUUUCUCAUUAGUUUGUA		6558-6578	UACAAACUAAUGAGAAACUGAGG		6556-6578
AD-1736234	CUGCAUAUAUAAGAACGAAAA		3976-3996	UUUUCGUUCUUAUAUAUGCAGAA		3974-3996

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3
AD-1736235	UGAGCCAAAAAUAUUAAAAUUCA		7927-7947	UGAAUUUAAUAUUUUGGCUCAGA		7925-7947
AD-1736236	AGAAUGAUAUUUUCCUGUUUUA		4035-4055	UAAAACAGGAAAUAUCAUUCUUG		4033-4055
AD-1736237	GUGCUCUAUAUAAAAUCUUCCA		7385-7405	UGGAAGAUUUAUAUAGAGCACAA		7383-7405
AD-1736238	UUUACAGAGAAGCAUCUUAUA		7468-7488	UAUAAGAUGCUUCUCUGUAAAAU		7466-7488
AD-1736239	GUCUUGAGUUCUGCAUGACAA		3761-3781	UUGUCAUGCAGAACUCAAGACAU		3759-3781
AD-1736240	CUUCAAAUCUAUAAUUUUACA		3017-3037	UGUAAAAUUAUAGAUUUGAAGGG		3015-3037
AD-1736241	GAAGCAUAUAGAACUCUAUUA		8810-8830	UAAUAGAGUUCUAUAUGCUUCAC		8808-8830
AD-1736242	GAGCUGCUUCUAAAUAACAAA		5678-5698	UUUGUUAUUUAGAAGCAGCUCUC		5676-5698
AD-1736243	UGACUGUAUUUCCUGAUCAUA		7197-7217	UAUGAUCAGGAAAUACAGUCACA		7195-7217
AD-1736244	GUUCUGAAGGAUAUACUUCUA		3402-3422	UAGAAGUAUAUCCUUCAGAACGC		3400-3422
AD-1736245	GUGAAGCAUGAUUCAAUACUA		1256-1276	UAGUAUUGAAUCAUGCUUCACAG		1254-1276
AD-1736246	AAUGCUGCUUCACAGAUUUUA		474-494	UAAAAUCUGUGAAGCAGCAUUCG		472-494
AD-1736247	UGUGGGUUAUGUUAAUCUGAA		7283-7303	UUCAGAUUAACAUAACCCACAGU		7281-7303
AD-1736248	GAGUACAGAAGAAUGCUCAUA		2926-2946	UAUGAGCAUUCUUCUGUACUCAC		2924-2946
AD-1736249	CUGUAUUUCAUCCUAGAUUUA		7162-7182	UAAAUCUAGGAUGAAAUACAGCU		7160-7182
AD-1736250	AAUCUGGUAAAAUGCUGGAAAA		695-715	UUUUCCAGCAUUUACCAGAUUGC		693-715
AD-1736251	UGCUCAGAUUACCUGAUCGUA		3293-3313	UACGAUCAGGUAAUCUGAGCAAU		3291-3313
AD-1736252	GACAGCUAUGGAGUUUGCGUA		3531-3551	UACGCAAACUCCAUAGCUGUCAG		3529-3551
AD-1736253	UAGAACAUGCUCACUUACAAA		4391-4411	UUUGUAAGUGAGCAUGUUCUAUA		4389-4411
AD-1736254	AUUAUGCUUCAUUUCACUAUA		3450-3470	UAUAGUGAAAUGAAGCAUAAUCA		3448-3470
AD-1736255	CAACAGCAAGUCAUAAAAGUA		8624-8644	UACUUUUAUGACUUGCUGUUGGU		8622-8644
AD-1736256	UUGUCUGAAAAAUGUCUUUAAA		2702-2722	UUUAAAGACAUUUUCAGACAAUG		2700-2722
AD-1736257	UGUUGGUUCAAAGGACAAUUA		774-794	UAAUUGUCCUUUGAACCAACAGA		772-794
AD-1736258	UCUAAACUUUAAUAUAUCGAA		2190-2210	UUCGAUAUAUUAAAGUUUAGAGC		2188-2210
AD-1736259	AAGUGAAACAUGACUGUCGUA		4875-4895	UACGACAGUCAUGUUUCACUUAA		4873-4895
AD-1736260	AUCGUCCAUACAGUUUUCAUA		7719-7739	UAUGAAAACUGUAUGGACGAUAU		7717-7739

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3
AD-1736261	CUUCAGGAAAUAGUAGGAAAA		809-829	UUUUCCUACUAUUUCCUGAAGCA		807-829
AD-1736262	CACCCUUUCUGUAAGGACUGA		6426-6446	UCAGUCCUUACAGAAAGGGUGGG		6424-6446
AD-1736263	AAAGAGAUACCUGACAUCCUA		2354-2374	UAGGAUGUCAGGUAUCUCUUUUG		2352-2374
AD-1736264	AUGAGCAUUAAUGUUUUCUGA		2647-2667	UCAGAAAACAUUAAUGCUCAUUA		2645-2667
AD-1736265	UGACAUUUUUUUCUCAUAGAAA		2603-2623	UUUCUAUGAGAAAAAAAUGUCAAC		2601-2623
AD-1736266	CAGAGAUUAAAUGACUACUAA		6032-6052	UUAGUAGUCAUUUAAUCUCUGAU		6030-6052
AD-1736267	GCUGUCAAAUGUUAUAUUGUA		4463-4483	UACAAUAUAACAUUUGACAGCAU		4461-4483
AD-1736268	AAUAUAAUACUACAGCAAAAA		7041-7061	UUUUUGCUGUAGUAUUAUAUUCC		7039-7061
AD-1736269	GGUGUCUAAAUAUAAUUUCAA		4153-4173	UUGAAAUUAUAUUUAGACACCCU		4151-4173
AD-1736270	CUCUUUAUACAAAAUGAGAGA		7903-7923	UCUCUCAUUUUGUAUAAAGAGAA		7901-7923
AD-1736271	GCAGUACCAAAUGAAUAAAAA		5410-5430	UUUUUAUUCAUUUGGUACUGCUA		5408-5430
AD-1736272	UUGUUGGUACACAAGGUAAAA		1149-1169	UUUUACCUUGUGUACCAACAAUC		1147-1169
AD-1736273	CUCUUAUUUAACUUAACCGUA		5917-5937	UACGGUUAAGUUAAAUAAGAGUU		5915-5937
AD-1736274	UGCUUGAUGAUACAAUGAAUA		1338-1358	UAUUCAUUGUAUCAUCAAGCAUU		1336-1358
AD-1736275	AACUGGGAAAGACAAUUUGAA		6920-6940	UUCAAAUUGUCUUUCCCAGUUAC		6918-6940
AD-1736276	CUCCUUAUAUGACUAUUUUGAA		1048-1068	UUCAAAUAGUCAUAUAAGGAGCC		1046-1068
AD-1736277	AGUCAUGCUAACCAAUGGAAA		367-387	UUUCCAUUGGUUAGCAUGACUGA		365-387
AD-1736278	CCUGAAGUCACACAGCUAAUA		2391-2411	UAUUAGCUGUGUGUGACUUCAGGAC		2389-2411
AD-1736279	UUGCUGCUGACAACAAAGAUA		978-998	UAUCUUUGUUGUCAGCAGCAAUG		976-998
AD-1736280	UACUGACUUUUGCCUGUAAAGA		7757-7777	UCUUUACAGGCAAAGUCAGUAAU		7755-7777
AD-1736281	AAUCCCUAUUUUUAAAAUUCCA		7070-7090	UGGAAUUUUUAAAAUAGGGAUUGU		7068-7090
AD-1736282	GUGCCUUAGGAGAUUACCCUA		7330-7350	UAGGGUAAUCUCCUAAGGCACUC		7328-7350
AD-1736283	GACAAUCUAAAUAUAUCAUCA		3857-3877	UGAUGAUAUAUUUAGAUUGUCUG		3855-3877
AD-1736284	UGUGAUAAUGAACACCGUAAA		2438-2458	UUUACGGUGUUCAUUAUCACAAG		2436-2458
AD-1736285	UCACCGUUGUAAAGACUUUUA		8242-8262	UAAAAGUCUUUACAACGGUGAUU		8240-8262
AD-1736286	UUAGAGAAGCUUCCUGACAUA		6402-6422	UAUGUCAGGAAGCUUCUCUAAUC		6400-6422

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3
AD-1736287	AACAGUAAAGAAAUGCUACUA		3252-3272	UAGUAGCAUUUCUUUACUGUUAU		3250-3272
AD-1736288	UAUGUUCUGACUUGAGAGUUA		4855-4875	UAACUCUCAAGUCAGAACAUAAA		4853-4875
AD-1736289	UUAGAGCAUGCUAUCUUUAGA		2109-2129	UCUAAAGAUAGCAUGCUCUAAUU		2107-2129
AD-1736290	UAGUCUUUGAUUGAAAUAAGA		5314-5334	UCUUAUUUCAAUCAAAGACUAUG		5312-5334
AD-1736291	UUGGUAAACGAGAUUUAACAA		3038-3058	UUGUUAAAUCUCGUUUACCAAAG		3036-3058
AD-1736292	GUCUGAAAAUUGCUUUCAUUA		3798-3818	UAAUGAAAGCAAUUUUCAGACCU		3796-3818
AD-1736293	AUGAACUUGUUGCCUUGUAAA		4741-4761	UUUACAAGGCAACAAGUUCAUGC		4739-4761
AD-1736294	GGGCAAUAAACUGUAUCAAAA		8379-8399	UUUUGAUACAGUUUAUUGCCCAA		8377-8399
AD-1736295	ACAUGUUAGCAUAUAAUGUAA		3175-3195	UUACAUUAUAUGCUAACAUGUAC		3173-3195
AD-1736296	UGUGAGAGUAUAGAAUUUCUA		6367-6387	UAGAAAUUCUAUACUCUCACAGU		6365-6387
AD-1736297	AUCCUUCAUUUGGCACUAUAA		6764-6784	UUAUAGUGCCAAAUGAAGGAUUA		6762-6784
AD-1736298	ACAUUUAGAAAGUAGCUUUAA		3824-3844	UUAAAGCUACUUUCUAAAUGUGU		3822-3844
AD-1736299	AACUGUUCUAUAAAGCAAAGA		3364-3384	UCUUUGCUUUAUAGAACAGUUAA		3362-3384
AD-1736300	CCUCCAGAGAUGAAAGAUCUA		894-914	UAGAUCUUUCAUCUCUGGAGGAG		892-914
AD-1736301	UUGUUUAACUAUGACUCCUAA		4249-4269	UUAGGAGUCAUAGUUAAACAACA		4247-4269
AD-1736302	CUGUUUGACAAUGCUUUGUUA		5585-5605	UAACAAAGCAUUGUCAAACAGAA		5583-5605
AD-1736303	UGUCCUAAAAGAAAUUUUUCA		7227-7247	UGAAAAAUUUCUUUUAGGACAAC		7225-7247
AD-1736304	ACAGAUUGAACAAAGAACUUA		7572-7592	UAAGUUCUUUGUUCAAUCUGUAG		7570-7592
AD-1736305	GUUUAACCUGUCCAAACUUCA		6673-6693	UGAAGUUUGGACAGGUUAAACGA		6671-6693
AD-1736306	CAAAAUGUUUAACUUUACCAA		8606-8626	UUGGUAAAGUUAAACAUUUUGGU		8604-8626
AD-1736307	UCCCAUUGUGUAAUAUUUAUA		4494-4514	UAUAAAUAUUACACAAUGGGACU		4492-4514
AD-1736308	GUUGGGUAAAUAUGCUUAUUA		4065-4085	UAAUAAGCAUAUUUACCCAACAU		4063-4085
AD-1736309	CAGGGUUGUCUUUGAGUCUGA		5187-5207	UCAGACUCAAAGACAACCCUGAG		5185-5207
AD-1736310	GCUAAAAUCCAACUGCAAUUA		7425-7445	UAAUUGCAGUUGGAUUUUAGCCC		7423-7445
AD-1736311	CAGGACUGAAGUGUGUAUGUA		291-311	UACAUACACACUUCAGUCCUGGC		289-311
AD-1736312	GAGUACCAAUUGCCUUAUUAA		1457-1477	UUAAUAAGGCAAUUGGUACUCCU		1455-1477

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3
AD-1736313	AAGUGCCUAUGUGAAGUGAUA		3886-3906	UAUCACUUCACAUAGGCACUUUU		3884-3906
AD-1736314	UAACAAUAAUAGAACUGCCAA		7092-7112	UUGGCAGUUCUAUUAUUGUUAGG		7090-7112
AD-1736315	GCUGUUCCAUACCAUUGCUUA		6978-6998	UAAGCAAUGGUAUGGAACAGCAG		6976-6998
AD-1736316	UAGACUGGAGAAGAUUAUUCA		7997-8017	UGAAUAAUCUUCUCCAGUCUAGA		7995-8017
AD-1736317	UUCCAACAGCAUCACCAAAUA		516-536	UAUUUGGUGAUGCUGUUGGAAGG		514-536
AD-1736318	UAAUUGGUACAGAUUCUGUUA		4779-4799	UAACAGAAUCUGUACCAAUUACA		4777-4799
AD-1736319	GAGAAACAUUAUUUGUUGUCA		4710-4730	UGACAACAAAUAAUGUUUCUCUU		4708-4730
AD-1736320	CGCUCUCAAUUGCUAGUGGUA		1107-1127	UACCACUAGCAAUUGAGAGCGCC		1105-1127
AD-1736321	CGGUAUCAGAAACAGCAAAUA		2873-2893	UAUUUGCUGUUUCUGAUACCGUC		2871-2893
AD-1736322	CCCAGACAUAAUUUUAUAUUA		7449-7469	UAAUAUAAAAUUAUGUCUGGGAG		7447-7469
AD-1736323	UAGUACAUUUUGAGGUAUUUA		4215-4235	UAAAUACCUCAAAAUGUACUAAC		4213-4235
AD-1736324	AAAUGCUAUUGAUAACAGUAA		3211-3231	UUACUGUUAUCAAUAGCAUUUAC		3209-3231
AD-1736325	UAGCUGAAUUUGGGACUAUGA		6490-6510	UCAUAGUCCCAAAUUCAGCUAUC		6488-6510
AD-1736326	AUUGUGGUUUUCAAAGAUAUA		5535-5555	UAUAUCUUUGAAAACCACACAAUGG		5533-5555
AD-1736327	CCUGGUUGCAGUAUCUGAAAA		4985-5005	UUUUCAGAUACUGCAACCAGGUU		4983-5005
AD-1736328	UAGAAUGGUUGUUGAGCUAAA		6297-6317	UUUAGCUCAACAACCAUUCUACA		6295-6317
AD-1736329	CUGGCCAUCAUUAUUACUGUA		560-580	UACAGUAAUAAUGAUGGCCAGCU		558-580
AD-1736330	UUGACAGAUAAAAAUACGAAGA		3735-3755	UCUUCGUAUUUUAUCUGUCAAUU		3733-3755
AD-1736331	UCACAAACACAUCAUUACAAA		5473-5493	UUUGUAAUGAUGUGUUUGUGAAU		5471-5493
AD-1736332	CCAUGAUUGUAUGAAAAUAGA		4962-4982	UCUAUUUUCAUACAAUCAUGGAA		4960-4982
AD-1736333	CACAGAGUAAUGAAUAUUUAA		2978-2998	UUAAAUAUUCAUUACUCUGUGUC		2976-2998
AD-1736334	AGCUGCUUAGUGGAAGAUGUA		2222-2242	UACAUCUUCCACUAAGCAGCUCC		2220-2242
AD-1736335	UAGCUCUGUGUGCUGAUACCA		5606-5626	UGGUAUCAGCACACAGAGCUAGA		5604-5626
AD-1736336	CAUUCGAGAGAAUAUGAGCUA		7144-7164	UAGCUCAUAUUCUCUCGAAUGUA		7142-7164
AD-1736337	AUGCAUUUUCUGAAAAUGUAA		8734-8754	UUACAUUUUCAGAAAAUGCAUAC		8732-8754
AD-1736338	GUUUCGACCAAGUAUCCCAAA		1537-1557	UUUGGGAUACUUGGUCGAAACUU		1535-1557

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3
AD-1736339	UCUUGCUUGCCACAAUAUCGA		3610-3630	UCGAUAUUGUGGCAAGCAAGAUA		3608-3630
AD-1736340	GGGUACAAGAGGGAAUACAAA		3629-3649	UUUGUAUUCCCUCUUGUACCCGA		3627-3649
AD-1736341	GGUGAUCAAAUCCUGUGUCUA		394-414	UAGACACAGGAUUUGAUCACCUG		392-414
AD-1736342	CAGUGGGUUUCUAGGAUAGGA		3779-3799	UCCUAUCCUAGAAACCCACUGUC		3777-3799
AD-1736343	AACUAAGUAUUUUUUAAGGACA		7869-7889	UGUCCUUAAAAAUACUUAGUUAC		7867-7889
AD-1736344	CAUAAUGUGAUUGUUAAAUUA		6951-6971	UAAUUUAACAAUCACAUUAUGGG		6949-6971
AD-1736345	GAGAAGAAUUAAGAAAACUCA		2820-2840	UGAGUUUUCUUAAUUCUUCUCAA		2818-2840
AD-1736346	GAAGAGAAAUUGAUUGUUUAA		7635-7655	UUAAACAAUCAAUUUCUCUUCUC		7633-7655
AD-1736347	AGUGUGAAACUUGUGCCAUAA		1218-1238	UUAUGGCACAAGUUUCACACUUU		1216-1238
AD-1736348	CUGAGACACUGAGAAAUGUCA		2372-2392	UGACAUUUCUCAGUGUCUCAGGA		2370-2392
AD-1736349	UGGCUUAUAUGUGUUUAAAGA		7488-7508	UCUUUAAACACAUAUAAGCCAAU		7486-7508
AD-1736350	UGCAUUUUGACAUUGCAAAAA		8188-8208	UUUUUGCAAUGUCAAAAUGCAAU		8186-8208
AD-1736351	UUAGGUUAGAAGUUCCAGAAA		5053-5073	UUUCUGGAACUUCUAACCUAAUG		5051-5073
AD-1736352	UGCGACAUGAAAACAUCCUUA		951-971	UAAGGAUGUUUUCAUGUCGCAGC		949-971
AD-1736353	GAGAGGAUUUUUUACCAUCUA		4095-4115	UAGAUGGUAAAAAAAUCCUCUCUU		4093-4115
AD-1736354	GAAGGUGAAGAGAAUUUUCAAA		8438-8458	UUUGAAAUUCUCUUCACCUUCCA		8436-8458
AD-1736355	UGGUAUCUGAAUAUCAUGAAA		1023-1043	UUUCAUGAUAUUCAGAUACCAGC		1021-1043
AD-1736356	UGUUGGUUUAAUUUUUUCAACA		7658-7678	UGUUGAAAAAAUUAAACCAACAUG		7656-7678
AD-1736357	UAGUUGUAAUUUAAAUGUGGA		8419-8439	UCCACAUUUAAAUUACAACUACU		8417-8439
AD-1736358	GUGAAUGUUUUUUGCCAUUUUA		1763-1783	UAAAAUGGCAAAAACAUUCACAU		1761-1783
AD-1736359	CAGAGAUGAUUUUUUCUUUUAA		6800-6820	UUAAAAGAAAAAUCAUCUCUGCC		6798-6820
AD-1736360	AGAAAAUUAGAUUCAGAUCUA		8058-8078	UAGAUCUGAAUCUAAUUUUUCUGU		8056-8078
AD-1736361	ACUGGAAAAUUAAGAAAGUAA		5390-5410	UUACUUUCUUAAUUUUUCCAGUGG		5388-5410
AD-1736362	UAAAGUGGGAAAGAUAAUAAA		8762-8782	UUUAUUAUCUUUUCCCACUUUACA		8760-8782
AD-1736363	CUAGGCUAAGAAAGAGUUGUA		6278-6298	UACAACUCUUUUCUUAGCCUAGUU		6276-6298
AD-1736364	GCUGAUAAAAUUAAUGGAUAA		6335-6355	UUAUCCAUUAAUUUUAUCAGCAC		6333-6355

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3
AD-1736365	CCUGUAUUUCUUUAGUUGUCA		6653-6673	UGACAACUAAAGAAAUACAGGAA		6651-6673
AD-1736366	UUUGUUUUGCUUUUGACAAAA		6996-7016	UUUUGUCAAAAGCAAAACAAAGC		6994-7016
AD-1736367	UGGCUGUGAAAAUAUUCUCCA		876-896	UGGAGAAUAUUUUCACAGCCACA		874-896
AD-1736368	ACUAUUUUAGGCAUAGCACUA		4897-4917	UAGUGCUAUGCCUAAAAUAGUGC		4895-4917
AD-1736369	UUUCAGUACUGUAUAAAGUGA		4651-4671	UCACUUUAUACAGUACUGAAAAU		4649-4671
AD-1736370	GUGAUGCAAUCUAUGUUUCCA		2129-2149	UGGAAACAUAGAUUGCAUCACCU		2127-2149
AD-1736371	UGUUUGGCAGAUCUCAUCAAA		6613-6633	UUUGAUGAGAUCUGCCAAACAUU		6611-6633
AD-1736372	AAGGUUGUUUGUGACCAGAAA		1517-1537	UUUCUGGUCACAAACAACCUUUC		1515-1537
AD-1736373	GGAAGGAAAUAUUUUGAGAAA		2794-2814	UUUCUCAAAAUAUUUCCUUCCUU		2792-2814
AD-1736374	UUUUGGUAGCGUGACUCUUCA		8132-8152	UGAAGAGUCACGCUACCAAAAGA		8130-8152
AD-1736375	UGAACAGGAAAAGAUGUAAAA		2045-2065	UUUUACAUCUUUUCCUGUUCAUU		2043-2065
AD-1736376	GGGAACCAAGAGGUAUAUGGA		1309-1329	UCCAUAUACCUCUUGGUUCCCAC		1307-1329
AD-1736377	UGGCACUAGGUCCAAAUCUUA		2419-2439	UAAGAUUUGGACCUAGUGCCAGU		2417-2439
AD-1736378	CACACCUUCAUAUGGAGAUUA		1131-1151	UAAUCUCCAUAUGAAGGUGUGCC		1129-1151
AD-1736379	CUGGUUUACUGGGAAAUAGCA		1406-1426	UGCUAUUUCCCAGUAAACCAGAC		1404-1426
AD-1736380	GCCCAAAGGAAUGUAUAUAAA		8316-8336	UUUAUAUACAUUCCUUUGGGCCU		8314-8336
AD-1736381	UUAACUGCAAGAGUUUACUGA		7265-7285	UCAGUAAACUCUUGCAGUUAAAA		7263-7285
AD-1736382	GAACCACUCUCUGAGUGCAAA		677-697	UUUGCACUCAGAGAGUGGUUCCU		675-697
AD-1736383	UUAUCUUUUCAUCCUGGCAUA		7607-7627	UAUGCCAGGAUGAAAAGAUAAAG		7605-7627
AD-1736384	GUGAGUGUUGGUAUGCCAACA		1605-1625	UGUUGGCAUACCAACACUCACGC		1603-1625
AD-1736385	AGAAUGUAUUUGGCUAAAUAA		5338-5358	UUAUUUAGCCAAAUACAUUCUCA		5336-5358
AD-1736386	GAACCCUUUUAUUAAGAGGAA		3317-3337	UUCCUCUUAAUAAAAGGGUUCCA		3315-3337
AD-1736387	CUCCUGUCCAUAGCUGCGAUA		590-610	UAUCGCAGCUAUGGACAGGAGGC		588-610
AD-1736388	ACUGAGUUGAAAUAAGGAAGA		3501-3521	UCUUCCUUAUUUCAACUCAGUAA		3499-3521
AD-1736389	CUGCCAAACAGAAGGAGCAUA		337-357	UAUGCUCCUUCUGUUUGGCAGGU		335-357
AD-1736390	GGCAAAGUUGUGAAGCACUCA		1563-1583	UGAGUGCUUCACAACUUUGCCAC		1561-1583

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_145259.3
AD-1736391	AUAGGAUGAUGAAGUUUAGAA		4413-4433	UUCUAAACUUCAUCAUCCUAUUU		4411-4433
AD-1736392	AUUCGUAUCUUAAAAUGGCAA		5513-5533	UUGCCAUUUUAAGAUACGAAUAC		5511-5533
AD-1736393	CACAGCUUGGGUAAUAGCGUA		3384-3404	UACGCUAUUACCCAAGCUGUGCU		3382-3404
AD-1736394	UUUGCAACAACAUAACACUGA		492-512	UCAGUGUUAUGUUGUUGCAAAAA		490-512
AD-1736395	UGCCACCAUGUGACUUAUUGA		5153-5173	UCAAUAAGUCACAUGGUGGCAAA		5151-5173
AD-1736396	UCGAUAGAGGAAAUGAGAAAA		1499-1519	UUUUCUCAUUUCCUCUAUCGAGG		1497-1519
AD-1736397	UUUUUAAGUUAGCAGGACUUA		2152-2172	UAAGUCCUGCUAACUUAAAAAGG		2150-2172
AD-1736398	UGUAAAUAAUUAUCUGCCUAA		8696-8716	UUAGGCAGAUAAUUAUUUACAUC		8694-8716
AD-1736399	UGGUUGUACGUGCCUCAAAUA		4010-4030	UAUUUGAGGCACGUACAACCAUA		4008-4030
AD-1736400	CCACACUGACUAGAGCCAACA		70-90	UGUUGGCUCUAGUCAGUGUGGGC		68-90

Table 7. Modified Sense and Antisense Strand Sequences of ACVR1C dsRNA Agents Comprising a GalNAc Derivative Targeting Ligand

Duplex Name	Antisense 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-1736131	usususuuuCfaAfAfCfuccauuccsusa		VPusAfsggaAfuGfGfaguuUfgAfaaaasgsa		UCUUUUUUCAAACUCCAUUCCUU	
AD-1736132	ascsuuucAfuCfUfGfucuucagasusa		VPusAfsucuGfaAfGfacagAfuGfaaagususa		UAACUUUCAUCUGUCUUCAGAUG	
AD-1736133	cscsucauAfaCfUfUfcuccaguasasa		VPusUfsuacUfgGfAfgaagUfuAfugaggsusg		CACCUCAUAACUUCUCCAGUAAU	
AD-1736134	csuscacuAfuCfUfUfucaacauusasa		VPusUfsaauGfuUfGfaaagAfuAfgugagsgsg		CCCUCACUAUCUUUCAACAUUAU	
AD-1736135	csuscguuAfaUfGfCfucucauccsasa		VPusUfsggaUfgAfGfagcaUfuAfacgagsusa		UACUCGUUAAUGCUCUCAUCCAC	
AD-1736136	gsusucuuCfaUfAfAfuccacuacsusa		VPusAfsguaGfuGfGfauuaUfgAfagaacsasg		CUGUUCUUCAUAAUCCACUACUG	
AD-	gsusugacUfuCfAfUfccaaucu		VPusAfsgagAfuUfGfgaugAfaGfuca		GAGUUGACUUCAUCCAAUCU	

Duplex Name	Antisense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
1736137	csusa		acsusc		CUA	
AD-1736138	csusacacAfaUfGfAfacuucuu asasa		VPusUfsuaaGfaAfGfuucaUfuGfugu agsasa		UUCUACACAAUGAACUUCUU AAC	
AD-1736139	csascaucUfaGfAfAfuucuuaa usasa		VPusAfsauuAfaGfAfauucUfaGfaug ugsasc		GUCACAUCUAGAAUUCUUAA UUU	
AD-1736140	asasaucuCfuCfAfUfagcuuuc ususa		VPusAfsagaAfaGfCfuaugAfgAfgau uuscsu		AGAAAUCUCUCAUAGCUUUC UUU	
AD-1736141	cscsuacuAfuUfGfUfagaauua csusa		VPusAfsguaAfuUfCfuacaAfuAfgua ggsusg		CACCUACUAUUGUAGAAUUA CUA	
AD-1736142	asuscuucUfuUfUfAfgugcauu asasa		VPusUfsuaaUfgCfAfcuaaAfaGfaag ausgsa		UCAUCUUCUUUUAGUGCAUU AAA	
AD-1736143	csuscaugUfaCfUfCfuucugau uscsa		VPusGfsaauCfaGfAfagagUfaCfaug agscsu		AGCUCAUGUACUCUUCUGAU UCU	
AD-1736144	ususucucUfuUfGfUfaccuugg asasa		VPusUfsuccAfaGfGfuacaAfaGfaga aasgsa		UCUUUCUCUUUGUACCUUGG AAU	
AD-1736145	usgsgcuuAfuAfCfAfucuucag asasa		VPusUfsucuGfaAfGfauguAfuAfagc casgsa		UCUGGCUUAUACAUCUUCAG AAA	
AD-1736146	csasaaacAfaAfAfCfuacuccua susa		VPusAfsuagGfaGfUfaguuUfuGfuuu ugsusu		AACAAAACAAAACUACUCCU AUU	
AD-1736147	ascsuagcAfgAfAfCfucuuaug asasa		VPusUfsucaUfaAfGfaguuCfuGfcua gusasa		UUACUAGCAGAACUCUUAUG AAA	
AD-1736148	cscsaaguCfaCfUfCfuauaauuc scsa		VPusGfsgaaUfuAfUfagagUfgAfcuu ggsgsa		UCCCAAGUCACUCUAUAAUU CCU	
AD-1736149	uscscauuUfuUfCfUfugucauu asusa		VPusAfsuaaUfgAfCfaagaAfaAfaug gasgsa		UCUCCAUUUUUCUUGUCAUU AUG	
AD-1736150	csasacacCfuCfAfAfcucaucuu susa		VPusAfsaagAfuGfAfguugAfgGfug uugscsu		AGCAACACCUCAACUCAUCU UUU	
AD-1736151	ascsucugAfaAfGfAfucugauu usasa		VPusUfsaaaUfcAfGfaucuUfuCfaga gususu		AAACUCUGAAAGAUCUGAUU UAU	
AD-1736152	csusaguuCfuUfUfUfcgcaau gsasa		VPusUfscauUfgCfGfgaaaAfgAfacu agsasa		UUCUAGUUCUUUUCCGCAAU GAC	
AD-1736153	csusuucaCfuCfUfGfaagaaauc scsa		VPusGfsgauUfuCfUfucagAfgUfgaa agsusu		AACUUUCACUCUGAAGAAAU CCG	

Duplex Name	Antisense 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-1736154	uscsuaacUfuUfUfCfucucuuu csusa		VPusAfsgaaAfgAfGfagaaAfaGfuua gasusa		UAUCUAACUUUUCUCUCUUU CUC	
AD-1736155	uscsucaaCfuUfUfGfugucaaa gsasa		VPusUfscuuUfgAfCfacaaAfgUfuga gasusa		UAUCUCAACUUUGUGUCAAA GAA	
AD-1736156	csusucaaUfaAfUfCfauuccuu usasa		VPusUfsaaaGfgAfAfugauUfaUfuga agsasc		GUCUUCAAUAAUCAUUCCUU UAA	
AD-1736157	usasacugCfuCfUfUfcguauua asgsa		VPusCfsuuaAfuAfCfgaagAfgCfagu uasgsg		CCUAACUGCUCUUCGUAUUA AGA	
AD-1736158	uscsuucuGfuCfAfUfaguucca ascsa		VPusGfsuugGfaAfCfuaugAfcAfgaa gascsu		AGUCUUCUGUCAUAGUUCCA ACA	
AD-1736159	asuscucaGfaAfCfCfauaucug ususu		VPusAfsacaGfaUfAfugguUfcUfgag aususu		AAAUCUCAGAACCAUAUCUG UUG	
AD-1736160	usgsaaucUfaUfCfUfucauuuu ascsa		VPusGfsuaaAfaUfGfaagaUfaGfauu casgsu		ACUGAAUCUAUCUUCAUUUU ACU	
AD-1736161	ascscacuAfaAfCfUfuguuccu ususa		VPusAfsaagGfaAfCfaaguUfuAfgug gsusc		GAACCACUAAACUUGUUCCU UUC	
AD-1736162	asgsuguuCfuUfUfAfcuccuua csasa		VPusUfsguaAfgGfAfguaaAfgAfaca cusgsa		UCAGUGUUCUUUACUCCUUA CAG	
AD-1736163	csusuuacUfcUfUfAfacaggau usasa		VPusUfsaauCfcUfGfuuaaGfaGfuaa agsgsa		UCCUUUACUCUUAACAGGAU UAU	
AD-1736164	usasuaccUfaAfGfAfacauauu ascsa		VPusGfsuaaUfaUfGfuucuUfaGfgua uasasg		CUUAUACCUAAGAACAUAUU ACA	
AD-1736165	csusucuaCfuGfAfGfaugaucc asasa		VPusUfsuggAfuCfAfucucAfgUfaga agsasa		UUCUUCUACUGAGAUGAUCC AAG	
AD-1736166	csusguauUfuUfCfUfcauagag usasa		VPusUfsacuCfuAfUfgagaAfaAfuac agsasa		UUCUGUAUUUUCUCAUAGAG UAC	
AD-1736167	ascsuuuuCfuCfUfUfucaguug usasa		VPusUfsacaAfcUfGfaaagAfgAfaaa gusasu		AUACUUUUCUCUUUCAGUUG UAG	
AD-1736168	asusuaauUfuCfUfAfgucugug asasa		VPusUfsucaCfaGfAfcuagAfaAfuua ausgsa		UCAUUAAUUUCUAGUCUGUG AAA	
AD-1736169	csuscuguAfuAfAfGfagguuuc ascsa		VPusGfsugaAfaCfCfucuuAfuAfcag agsasa		UUCUCUGUAUAAGAGGUUUC ACC	
AD-	gsascuuuCfaAfAfGfuacuaau		VPusGfsuauUfaGfUfacuuUfgAfaag		UUGACUUUCAAAGUACUAAU	

Duplex Name	Antisense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
1736170	ascsa		ucsasa		ACU	
AD-1736171	ususugccAfuUfAfUfacaaagu ususa		VPusAfsaacUfuUfGfuauaAfuGfgca aascsa		UGUUUGCCAUUAUACAAAGU UUG	
AD-1736172	gsasacacUfaUfCfGfacauaccu scsa		VPusGfsaggUfaUfGfucgaUfaGfugu ucsasg		CUGAACACUAUCGACAUACC UCA	
AD-1736173	usasgaauGfaCfAfUfuuacuaa usasa		VPusUfsauuAfgUfAfaaugUfcAfuuc uascsg		CGUAGAAUGACAUUUACUAA UAU	
AD-1736174	asasgcuaCfuUfAfGfaaaguu usasa		VPusUfsaaaCfaUfUfucuaAfgUfagc uusgsu		ACAAGCUACUUAGAAAUGUU UAG	
AD-1736175	cscsuuagUfaCfUfCfcagaga ususa		VPusAfsaucUfcUfGfagagUfaCfuaa ggsgsa		UCCCUUAGUACUCUCAGAGA UUA	
AD-1736176	usgsaaugCfaCfAfCfuaacguaa susa		VPusAfsuuaCfgUfUfagugUfgCfauu casasg		CUUGAAUGCACACUAACGUA AUG	
AD-1736177	asasgccuAfaUfGfAfugauaau usasa		VPusUfsaauUfaUfCfaucaUfuAfggc uususg		CAAAGCCUAAUGAUGAUAAU UAU	
AD-1736178	asasacuuUfuUfAfCfuauccca usasa		VPusUfsaugGfgAfUfaguaAfaAfagu uuscsc		GGAAACUUUUUACUAUCCCA UAU	
AD-1736179	csusagcuGfaUfAfCfucuuaag usasa		VPusUfsacuUfaAfGfaguaUfcAfgcu agscsu		AGCUAGCUGAUACUCUUAAG UAU	
AD-1736180	asgscaugAfaAfAfGfauaacuc usasa		VPusUfsagaGfuUfAfucuuUfuCfaug cusgsc		GCAGCAUGAAAAGAUAACUC UAA	
AD-1736181	usasagccAfuUfAfUfgcuauua gsusa		VPusAfscuaAfuAfGfcauaAfuGfgcu uasgsu		ACUAAGCCAUUAUGCUAUUA GUU	
AD-1736182	uscsuagcUfuUfUfAfgcuaaca usasa		VPusUfsaugUfuAfGfgcuaaAfaGfcua gasasu		AUUCUAGCUUUUAGCUAACA UAU	
AD-1736183	gsusgugaUfuCfUfUfcaaacuu csasa		VPusUfsgaaGfuUfUfUfgaagAfaUfcac acsasa		UUGUGUGAUUCUUCAAACUU CAC	
AD-1736184	uscsuccaGfaCfCfUfaacaguuu susa		VPusAfsaaaCfuGfUfuaggUfcUfgga gasgsa		UCUCUCCAGACCUAACAGUU UUA	
AD-1736185	csusuuuuUfuCfAfUfcuagccu usgsa		VPusCfsaagGfcUfAfgaugAfaAfaaa agsasa		UUCUUUUUUUCAUCUAGCCU UGC	
AD-1736186	csasaaauAfaUfUfCfuugacauc susa		VPusAfsgauGfuCfAfagaaUfuAfuuu ugsasc		GUCAAAAUAAUUCUUGACAU CUA	

Duplex Name	Antisense 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-1736187	gscsaucaCfuUfUfCfugaaaaua sasa		VPusUfsuauUfuUfCfagaaAfgUfgau gcsusg		CAGCAUCACUUUUCUGAAAAU AAG	
AD-1736188	uscsuuuuuGfuGfAfAfacauacu asusa		VPusAfsuagUfaUfGfuuucAfcAfaaa gasusg		CAUCUUUUGUGAAACAUACU AUU	
AD-1736189	csusauuuCfuUfCfCfauaggcu asasa		VPusUfsuagCfcUfAfuggaAfgAfaau agsasa		UUCUAUUUCUUCCAUAGGCU AAA	
AD-1736190	csusucaaUfgAfAfGfuguuaac asasa		VPusUfsuguUfaAfCfacuuCfaUfuga agsasg		CUCUUCAAUGAAGUGUUAAC AAC	
AD-1736191	ususugccUfuCfAfUfucuacuu uscsa		VPusGfsaaaGfuAfGfaaugAfaGfgca aasasc		GUUUUGCCUUCAUUCUACUU UCU	
AD-1736192	asgsguuuUfuAfAfAfuguccua asasa		VPusUfsuuaGfgAfCfauuuAfaAfaac cusgsa		UCAGGUUUUUAAAUGUCCUA AAA	
AD-1736193	gsasauauCfuUfUfUfGfaguccuu csasa		VPusUfsgaaGfgAfCfucaaAfgAfuau ucsasc		GUGAAUAUCUUUGAGUCCUU CAA	
AD-1736194	gsasacacUfuCfCfAfaagauuaa susa		VPusAfsuuaAfuCfUfuuggAfaGfugu ucsasg		CUGAACACUUCCAAAGAUUA AUC	
AD-1736195	csusaaauUfuUfGfUfcuaacaaa susa		VPusAfsuuuGfuUfAfgacaAfaAfuuu agsgsc		GCCUAAAUUUUGUCUAACAA AUG	
AD-1736196	gsusaaacAfaCfUfUfaaaauugc susa		VPusAfsgcaAfuUfUfuaagUfuGfuuu acsusc		GAGUAAACAACUUAAAAUUG CUU	
AD-1736197	asasaauaAfuUfUfAfcucacuca sgsa		VPusCfsugaGfuGfAfguaaAfuUfauu uusasg		CUAAAAUAAUUUACUCACUC AGA	
AD-1736198	gsascaucUfaUfUfCfuguuggu csusa		VPusAfsgacCfaAfCfagaaUfaGfaug ucsasg		CUGACAUCUAUUCUGUUGGU CUG	
AD-1736199	usasacugAfgUfAfGfucuuaua ususa		VPusAfsauaUfaAfGfacuaCfuCfagu uasgsg		CCUAACUGAGUAGUCUUAUA UUU	
AD-1736200	uscsuggaAfuUfUfAfgccuucu asasa		VPusUfsuagAfaGfGfGfcuaaAfuUfcca gascsg		CGUCUGGAAUUUAGCCUUCU AAU	
AD-1736201	ascsaugcCfuUfGfGfAfacucuug asasa		VPusUfsucaAfgAfGfuucaAfgGfcau gususu		AAACAUGCCUUGAACUCUUG AAC	
AD-1736202	asuscaagCfaCfUfUfcuugcacu susa		VPusAfsaguGfcAfAfgaagUfgCfuug aususu		AAAUCAAGCACUUCUUGCAC UUG	
AD-	csusugcuUfuUfCfAfucuuuau		VPusGfsuauAfaAfGfaugaAfaAfgca		CACUUGCUUUUCAUCUUUAU	

Duplex Name	Antisense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
1736203	ascsa		agsusg		ACU	
AD-1736204	ususuucuCfcCfUfAfuguaaua uscsa		VPusGfsauaUfuAfCfauagGfgAfgaa aasgsc		GCUUUUCUCCCUAUGUAAUA UCU	
AD-1736205	usgscuuuuCfuUfCfUfaugucua asasa		VPusUfsuuaGfaCfAfuagaAfgAfaag casusa		UAUGCUUUCUUCUAUGUCUA AAA	
AD-1736206	ascscugcUfuAfGfCfaaaucgu csusa		VPusAfsgacGfaUfUfugcuAfaGfcag gususc		GAACCUGCUUAGCAAAUCGU CUG	
AD-1736207	asusauucCfuCfUfAfcccuuuc ascsa		VPusGfsugaAfaGfGfguagAfgGfaau auscsu		AGAUAUUCCUCUACCCUUUC ACA	
AD-1736208	uscsccacUfuUfUfCfuuugggu ususa		VPusAfsaacCfcAfAfagaaAfaGfugg gasusu		AAUCCCACUUUUCUUUGGGU UUC	
AD-1736209	asgsgcuuCfuUfGfUfauauacu usasa		VPusUfsaagUfaUfAfuacaAfgAfagc cusgsc		GCAGGCUUCUUGUAUAUACU UAU	
AD-1736210	asasacuuGfaUfCfUfguguuuc asgsa		VPusCfsugaAfaCfAfcagaUfcAfagu uusgsa		UCAAACUUGAUCUGUGUUUC AGG	
AD-1736211	ususugcuUfuAfAfUfgcuaaau uscsa		VPusGfsaauUfuAfGfcauuAfaAfgca aasasg		CUUUUGCUUUAAUGCUAAAU UCC	
AD-1736212	asgsacuaGfcUfGfUfuauuugu asusa		VPusAfsuacAfaAfUfaacaGfcUfagu cususu		AAAGACUAGCUGUUAUUUGU AUU	
AD-1736213	ususccuaCfuUfUfCfccuugaa usasa		VPusUfsauuCfaAfGfggaaAfgUfagg aasgsc		GCUUCCUACUUUCCCUUGAA UAG	
AD-1736214	csasgaacUfgAfAfUfgcucaag uscsa		VPusGfsacuUfgAfGfcauuCfaGfuuc ugsgsa		UCCAGAACUGAAUGCUCAAG UCU	
AD-1736215	uscsuuguUfaCfUfAfauuucuc asusa		VPusAfsugaGfaAfAfuuagUfaAfcaa gasasc		GUUCUUGUUACUAAUUUCUC AUA	
AD-1736216	csuscaguGfaUfAfGfccuuuau ascsa		VPusGfsuauAfaAfGfgcuaUfcAfcug agsusu		AACUCAGUGAUAGCCUUUAU ACC	
AD-1736217	ususuuauGfcUfCfCfuaaaaca uscsa		VPusGfsaugUfuUfUfaggaGfcAfuaa aasgsa		UCUUUUAUGCUCCUAAAACA UCU	
AD-1736218	ususcuccUfuAfGfGfuuauguu csasa		VPusUfsgaaCfaUfAfaccuAfaGfgag aasusu		AAUUCUCCUUAGGUUAUGUU CAG	
AD-1736219	asusugcuCfaUfCfGfagacauaa sasa		VPusUfsuuaUfgUfCfucgaUfgAfgca ausasg		CUAUUGCUCAUCGAGACAUA AAA	

Duplex Name	Antisense 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-1736220	cscsuuugUfaCfAfUfacacacu usasa		VPusUfsaagUfgUfGfuaugUfaCfaaaggsasa		UUCCUUUGUACAUACACACU UAG	
AD-1736221	ususgaacCfaAfGfAfgcacaug asasa		VPusUfsucaUfgUfGfcucuUfgGfuucaasgsu		ACUUGAACCAAGAGCACAUG AAU	
AD-1736222	uscsagggAfuUfUfUfaaagucu asasa		VPusUfsuagAfcUfUfuaaaAfuCfccugasgsg		CCUCAGGGAUUUUAAAGUCU AAU	
AD-1736223	usascuugCfuUfAfUfaaaguga usasa		VPusUfsaucAfcUfUfuauaAfgCfaaguascsc		GGUACUUGCUUAUAAAGUGA UAG	
AD-1736224	asusgcauCfuAfAfAfccuaccu usgsa		VPusCfsaagGfuAfGfguuuAfgAfugcausgsc		GCAUGCAUCUAAACCUACCU UGA	
AD-1736225	ususgggaAfaAfCfAfcuauuau gsasa		VPusUfscauAfaUfAfguguUfuUfcccaasgsu		ACUUGGGAAAACACUAUUAU GAA	
AD-1736226	asasacucCfaAfAfGfagaaauga sasa		VPusUfsucaUfuUfCfucuuUfgGfaguuusgsa		UCAAACUCCAAAGAGAAAUG AAU	
AD-1736227	asusgggcAfuUfUfUfucaaaac asusa		VPusAfsuguUfuUfGfaaaaAfuGfcccausasu		AUAUGGGCAUUUUUCAAAAC AUU	
AD-1736228	asusaaugGfaAfCfUfuggacuc asasa		VPusUfsugaGfuCfCfaaguUfcCfauuauscsu		AGAUAAUGGAACUUGGACUC AAC	
AD-1736229	usgsuguaGfaUfGfAfcgaaacc asasa		VPusUfsuggUfuUfCfgucaUfcUfacacasasa		UUUGUGUAGAUGACGAAACC AAG	
AD-1736230	ususcuacCfuCfAfAfagauaag ascsa		VPusGfsucuUfaUfCfuuugAfgGfuagaascsa		UGUUCUACCUCAAAGAUAAG ACA	
AD-1736231	asgsaaggCfaUfAfUfugaguua ususa		VPusAfsauaAfcUfCfaauaUfgCfcuucusasa		UUAGAAGGCAUAUUGAGUUA UUU	
AD-1736232	asusggagUfuUfUfUfcugcuau ususa		VPusAfsaauAfgCfAfgaaaAfaCfucausgsu		ACAUGGAGUUUUUCUGCUAU UUU	
AD-1736233	uscsaguuUfcUfCfAfuuaguuu gsusa		VPusAfscaaAfcUfUfAfaugaGfaAfacugasgsg		CCUCAGUUUCUCAUUAGUUU GUC	
AD-1736234	csusgcauAfuAfUfAfagaacga asasa		VPusUfsuucGfuUfCfuuauAfuAfugcagsasa		UUCUGCAUAUAUAAGAACGA AAU	
AD-1736235	usgsagccAfaAfAfUfauuaaau uscsa		VPusGfsaauUfuAfAfuauuUfuGfgcucasgsa		UCUGAGCCAAAAUAUUAAAU UCU	
AD-	asgsaaugAfuAfUfUfuccuguu		VPusAfsaaaCfaGfGfaaauAfuCfauu		CAAGAAUGAUAUUUCCUGUU	

Duplex Name	Antisense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
1736236	ususa		cususg		UUA	
AD-1736237	gsusgcucUfaUfAfUfaaaucuu cscsa		VPusGfsgaaGfaUfUfuauaUfaGfagc acsasa		UUGUGCUCUAUAUAAAUCUU CCC	
AD-1736238	ususuacaGfaGfAfAfgcaucuu asusa		VPusAfsuaaGfaUfGfcuucUfcUfgua aasasu		AUUUUACAGAGAAGCAUCUU AUU	
AD-1736239	gsuscuugAfgUfUfCfugcauga csasa		VPusUfsgucAfuGfCfagaaCfuCfaag acsasu		AUGUCUUGAGUUCUGCAUGA CAG	
AD-1736240	csusucaaAfuCfUfAfuaauuuu ascsa		VPusGfsuaaAfaUfUfauagAfuUfuga agsgsg		CCCUUCAAAUCUAUAAUUUU ACU	
AD-1736241	gsasagcaUfaUfAfGfaacucua ususa		VPusAfsauaGfaGfUfucuaUfaUfgcu ucsasc		GUGAAGCAUAUAGAACUCUA UUU	
AD-1736242	gsasgcugCfuUfCfUfaaauaaca sasa		VPusUfsuguUfaUfUfuagaAfgCfagc ucsusc		GAGAGCUGCUUCUAAAUAAC AAA	
AD-1736243	usgsacugUfaUfUfUfccugauc asusa		VPusAfsugaUfcAfGfgaaaUfaCfagu cascsa		UGUGACUGUAUUUCCUGAUC AUU	
AD-1736244	gsusucugAfaGfGfAfuauacuu csusa		VPusAfsgaaGfuAfUfauccUfuCfaga acsgsc		GCGUUCUGAAGGAUAUACUU CUG	
AD-1736245	gsusgaagCfaUfGfAfuucaaua csusa		VPusAfsguaUfuGfAfaucaUfgCfuuc acsasg		CUGUGAAGCAUGAUUCAAUA CUG	
AD-1736246	asasugcuGfcUfUfCfacagauu ususa		VPusAfsaaaUfcUfGfugaaGfcAfgca uuscsg		CGAAUGCUGCUUCACAGAUU UUU	
AD-1736247	usgsugggUfuAfUfGfuuaaucu gsasa		VPusUfscagAfuUfAfacauAfaCfcca casgsu		ACUGUGGGUUAUGUUAAUCU GAA	
AD-1736248	gsasguacAfgAfAfGfaaugcuc asusa		VPusAfsugaGfcAfUfucuuCfuGfuac ucsasc		GUGAGUACAGAAGAAUGCUC AUG	
AD-1736249	csusguauUfuCfAfUfccuagau ususa		VPusAfsaauCfuAfGfgaugAfaAfuac agscsu		AGCUGUAUUUCAUCCUAGAU UUU	
AD-1736250	asasucugGfuAfAfAfugcugga asasa		VPusUfsuucCfaGfCfauuuAfcCfaga uusgsc		GCAAUCUGGUAAAUGCUGGA AAA	
AD-1736251	usgscucaGfaUfUfAfccugauc gsusa		VPusAfscgaUfcAfGfguaaUfcUfgag casasu		AUUGCUCAGAUUACCUGAUC GUG	
AD-1736252	gsascagcUfaUfGfGfaguuugc gsusa		VPusAfscgcAfaAfCfuccaUfaGfcug ucsasg		CUGACAGCUAUGGAGUUUGC GUG	

Duplex Name	Antisense 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-1736253	usasgaacAfuGfCfUfcacuuaca sasa		VPusUfsuguAfaGfUfgagcAfuGfuuc uasusa		UAUAGAACAUGCUCACUUAC AAA	
AD-1736254	asusuaugCfuUfCfAfuuucacu asusa		VPusAfsuagUfgAfAfaugaAfgCfaua auscsa		UGAUUAUGCUUCAUUUCACU AUG	
AD-1736255	csasacagCfaAfGfUfcauaaaag susa		VPusAfscuuUfuAfUfgacuUfgCfugu ugsgsu		ACCAACAGCAAGUCAUAAAA GUA	
AD-1736256	ususgucuGfaAfAfAfugucuuu asasa		VPusUfsuaaAfgAfCfauuuUfcAfgac aasusg		CAUUGUCUGAAAAUGUCUUU AAG	
AD-1736257	usgsuuggUfuCfAfAfaggacaa ususa		VPusAfsauuGfuCfCfuuugAfaCfcaa casgsa		UCUGUUGGUUCAAAGGACAA UUG	
AD-1736258	uscsuaaaCfuUfUfAfauauauc gsasa		VPusUfscgaUfaUfAfuuaaAfgUfuua gasgsc		GCUCUAAACUUUAAUAUAUC GAA	
AD-1736259	asasgugaAfaCfAfUfgacuguc gsusa		VPusAfscgaCfaGfUfcaugUfuUfcac uusasa		UUAAGUGAAACAUGACUGUC GUG	
AD-1736260	asuscgucCfaUfAfCfaguuuuc asusa		VPusAfsugaAfaAfCfuguaUfgGfacg ausasu		AUAUCGUCCAUACAGUUUUC AUU	
AD-1736261	csusucagGfaAfAfUfaguagga asasa		VPusUfsuucCfuAfCfuauuUfcCfuga agscsa		UGCUUCAGGAAAUAGUAGGA AAA	
AD-1736262	csascccuUfuCfUfGfuaaggac usgsa		VPusCfsaguCfcUfUfacagAfaAfggg ugsgsg		CCCACCCUUUCUGUAAGGAC UGU	
AD-1736263	asasagagAfuAfCfCfCfugacaucc susa		VPusAfsggaUfgUfCfagguAfuCfucu uususg		CAAAAGAGAUACCUGACAUC CUG	
AD-1736264	asusgagcAfuUfAfAfuguuuuc usgsa		VPusCfsagaAfaAfCfauuaAfuGfcuc aususa		UAAUGAGCAUUAAUGUUUUC UGA	
AD-1736265	usgsacauUfuUfUfUfucucauag asasa		VPusUfsucuAfuGfAfgaaaAfaAfugu casasc		GUUGACAUUUUUUCUCAUAG AAA	
AD-1736266	csasgagaUfuAfAfAfAfugacuac usasa		VPusUfsaguAfgUfCfauuuAfaUfcuc ugsasu		AUCAGAGAUUAAAUGACUAC UAG	
AD-1736267	gscsugucAfaAfUfGfuuauauu gsusa		VPusAfscaaUfaUfAfacauUfuGfaca gcsasu		AUGCUGUCAAAUGUUAUAUU GUU	
AD-1736268	asasuauaAfuAfCfUfacagcaaa sasa		VPusUfsuuuGfcUfGfuaguAfuUfaua uuscsc		GGAAUAUAAUACUACAGCAA AAU	
AD-	gsgsugucUfaAfAfUfauaauuu		VPusUfsgaaAfuUfAfuauuUfaGfaca		AGGGUGUCUAAAUAUAAUUU	

Duplex Name	Antisense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
1736269	csasa		ccscsu		CAU	
AD-1736270	csuscuuuAfuAfCfAfaaaugag asgsa		VPusCfsucuCfaUfUfuuguAfuAfaag agsasa		UUCUCUUUAUACAAAAUGAG AGU	
AD-1736271	gscsaguaCfcAfAfAfugaauaa asasa		VPusUfsuuuAfuUfCfauuuGfgUfacu gcsusa		UAGCAGUACCAAAUGAAUAA AAG	
AD-1736272	ususguugGfuAfCfAfcaaggua asasa		VPusUfsuuaCfcUfUfguguAfcCfaac aasusc		GAUUGUUGGUACACAAGGUA AAC	
AD-1736273	csuscuuaUfuUfAfAfcuuaacc gsusa		VPusAfscggUfuAfAfguuaAfaUfaag agsusu		AACUCUUAUUUAACUUAACC GUC	
AD-1736274	usgscuugAfuGfAfUfUfcacauga asusa		VPusAfsuucAfuUfUfGfuuucAfuCfaag casusu		AAUGCUUGAUGAUACAAUGA AUG	
AD-1736275	asascuggGfaAfAfAfGfacaauuu gsasa		VPusUfscaaAfuUfUfGfucuuUfcCfcag uusasc		GUAACUGGGAAAGACAAUUU GAA	
AD-1736276	csusccuuAfuAfUfUfGfacuauuu gsasa		VPusUfscaaAfuAfUfGfucauAfuAfagg agscsc		GGCUCCUUAUAUGACUAUUU GAA	
AD-1736277	asgsucauGfcUfAfAfAfccaaugg asasa		VPusUfsuccAfuUfUfGfguuaGfcAfuga cusgsa		UCAGUCAUGCUAACCAAUGG AAA	
AD-1736278	cscsugaaGfuCfAfCfacagcuaa susa		VPusAfsuuaGfcUfUfGfugugAfcUfuca ggsasc		GUCCUGAAGUCACACAGCUA AUG	
AD-1736279	ususgcugCfuGfAfCfaacaaag asusa		VPusAfsucuUfuGfUfUfgucAfgCfagc aasusg		CAUUGCUGCUGACAACAAAG AUA	
AD-1736280	usascugaCfuUfUfGfccuguaa asgsa		VPusCfsuuuAfcAfUfGfgcaaAfgUfcag uasasu		AUUACUGACUUUGCCUGUAA AGA	
AD-1736281	asasucccUfaUfUfUfUfuaaaauuc scsa		VPusGfsgaaUfuUfUfUfaaaaUfaGfgga uusgsu		ACAAUCCCUAUUUUAAAAUU CCC	
AD-1736282	gsusgccuUfaGfGfAfgauuacc csusa		VPusAfsgggUfaAfUfcuccUfaAfggc acsusc		GAGUGCCUUAGGAGAUUACC CUU	
AD-1736283	gsascaauCfuAfAfAfAfuauauca uscsa		VPusGfsaugAfuAfUfauuuAfgAfuu gucsusg		CAGACAAUCUAAAUAUAUCA UCA	
AD-1736284	usgsugauAfaUfGfAfacaccgu asasa		VPusUfsuacGfgUfGfuucaUfuAfuca casasg		CUUGUGAUAAUGAACACCGU AAG	
AD-1736285	uscsaccgUfuGfUfAfaagacuu ususa		VPusAfsaaaGfuCfUfuuacAfaCfggu gasusu		AAUCACCGUUGUAAAGACUU UUU	

Duplex Name	Antisense 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-1736286	ususagagAfaGfCfUfuccugac asusa		VPusAfsuguCfaGfGfaagcUfuCfucu aasusc		GAUUAGAGAAGCUUCCUGAC AUC	
AD-1736287	asascaguAfaAfGfAfaaugcua csusa		VPusAfsguaGfcAfUfuucuUfuAfcug uusasu		AUAACAGUAAAGAAAUGCUA CUU	
AD-1736288	usasuguuCfuGfAfCfuugagag usasa		VPusAfsacuCfuCfAfagucAfgAfaca uasasa		UUUAUGUUCUGACUUGAGAG UUA	
AD-1736289	ususagagCfaUfGfCfuaucuuu asgsa		VPusCfsuaaAfgAfUfagcaUfgCfucu aasusu		AAUUAGAGCAUGCUAUCUUU AGG	
AD-1736290	usasgucuUfuGfAfUfugaaaua asgsa		VPusCfsuuaUfuUfCfaaucAfaAfgac uasusg		CAUAGUCUUUGAUUGAAAUA AGU	
AD-1736291	ususgguaAfaCfGfAfgauuuaa csasa		VPusUfsguuAfaAfUfcucgUfuUfacc aasasg		CUUUGGUAAACGAGAUUUAA CAU	
AD-1736292	gsuscugaAfaAfUfUfUfgcuuuca ususa		VPusAfsaugAfaAfGfcaauUfuUfcag acscsu		AGGUCUGAAAAUUGCUUUCA UUU	
AD-1736293	asusgaacUfuGfUfUfUfgccuugu asasa		VPusUfsuacAfaGfGfcaacAfaGfuuc ausgsc		GCAUGAACUUGUUGCCUUGU AAA	
AD-1736294	gsgsgcaaUfaAfaAfCfuguauca asasa		VPusUfsuugAfuAfCfaguuUfaUfugc ccsasa		UUGGGCAAUAAACUGUAUCA AAA	
AD-1736295	ascsauguUfaGfCfAfuauaaug usasa		VPusUfsacaUfuAfUfaugcUfaAfcau gusasc		GUACAUGUUAGCAUAUAAUG UAU	
AD-1736296	usgsugagAfgUfAfUfagaauuu csusa		VPusAfsgaaAfuUfCfuauaCfuCfuca casgsu		ACUGUGAGAGUAUAGAAUUU CUU	
AD-1736297	asusccuuCfaUfUfUfggcacua usasa		VPusUfsauaGfuGfUfCfcaaaUfgAfagg aususa		UAAUCCUUCAUUUGGCACUA UAG	
AD-1736298	ascsauuuAfgAfAfAfguagcuu usasa		VPusUfsaaaGfcUfAfcuuuCfuAfaau gusgsu		ACACAUUUAGAAAGUAGCUU UAU	
AD-1736299	asascuguUfcUfAfUfaaagcaaa sgsa		VPusCfsuuuGfcUfUfuauaGfaAfcag uusasa		UUAACUGUUCUAUAAAGCAA AGC	
AD-1736300	cscsuccaGfaGfAfUfgaaagauc susa		VPusAfsgauCfuUfUfcaucUfcUfgga ggsasg		CUCCUCCAGAGAUGAAAGAU CUU	
AD-1736301	ususguuuAfaCfUfAfugacucc usasa		VPusUfsaggAfgUfCfauagUfuAfaac aascsa		UGUUGUUUAACUAUGACUCC UAA	
AD-	csusguuuGfaCfAfAfugcuuug		VPusAfsacaAfaGfCfauugUfcAfaac		UUCUGUUUGACAAUGCUUUG	

Duplex Name	Antisense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
1736302	ususa		agsasa		UUC	
AD-1736303	usgsuccuAfaAfAfGfaaauuuuuscsa		VPusGfsaaaAfaUfUfucuuUfuAfggacasasc		GUUGUCCUAAAAGAAAUUUUUCU	
AD-1736304	ascsagauUfgAfAfCfaaagaacususa		VPusAfsaguUfcUfUfuguuCfaAfucugusasg		CUACAGAUUGAACAAAGAACUUA	
AD-1736305	gsusuuaaCfcUfGfUfccaaacuuscsa		VPusGfsaagUfuUfGfgacaGfgUfuaaacsgsa		UCGUUUAACCUGUCCAAACUUCU	
AD-1736306	csasaaauGfuUfUfAfacuuuacccsasa		VPusUfsgguAfaAfGfuuaaAfcAfuuuugsgsu		ACCAAAAUGUUUAACUUUACCAA	
AD-1736307	uscsccauUfgUfGfUfaauauuuasusa		VPusAfsuaaAfuAfUfuacaCfaAfugggascsu		AGUCCCAUUGUGUAAUAUUUAUU	
AD-1736308	gsusugggUfaAfAfUfaugcuuaususa		VPusAfsauaAfgCfAfuauuUfaCfccaacsasu		AUGUUGGGUAAAUAUGCUUAUUG	
AD-1736309	csasggguUfgUfCfUfuugagucusgsa		VPusCfsagaCfuCfAfaagaCfaAfcccugsasg		CUCAGGGUUGUCUUUGAGUCUGC	
AD-1736310	gscsuaaaAfuCfCfAfacugcaaususa		VPusAfsauuGfcAfGfuuggAfuUfuuagcscsc		GGGCUAAAAUCCAACUGCAAUUG	
AD-1736311	csasggacUfgAfAfGfuguguaugsusa		VPusAfscauAfcAfCfacuuCfaGfuccugsgsc		GCCAGGACUGAAGUGUGUAUGUC	
AD-1736312	gsasguacCfaAfUfUfgccuuauusasa		VPusUfsaauAfaGfGfcaauUfgGfuacucscsu		AGGAGUACCAAUUGCCUUAUUAU	
AD-1736313	asasgugcCfuAfUfGfugaagugasusa		VPusAfsucaCfuUfCfacauAfgGfcacuususu		AAAAGUGCCUAUGUGAAGUGAUU	
AD-1736314	usasacaaUfaAfUfAfgaacugccsasa		VPusUfsggcAfgUfUfcuauUfaUfuguuasgsg		CCUAACAAUAAUAGAACUGCCAG	
AD-1736315	gscsuguuCfcAfUfAfccauugcususa		VPusAfsagcAfaUfGfguauGfgAfacagcsasg		CUGCUGUUCCAUACCAUUGCUUU	
AD-1736316	usasgacuGfgAfGfAfagauuauuscsa		VPusGfsaauAfaUfCfuucuCfcAfgucuasgsa		UCUAGACUGGAGAAGAUUAUUCA	
AD-1736317	ususccaaCfaGfCfAfucaccaaasusa		VPusAfsuuuGfgUfGfaugcUfgUfuggaasgsg		CCUUCCAACAGCAUCACCAAAUG	
AD-1736318	usasauugGfuAfCfAfgauucugususa		VPusAfsacaGfaAfUfcuguAfcCfaauuascsa		UGUAAUUGGUACAGAUUCUGUUG	

Duplex Name	Antisense 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-1736319	gsasgaaaCfaUfUfAfuuuguug uscsu		VPusGfsacaAfcAfAfauaaUfgUfuuc ucsusu		AAGAGAAACAUUAUUUGUUG UCA	
AD-1736320	csgscucuCfaAfUfUfgcuagug gsusa		VPusAfsccaCfuAfGfcaauUfgAfgag cgscsc		GGCGCUCUCAAUUGCUAGUG GUC	
AD-1736321	csgsguauCfaGfAfAfacagcaaa susa		VPusAfsuuuGfcUfGfuuucUfgAfuac cgsusc		GACGGUAUCAGAAACAGCAA AUA	
AD-1736322	cscscagaCfaUfAfAfAfuuuuaua ususa		VPusAfsauaUfaAfAfauuaUfgUfcug ggsasg		CUCCCAGACAUAAAUUUUAUA UUU	
AD-1736323	usasguacAfuUfUfUfgagguau ususa		VPusAfsaauAfcCfUfcaaaAfuGfuac uasasc		GUUAGUACAUUUUGAGGUAU UUU	
AD-1736324	asasaugcUfaUfUfGfauaacag usasa		VPusUfsacuGfuUfAfucaaUfaGfcau uusasc		GUAAAUGCUAUUGAUAACAG UAA	
AD-1736325	usasgcugAfaUfUfUfgggacua usgsa		VPusCfsauaGfuCfCfcaaaUfuCfagcu asusc		GAUAGCUGAAUUUGGGACUA UGU	
AD-1736326	asusugugGfuUfUfUfcaaagau asusa		VPusAfsuauCfuUfUfgaaaAfcCfaca ausgsg		CCAUUGUGGUUUUCAAAGAU AUU	
AD-1736327	cscsugguUfgCfAfGfuaucuga asasa		VPusUfsuucAfgAfUfacugCfaAfcca ggsusu		AACCUGGUUGCAGUAUCUGA AAA	
AD-1736328	usasgaauGfgUfUfGfuugagcu asasa		VPusUfsuagCfuCfAfacaaCfcAfuuc uascsa		UGUAGAAUGGUUGUUGAGCU AAG	
AD-1736329	csusggccAfuCfAfUfuauuacu gsusa		VPusAfscagUfaAfUfaaugAfuGfgcc agscsu		AGCUGGCCAUCAUUAUUACU GUG	
AD-1736330	ususgacaGfaUfAfAfaauacga asgsa		VPusCfsuucGfuAfUfuuuaUfcUfguc aasusu		AAUUGACAGAUAAAAUACGA AGU	
AD-1736331	uscsacaaAfcAfCfAfucauuaca sasa		VPusUfsuguAfaUfGfauguGfuUfug ugasasu		AUUCACAAACACAUCAUUAC AAG	
AD-1736332	cscsaugaUfuGfUfAfugaaaau asgsa		VPusCfsuauUfuUfCfauacAfaUfcau ggsasa		UUCCAUGAUUGUAUGAAAAU AGU	
AD-1736333	csascagaGfuAfAfUfgaauauu usasa		VPusUfsaaaUfaUfUfcauuAfcUfcug ugsusc		GACACAGAGUAAUGAAUAUU UAA	
AD-1736334	asgscugcUfuAfGfUfggaagau gsusa		VPusAfscauCfuUfCfcacuAfaGfcag cuscsc		GGAGCUGCUUAGUGGAAGAU GUA	
AD-	usasgcucUfgUfGfUfgcugaua		VPusGfsguaUfcAfGfcacaCfaGfagc		UCUAGCUCUGUGUGGCUGAUA	

Duplex Name	Antisense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
1736335	cscsa		uasgsa		CCU	
AD-1736336	csasuucgAfgAfGfAfauaugagcsusa		VPusAfsgcuCfaUfAfuucuCfuCfgaaugsusa		UACAUUCGAGAGAAUAUGAGCUG	
AD-1736337	asusgcauUfuUfCfUfgaaaaugusasa		VPusUfsacaUfuUfUfcagaAfaAfugcausasc		GUAUGCAUUUUCUGAAAAUGUAU	
AD-1736338	gsusuucgAfcCfAfAfguaucccasasa		VPusUfsuggGfaUfAfcuugGfuCfgaaacsusu		AAGUUUCGACCAAGUAUCCCAAA	
AD-1736339	uscsuugcUfuGfCfCfacaauaucsgsa		VPusCfsgauAfuUfGfuggcAfaGfcaagasusa		UAUCUUGCUUGCCACAAUAUCGG	
AD-1736340	gsgsguacAfaGfAfGfggaauacasasa		VPusUfsuguAfuUfCfccucUfuGfuaccsgsa		UCGGGUACAAGAGGGAAUACAAA	
AD-1736341	gsgsugauCfaAfAfUfccugugucsusa		VPusAfsgacAfcAfGfgauuUfgAfucaccsusg		CAGGUGAUCAAAUCCUGUGUCUC	
AD-1736342	csasguggGfuUfUfCfuaggauagsgsa		VPusCfscuaUfcCfUfagaaAfcCfcacugsusc		GACAGUGGGUUUCUAGGAUAGGU	
AD-1736343	asascuaaGfuAfUfUfuuuaaggascsa		VPusGfsuccUfuAfAfaaauAfcUfuaguusasc		GUAACUAAGUAUUUUUAAGGACA	
AD-1736344	csasuaauGfuGfAfUfuguuaaaususa		VPusAfsauuUfaAfCfaaucAfcAfuuaugsgsg		CCCAUAAUGUGAUUGUUAAAUUU	
AD-1736345	gsasgaagAfaUfUfAfagaaaacuscsa		VPusGfsaguUfuUfCfuuaaUfuCfuucucsasa		UUGAGAAGAAUUAAGAAAACUCU	
AD-1736346	gsasagagAfaAfUfUfgauuguuusasa		VPusUfsaaaCfaAfUfcaauUfuCfucuucsusc		GAGAAGAGAAAUUGAUUGUUUAU	
AD-1736347	asgsugugAfaAfCfUfugugccausasa		VPusUfsaugGfcAfCfaaguUfuCfacacususu		AAAGUGUGAAACUUGUGCCAUAG	
AD-1736348	csusgagaCfaCfUfGfagaaaguguscsa		VPusGfsacaUfuUfCfucagUfgUfcucagsgsa		UCCUGAGACACUGAGAAAUGUCC	
AD-1736349	usgsgcuuAfuAfUfGfuguuuaaasgsa		VPusCfsuuuAfaAfCfacauAfuAfagccasasu		AUUGGCUUAUAUGUGUUUAAAGA	
AD-1736350	usgscauuUfuGfAfCfauugcaaasasa		VPusUfsuuuGfcAfAfugucAfaAfaugcasasu		AUUGCAUUUUGACAUUGCAAAAC	
AD-1736351	ususagguUfaGfAfAfguuccagasasa		VPusUfsucuGfgAfAfcuucUfaAfccuaasusg		CAUUAGGUUAGAAGUUCCAGAAU	

Duplex Name	Antisense 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-1736352	usgscgacAfuGfAfAfaacaucc ususa		VPusAfsaggAfuGfUfuuucAfuGfucg casgsc		GCUGCGACAUGAAAACAUCC UUG	
AD-1736353	gsasgaggAfuUfUfUfuuaccau csusa		VPusAfsgauGfgUfAfaaaaAfuCfcuc ucsusu		AAGAGAGGAUUUUUUACCAU CUC	
AD-1736354	gsasagguGfaAfGfAfgaauuuc asasa		VPusUfsugaAfaUfUfUfcucuUfcAfccu ucscsa		UGGAAGGUGAAGAGAAUUUC AAA	
AD-1736355	usgsguauCfuGfAfAfuaucaug asasa		VPusUfsucaUfgAfUfauucAfgAfuac casgsc		GCUGGUAUCUGAAUAUCAUG AAC	
AD-1736356	usgsuuggUfuUfAfAfauuuuuca ascsa		VPusGfsuugAfaAfAfauuaAfaCfcaa casusg		CAUGUUGGUUUAAUUUUUCA ACC	
AD-1736357	usasguugUfaAfUfUfUfaaaugu gsgsa		VPusCfscacAfuUfUfUfaaauUfaCfaacu ascsu		AGUAGUUGUAAUUUAAAUGU GGA	
AD-1736358	gsusgaauGfuUfUfUfUfugccauu ususa		VPusAfsaaaUfgGfCfaaaaAfcAfuuc acsasu		AUGUGAAUGUUUUUGCCAUU UUU	
AD-1736359	csasgagaUfgAfUfUfUfuuucuuu usasa		VPusUfsaaaAfgAfAfaaauCfaUfcuc ugscsc		GGCAGAGAUGAUUUUUCUUU UAA	
AD-1736360	asgsaaaaUfuAfGfAfUfuucagau csusa		VPusAfsgauCfuGfAfaucuAfaUfuuu cusgsu		ACAGAAAAUUAGAUUCAGAU CUC	
AD-1736361	ascsugga AfaAfUfUfUfaagaaag usasa		VPusUfsacuUfuCfUfuaauUfuUfcca gusgsg		CCACUGGAAAAUUAAGAAAG UAG	
AD-1736362	usasaaguGfgGfAfAfagauaau asasa		VPusUfsuauUfaUfCfuuucCfcAfcuu uascsa		UGUAAAGUGGGAAAGAUAAU AAA	
AD-1736363	csusaggcUfaAfGfAfaagagu gsusa		VPusAfscaaCfuCfUfuucuUfaGfccu agsusu		AACUAGGCUAAGAAAGAGUU GUA	
AD-1736364	gscsugauAfaAfAfUfUfuaaugga usasa		VPusUfsaucCfaUfUfUfaauuUfuAfuca gcsasc		GUGCUGAUAAAAUUAAUGGA UAA	
AD-1736365	cscsuguaUfuUfCfUfuuaguug uscsa		VPusGfsacaAfcUfAfaagaAfaUfaca ggsasa		UUCCUGUAUUUCUUUAGUUG UCG	
AD-1736366	ususuguuUfuGfCfUfuuugaca asasa		VPusUfsuugUfcAfAfaagcAfaAfaca aasgsc		GCUUUGUUUUGCUUUUGACA AAC	
AD-1736367	usgsgcugUfgAfAfAfauauucu cscsa		VPusGfsgagAfaUfAfuuuuCfaCfagc cascsa		UGUGGCUGUGAAAAUAUUCU CCU	
AD-	ascsuauuUfuAfGfGfcauagca		VPusAfsgugCfuAfUfgccuAfaAfaua		GCACUAUUUUAGGCAUAGCA	

Duplex Name	Antisense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
1736368	csusa		gusgsc		CUU	
AD-1736369	ususucagUfaCfUfGfuauaaag usgsa		VPusCfsacuUfuAfUfacagUfaCfuga aasasu		AUUUUCAGUACUGUAUAAAG UGG	
AD-1736370	gsusgaugCfaAfUfCfuauguuu cscsa		VPusGfsgaaAfcAfUfagauUfgCfauc acscsu		AGGUGAUGCAAUCUAUGUUU CCC	
AD-1736371	usgsuuugGfcAfGfAfucucauc asasa		VPusUfsugaUfgAfGfaucuGfcCfaaa casusu		AAUGUUUGGCAGAUCUCAUC AAU	
AD-1736372	asasgguuGfuUfUfGfugaccag asasa		VPusUfsucuGfgUfCfacaaAfcAfacc uususc		GAAAGGUUGUUUGUGACCAG AAG	
AD-1736373	gsgsaaggAfaAfUfAfuuuugag asasa		VPusUfsucuCfaAfAfauauUfuCfcuu ccsusu		AAGGAAGGAAAUAUUUUGAG AAU	
AD-1736374	ususuuggUfaGfCfGfugacucu uscsa		VPusGfsaagAfgUfCfacgcUfaCfcaaa asgsa		UCUUUUGGUAGCGUGACUCU UCU	
AD-1736375	usgsaacaGfgAfAfAfagaugua asasa		VPusUfsuuaCfaUfCfuuuuCfcUfguu casusu		AAUGAACAGGAAAAGAUGUA AAA	
AD-1736376	gsgsgaacCfaAfGfAfgguauau gsgsa		VPusCfscauAfuAfCfcucuUfgGfuuc ccsasc		GUGGGAACCAAGAGGUAUAU GGC	
AD-1736377	usgsgcacUfaGfGfUfccaaauc ususa		VPusAfsagaUfuUfUfGfgaccUfaGfugc casgsu		ACUGGCACUAGGUCCAAAUC UUG	
AD-1736378	csascaccUfuCfAfUfauggaga ususa		VPusAfsaucUfcCfAfuaugAfaGfgug ugscsc		GGCACACCUUCAUAUGGAGA UUG	
AD-1736379	csusgguuUfaCfUfGfggaaaua gscsa		VPusGfscuaUfuUfCfccagUfaAfacc agsasc		GUCUGGUUUACUGGGAAAUA GCC	
AD-1736380	gscsccaaAfgGfAfAfuguauau asasa		VPusUfsuauAfuAfCfauucCfuUfugg gcscsu		AGGCCCAAAGGAAUGUAUAU AAG	
AD-1736381	ususaacuGfcAfAfGfaguuuac usgsa		VPusCfsaguAfaAfCfucuuGfcAfguu aasasa		UUUUAACUGCAAGAGUUUAC UGU	
AD-1736382	gsasaccaCfuCfUfCfugagugca sasa		VPusUfsugcAfcUfCfagagAfgUfggu ucscsu		AGGAACCACUCUCUGAGUGC AAU	
AD-1736383	ususaucuUfuUfCfAfuccuggc asusa		VPusAfsugcCfaGfGfaugaAfaAfgau aasasg		CUUUAUCUUUUCAUCCUGGC AUU	
AD-1736384	gsusgaguGfuUfGfGfuaugcca ascsa		VPusGfsuugGfcAfUfaccaAfcAfcuc acsgsc		GCGUGAGUGUUGGUAUGCCA ACG	

Duplex Name	Antisense 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-1736385	asgsaaugUfaUfUfUfggcuaaa usasa		VPusUfsauuUfaGfCfcaaaUfaCfauu cuscsa		UGAGAAUGUAUUUGGCUAAA UAA	
AD-1736386	gsasacccUfuUfUfAfuuaagag gsasa		VPusUfsccuCfuUfAfauaaAfaGfggu ucscsa		UGGAACCCUUUUAUUAAGAG GAG	
AD-1736387	csusccugUfcCfAfUfagcugcg asusa		VPusAfsucgCfaGfCfuaugGfaCfagg agsgsc		GCCUCCUGUCCAUAGCUGCG AUG	
AD-1736388	ascsugagUfuGfAfAfauaagga asgsa		VPusCfsuucCfuUfAfuuucAfaCfuca gusasa		UUACUGAGUUGAAAUAAGGA AGG	
AD-1736389	csusgccaAfaCfAfGfaaggagca susa		VPusAfsugcUfcCfUfucugUfuUfggc agsgsu		ACCUGCCAAACAGAAGGAGC AUG	
AD-1736390	gsgscaaaGfuUfGfUfgaagcac uscsa		VPusGfsaguGfcUfUfUfcacaAfcUfuug ccsasc		GUGGCAAAGUUGUGAAGCAC UCC	
AD-1736391	asusaggaUfgAfUfGfaaguuua gsasa		VPusUfscuaAfaCfUfucauCfaUfccu aususu		AAAUAGGAUGAUGAAGUUUA GAG	
AD-1736392	asusucguAfuCfUfUfaaaaugg csasa		VPusUfsgccAfuUfUfuaagAfuAfcga ausasc		GUAUUCGUAUCUUAAAAUGG CAC	
AD-1736393	csascagcUfuGfGfGfuaauagc gsusa		VPusAfscgcUfaUfUfUfacccAfaGfcug ugscsu		AGCACAGCUUGGGUAAUAGC GUU	
AD-1736394	ususugcaAfcAfAfCfauaacac usgsa		VPusCfsaguGfuUfAfuguuGfuUfgca aasasa		UUUUUGCAACAACAUAACAC UGC	
AD-1736395	usgsccacCfaUfGfUfgacuuau usgsa		VPusCfsaauAfaGfUfUfcacaUfgGfugg casasa		UUUGCCACCAUGUGACUUAU UGG	
AD-1736396	uscsgauaGfaGfGfAfaaugaga asasa		VPusUfsuucUfcAfUfuuccUfcUfauc gasgsg		CCUCGAUAGAGGAAAUGAGA AAG	
AD-1736397	ususuuuaAfgUfUfAfgcaggac ususa		VPusAfsaguCfcUfGfcuaaCfuUfaaa aasgsg		CCUUUUUAAGUUAGCAGGAC UUU	
AD-1736398	usgsuaaaUfaAfUfUfaucugcc usasa		VPusUfsaggCfaGfAfuaauUfaUfuua casusc		GAUGUAAAUAAUUAUCUGCC UAA	
AD-1736399	usgsguugUfaCfGfUfgccucaa asusa		VPusAfsuuuGfaGfGfcacgUfaCfaac casusa		UAUGGUUGUACGUGCCUCAA AUA	
AD-1736400	cscsacacUfgAfCfUfagagccaa scsa		VPusGfsuugGfcUfCfuaguCfaGfugu ggsgsc		GCCCACACUGACUAGAGCCA ACC	

Table 8. Unmodified Sense and Antisense Strand Sequences of PLIN1 dsRNA Agents Comprising anUnsaturated C22 Hydrocarbon Chain Conjugated to Position 6 on the Sense Strand, Counting from the 5'-end of the Sense Strand

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002666.5	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002666.5
AD-1735051	CAUCUCUUUAACCAAACUUGA		1995-2015	UCAAGUUUGGUUAAAGAGAUGAA		1993-2015
AD-1735052	CUCUAACAAAUAAACAGAACA		1740-1760	UGUUCUGUUUAUUUGUUAGAGAA		1738-1760
AD-1735053	UGCAUAGUCACUCUUUUGAUA		2390-2410	UAUCAAAAGAGUGACUAUGCAGG		2388-2410
AD-1735054	AACUUGAUUUUUCAUCUCUUA		1983-2003	UAAGAGAUGAAAAAUCAAGUUAG		1981-2003
AD-1735055	GACACAUUCUUAGCACUGAAA		2128-2148	UUUCAGUGCUAAGAAUGUGUCAA		2126-2148
AD-1735056	ACGCCUUAUUUGAUUUAACUA		2807-2827	UAGUUAAAUCAAAUAAGGCGUAU		2805-2827
AD-1735057	UAGUCUUCGAAAUGUUAAUAA		2474-2494	UUAUUAACAUUUCGAAGACUAGG		2472-2494
AD-1735058	GAUGGACUUUUAAGUUGUUUA		2838-2858	UAAACAACUUAAAAGUCCAUCAU		2836-2858
AD-1735059	UGCUUUUUUCACUUAAUAAUA		2702-2722	UAUUAUUAAGUGAAAAAAGCAGG		2700-2722
AD-1735060	ACAUAAUAACUACUGCAUAAA		2780-2800	UUUAUGCAGUAGUUAUUAUGUGG		2778-2800
AD-1735061	UACUAGUGUCACUUUCUGAGA		2271-2291	UCUCAGAAAGUGACACUAGUAUU		2269-2291
AD-1735062	CAAUCAGAUGCAAAAGCUCUA		2234-2254	UAGAGCUUUUGCAUCUGAUUGUU		2232-2254
AD-1735063	UAAGAGUAAUUGCCUAACUUA		1968-1988	UAAGUUAGGCAAUUACUCUUAUA		1966-1988
AD-1735064	GGCUUGUUUAUGAACAUUAAA		82-102	UUUAAUGUUCAUAAACAAGCCAU		80-102
AD-1735065	UUUUUGCUACUGCAAACGAUA		2871-2891	UAUCGUUUGCAGUAGCAAAAAAG		2869-2891

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002666.5	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002666.5
AD-1735066	AACGAUGCUAUAAUAAAUGUA		2885-2905	UACAUUUAUUAUAGCAUCGUUUG		2883-2905
AD-1735067	UGGUUGUUACUAUAAGAGUAA		1956-1976	UUACUCUUAUAGUAACAACCAAG		1954-1976
AD-1735068	CUGAUGAACAUCCUCUGAUGA		2181-2201	UCAUCAGAGGAUGUUCAUCAGAG		2179-2201
AD-1735069	CUGCGGAUAAAAUAUUUGCCAA		2059-2079	UUGGCAAAUAUUUAUCCGCAGAG		2057-2079
AD-1735070	CCAAAAUUCAGAUUCUGCCUA		2039-2059	UAGGCAGAAUCUGAAUUUUGGAA		2037-2059
AD-1735071	AAGGAUGUGUGUCUUUCUCCA		2547-2567	UGGAGAAAGACACACAUCCUUUU		2545-2567
AD-1735072	UGCGAAUGCUUCCAGAAGACA		231-251	UGUCUUCUGGAAGCAUUCGCAGG		229-251
AD-1735073	CGAAUGAGUAACUCCUGUCAA		2079-2099	UUGACAGGAGUUACUCAUUCGUG		2077-2099
AD-1735074	UGGGUGUUUAUUUAAAAUACA		2254-2274	UGUAUUUUAAAUAAACACCCAAG		2252-2274
AD-1735075	CAAAAGAUAUUUGACCGUUUA		2019-2039	UAAACGGUCAAAUAUCUUUUGGC		2017-2039
AD-1735076	AUACAGCUUGGAGAGAUUUUA		2720-2740	UAAAAUCUCUCCAAGCUGUAUUA		2718-2740
AD-1735077	AAAUGCAUUCAUACAAUUACA		2509-2529	UGUAAUUGUAUGAAUGCAUUUUC		2507-2529
AD-1735078	UCCCACUCGCUCUUUUUGAUA		2756-2776	UAUCAAAAAGAGCGAGUGGGAUU		2754-2776
AD-1735079	GCUUGUGUUUACACAAGCUGA		2664-2684	UCAGCUUGUGUAAACACAAGCGG		2662-2684
AD-1735080	CCUGCCUUACAUGGCUUGUUA		70-90	UAACAAGCCAUGUAAGGCAGGUG		68-90
AD-1735081	GAGAUUUUUGUAUCACAUUAA		2732-2752	UUAAUGUGAUACAAAAAUCUCUC		2730-2752
AD-	AGCACUUCAGACAAGGUCCUA		540-560	UAGGACCUUGUCUGAAGUGCUCG		538-560

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002666.5	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002666.5
1735082						
AD-1735083	UCACUCUCAGAGCCAGUUUUA		1895-1915	UAAAACUGGCUCUGAGAGUGAAG		1893-1915
AD-1735084	ACUGAACUCCUCUGUGAUCUA		2142-2162	UAGAUCACAGAGGAGUUCAGUGC		2140-2162
AD-1735085	UAGUUCCCUAAUGAUGGACUA		2826-2846	UAGUCCAUCAUUAGGGAACUAGU		2824-2846
AD-1735086	GGCGUUACUGACAACGUGGUA		1296-1316	UACCACGUUGUCAGUAACGCCCU		1294-1316
AD-1735087	UGAUCUAGGAUGAUCUGUUCA		2156-2176	UGAACAGAUCAUCCUAGAUCACA		2154-2176
AD-1735088	GUGAUGAUAUAUAGACUUUAA		2427-2447	UUAAAGUCUAUAUAUCAUCACCA		2425-2447
AD-1735089	GGCUACUUUGAAGGGAACAAA		2217-2237	UUUGUUCCCUUCAAAGUAGCCUG		2215-2237
AD-1735090	CUGCUCUGAUUCUAUGGCUUA		1937-1957	UAAGCCAUAGAAUCAGAGCAGGC		1935-1957
AD-1735091	AGAUUGCUUCUGAGCUGAAGA		463-483	UCUUCAGCUCAGAAGCAAUCUUU		461-483
AD-1735092	GCCAUCUCUUGUGUAUGCAGA		2607-2627	UCUGCAUACACAAGAGAUGGCAC		2605-2627
AD-1735093	AGCCACAUUUCCAUUUGCAUA		2354-2374	UAUGCAAAUGGAAAUGUGGCUGU		2352-2374
AD-1735094	UCCAGACAGAAGGUUUUGACA		2111-2131	UGUCAAAACCUUCUGUCUGGACC		2109-2131
AD-1735095	CUCUCGAUACACCGUGCAGAA		818-838	UUCUGCACGGUGUAUCGAGAGAG		816-838
AD-1735096	GGCGCACUUUUUAUUUUUAUA		1838-1858	UAUAAAAAUAAAAAGUGCGCCUU		1836-1858
AD-1735097	GAGCGUUGCCACUUUCAAAGA		1775-1795	UCUUUGAAAGUGGCAACGCUCGC		1773-1795
AD-1735098	UUGCAUCAUUACUGCCUUCAA		2368-2388	UUGAAGGCAGUAAUGAUGCAAAU		2366-2388

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002666.5	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002666.5
AD-1735099	GCGCAAGAAGAGCUGAGUCGA		1685-1705	UCGACUCAGCUCUUCUUGCGCAG		1683-1705
AD-1735100	UGCGGAAUUUGCUGCCAACAA		611-631	UUGUUGGCAGCAAAUUCCGCAGU		609-631
AD-1735101	GUGUGCAAUGCCUAUGAGAAA		291-311	UUUCUCAUAGGCAUUGCACACAG		289-311
AD-1735102	GAAUUCAAAUAUUGCAAAAGA		2530-2550	UCUUUUGCAAUAUUUGAAUUCUG		2528-2550
AD-1735103	CCUGUGUGCUUUGUAGAGCCA		2320-2340	UGGCUCUACAAAGCACACAGGCC		2318-2340
AD-1735104	UCCAGACAAGGAAGAGUCAGA		710-730	UCUGACUCUUCCUUGUCUGGAGG		708-730
AD-1735105	UGCCAGAAACAGCAUCAGCGA		509-529	UCGCUGAUGCUGUUUCUGGCACU		507-529
AD-1735106	GCAUAAUAUGGAUACGCCUUA		2794-2814	UAAGGCGUAUCCAUAUUAUGCAG		2792-2814
AD-1735107	AGCCUCAUCCUGAUGAUGCUA		1813-1833	UAGCAUCAUCAGGAUGAGGCUGA		1811-1833
AD-1735108	AAGCCUCUUGAGCAGGGUUGA		779-799	UCAACCCUGCUCAAGAGGCUUGG		777-799
AD-1735109	UAAAGGGAAGAAGUUGAAGCA		99-119	UGCUUCAACUUCUUCCCUUUAAU		97-119
AD-1735110	GGCAGCAUUGAGAAAGGUGGUA		675-695	UACCACCUUCUCAAUGCUGCCCA		673-695
AD-1735111	GUCAGCGACAGCUUCUUCCGA		1617-1637	UCGGAAGAAGCUGUCGCUGACCC		1615-1637
AD-1735112	CUGCUGUCUCCUCAACCAAGA		1243-1263	UCUUGGUUGAGGAGACAGCAGGG		1241-1263
AD-1735113	AGGAGGAAGAAUUGGAGACUA		1054-1074	UAGUCUCCAAUUCUUCCUCCUCC		1052-1074
AD-1735114	CCUGUCACCACUCUGAAGGUA		2092-2112	UACCUUCAGAGUGGUGACAGGAG		2090-2112
AD-	AGACUUUAUGUAUAGCCACAA		2439-2459	UUGUGGCUAUACAUAAAGUCUAU		2437-2459

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002666.5	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002666.5
1735115						
AD-1735116	GUUACGCAUGCCUGCUUUUUA		2690-2710	UAAAAAGCAGGCAUGCGUAACAC		2688-2710
AD-1735117	CCAGUUCACAGCUGCCAAUGA		377-397	UCAUUGGCAGCUGUGAACUGGGU		375-397
AD-1735118	CAGGCACGUGUGUAUGCACUA		2640-2660	UAGUGCAUACACACGUGCCUGCA		2638-2660
AD-1735119	AUGGCAGUCAACAAAGGCCUA		132-152	UAGGCCUUUGUUGACUGCCAUCC		130-152
AD-1735120	CAAACUUGUGGCCAAAAGAUA		2007-2027	UAUCUUUUGGCCACAAGUUUGGU		2005-2027
AD-1735121	UCUGACCAACACCCUCUCUCA		803-823	UGAGAGAGGGUGUUGGUCAGAGC		801-823
AD-1735122	UCACAUUAUAAAUCCCACUCA		2744-2764	UGAGUGGGAUUUAUAAUGUGAUA		2742-2764
AD-1735123	GAGGAGAACAAGUUCAGUGAA		1074-1094	UUCACUGAACUUGUUCUCCUCAG		1072-1094
AD-1735124	GAGCAGGAGAAUGUGCUGCAA		177-197	UUGCAGCACAUUCUCCUGCUCAG		175-197
AD-1735125	GAAGACCUACACCAGCACUAA		245-265	UUAGUGCUGGUGUAGGUCUUCUG		243-265
AD-1735126	AGGCCUCACCUUGCUGGAUGA		146-166	UCAUCCAGCAAGGUGAGGCCUUU		144-166
AD-1735127	AGCCAGCUGCUUGCUCACAGA		2336-2356	UCUGUGAGCAAGCAGCUGGCUCU		2334-2356
AD-1735128	GGGCUCUGUGAGACUGAGGUA		13-33	UACCUCAGUCUCACAGAGCCCAG		Nov-33
AD-1735129	CGAGAGCGAAUUCCGGGACAA		1367-1387	UUGUCCCGGAAUUCGCUCUCGGG		1365-1387
AD-1735130	GUGGCACAUACCCUGCAGAAA		1134-1154	UUUCUGCAGGGUAUGUGCCACAC		1132-1154
AD-1735131	GUGGACACAGUGGUGCAUUAA		1314-1334	UUAAUGCACCACUGUGUCCACCA		1312-1334

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002666.5	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002666.5
AD-1735132	AAGCCCAGAAGUCUCCCAAGA		751-771	UCUUGGGAGACUUCUGGGCUUGC		749-771
AD-1735133	GGCCAUGUCCCUAUCAGAUGA		1268-1288	UCAUCUGAUAGGGACAUGGCCCU		1266-1288
AD-1735134	GCCGGCGGGUUUCUCUAACAA		1728-1748	UUGUUAGAGAAACCCGCCGGCCC		1726-1748
AD-1735135	CUGAAGGACACCAUCUCCACA		477-497	UGUGGAGAUGGUGUCCUUCAGCU		475-497
AD-1735136	GACCACCAUCUCGGCUGUGAA		1163-1183	UUCACAGCCGAGAUGGUGGUCUG		1161-1183
AD-1735137	CCAGUUUUUAAGGGACACCAA		1907-1927	UUGGUGUCCCUUAAAAACUGGCU		1905-1927
AD-1735138	GGCCAGAGACACUGCGGAAUA		599-619	UAUUCCGCAGUGUCUCUGGCCAC		597-619
AD-1735139	CGUUCCCAUCGCGAGCACUUA		527-547	UAAGUGCUCGCGAUGGGAACGCU		525-547
AD-1735140	CCGGGACAUCGACAACCCACA		1379-1399	UGUGGGUUGUCGAUGUCCCGGAA		1377-1399
AD-1735141	UCUGAUGAUCUAGGCUCCCAA		2194-2214	UUGGGAGCCUAGAUCAUCAGAGG		2192-2214
AD-1735142	CUGCAGAAGACCCUCCAGACA		1146-1166	UGUCUGGAGGGUCUUCUGCAGGG		1144-1166
AD-1735143	CGCCAGUAGCUUGGCUGCCUA		323-343	UAGGCAGCCAAGCUACUGGCGCU		321-343
AD-1735144	CGCUUCACAGGCUGAGUCCAA		2298-2318	UUGGACUCAGCCUGUGAAGCGGC		2296-2318
AD-1735145	UUUUUUUAGCAUCCUUUUGGA		1871-1891	UCCAAAAGGAUGCUAAAAAAAAA		1869-1891
AD-1735146	GAAGCCAAAGCGCAGGGUCAA		1601-1621	UUGACCCUGCGCUUUGGCUUCUC		1599-1621
AD-1735147	GAGGAGGAUCAUGAGGACCAA		1005-1025	UUGGUCCUCAUGAUCCUCCUCCU		1003-1025
AD-	GCACGCAUUACAGCCAGCUGA		1666-1686	UCAGCUGGCUGUAAUGCGUGCGG		1664-1686

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002666.5	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002666.5
1735148						
AD-1735149	CUUCAUUGAAAACCACCACGA		2585-2605	UCGUGGUGGUUUUCAAUGAAGGG		2583-2605
AD-1735150	UUUUUGAUGGCCACAUAAUAA		2768-2788	UUAUUAUGUGGCCAUCAAAAAGA		2766-2788
AD-1735151	CCACCUGGAGGAAAAGAUCCA		419-439	UGGAUCUUUUCCUCCAGGUGGUC		417-439
AD-1735152	CAAGGCCAAGCCAAGCCUCUA		767-787	UAGAGGCUUGGCUUGGCCUUGGG		765-787
AD-1735153	GAGGACCAGACAGACACGGAA		1017-1037	UUCCGUGUCUGUCUGGUCCUCAU		1015-1037
AD-1735154	GAUGCCCUGAAGGGCGUUACA		1284-1304	UGUAACGCCCUUCAGGGCAUCUG		1282-1304
AD-1735155	CCAACACUCGAGCUGGCCGAA		625-645	UUCGGCCAGCUCGAGUGUUGGCA		623-645
AD-1735156	CAGGGCUAUGCACCUGCAGGA		2624-2644	UCCUGCAGGUGCAUAGCCCUGCA		2622-2644
AD-1735157	AAGGUGGUGGAGUACCUCCUA		687-707	UAGGAGGUACUCCACCACCUUCU		685-707
AD-1735158	UUGAAGCUUGAGGAGCGAGGA		112-132	UCCUCGCUCCUCAAGCUUCAACU		110-132
AD-1735159	CGUGGCCAUGUGGAUCCCAGA		869-889	UCUGGGAUCCACAUGGCCACGGU		867-889
AD-1735160	CAGCACUAAGGAAGCCCACCA		257-277	UGGUGGGCUUCCUUAGUGCUGGU		255-277
AD-1735161	GUCGCUGAUGGAGCCCGAGAA		1352-1372	UUCUCGGGCUCCAUCAGCGACAG		1350-1372
AD-1735162	UUCUUCCGGCCCAGCGUCAUA		1629-1649	UAUGACGCUGGGCCGGAAGAAGC		1627-1649
AD-1735163	CUGCUCCUGGACACCAGCAAA		733-753	UUUGCUGGUGUCCAGGAGCAGGG		731-753
AD-1735164	UUUCUGAGUACCCGCCGCUUA		2283-2303	UAAGCGGCGGGUACUCAGAAAGU		2281-2303

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002666.5	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002666.5
AD-1735165	CGCAGGCUGUCCACCCAGUUA		363-383	UAACUGGGUGGACAGCCUGCGGA		361-383
AD-1735166	GGCUGUGACACAUGGGCACCUGA		1175-1195	UCAGGUGCCCAUGUCACAGCCGA		1173-1195
AD-1735167	UCAGUGAGGUAGCAGCCCUGA		1087-1107	UCAGGGCUGCUACCUCACUGAAC		1085-1107
AD-1735168	AGCGUCAUGGAGCCCAUCCUA		1641-1661	UAGGAUGGGCUCCAUGACGCUGG		1639-1661
AD-1735169	CUGGAUGGAGACCUCCCUGAA		159-179	UUCAGGGAGGUCUCCAUCCAGCA		157-179
AD-1735170	UCAGCCGGAGUGAGUGUUGGA		38-58	UCCAACACUCACUCCGGCUGACC		36-58
AD-1735171	CUGGCCGACUGGCUUCUGGAA		637-657	UUCCAGAAGCCAGUCGGCCAGCU		635-657
AD-1735172	GGUGCUGCACCUCACACCAGA		1220-1240	UCUGGUGUGAGGUGCAGCACCCU		1218-1240
AD-1735173	GGCUGCCUGGAGCAUGGAGCA		335-355	UGCUCCAUGCUCCAGGCAGCCAA		333-355
AD-1735174	CCUGCAGCUGUGCUGGGCAUA		1191-1211	UAUGCCCAGCACAGCUGCAGGUG		1189-1211
AD-1735175	AGUGGCCAUGCAGGCGGUGUA		929-949	UACACCGCCUGCAUGGCCACUGA		927-949
AD-1735176	GACUUGGCCUUGGGCAGCAUA		663-683	UAUGCUGCCCAAGGCCAAGUCGG		661-683
AD-1735177	GAGCGAAGUGCGGGUACCCUA		959-979	UAGGGUACCCGCACUUCGCUCCU		957-979
AD-1735178	CUGGUGGCCUCUGUGUGCAAA		279-299	UUUGCACACAGAGGCCACCAGGG		277-299
AD-1735179	AACCCACCAGCCGAGGUCGAA		1392-1412	UUCGACCUCGGCUGGUGGGUUGU		1390-1412
AD-1735180	UGAUGCUGCCAAGGCGCACUA		1826-1846	UAGUGCGCCUUGGCAGCAUCAUC		1824-1846
AD-	CCAAUGAGCUGGCCUGCCGAA		391-411	UUCGGCAGGCCAGCUCAUUGGCA		389-411

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002666.5	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002666.5
1735181						
AD-1735182	GUGCUGCAGCGGGUCCUGCAA		189-209	UUGCAGGACCCGCUGCAGCACAU		187-209
AD-1735183	GGGCGUGCAGAGCGCCAGUAA		311-331	UUACUGGCGCUCUGCACGCCCUU		309-331
AD-1735184	GGUGAGUGGCACCUGCGAAUA		218-238	UAUUCGCAGGUGCCACUCACCAC		216-238
AD-1735185	ACGGAGGGAGAGGACACGGAA		1032-1052	UUCCGUGUCCUCUCCCUCCGUGU		1030-1052

Table 9. Modified Sense and Antisense Strand Sequences of PLIN1 dsRNA Agents Comprising anUnsaturated C22 Hydrocarbon Chain Conjugated to Position 6 on the Sense Strand, Counting from the 5'-end of the Sense Strand

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-1735051	csasucu(Cda)UfuUfAfAfccaaacuusgsa		VPusCfsaagUfuUfGfguuaAfaGfagaugsasa		UUCAUCUCUUUAACCAAACUUGU	
AD-1735052	csuscua(Ada)CfaAfAfUfaaacagaascsa		VPusGfsuucUfgUfUfuauuUfgUfuagagsasa		UUCUCUAACAAAUAAACAGAACC	
AD-1735053	usgscau(Ada)GfuCfAfCfucuuuugasusa		VPusAfsucaAfaAfGfagugAfcUfaugcasggg		CCUGCAUAGUCACUCUUUUGAUG	
AD-1735054	asascuu(Gda)AfuUfUfUfucaucucususa		VPusAfsagaGfaUfGfaaaaAfuCfaaguusasg		CUAACUUGAUUUUUCAUCUCUUU	
AD-1735055	gsascac(Ada)UfuCfUfUfagcacugasasa		VPusUfsucaGfuGfCfuaagAfaUfgugucsasa		UUGACACAUUCUUAGCACUGAAC	
AD-1735056	ascsgcc(Uda)UfaUfUfUfgauuuaacsusa		VPusAfsguuAfaAfUfcaaaUfaAfggcgusasu		AUACGCCUUAUUUGAUUUAACUA	
AD-1735057	usasguc(Uda)UfcGfAfAfauguuaausasa		VPusUfsauuAfaCfAfuuucGfaAfgacuasggg		CCUAGUCUUCGAAAUGUUAAUAU	
AD-1735058	gsasugg(Ada)CfuUfUfUfaaguuguususa		VPusAfsaacAfaCfUfuaaaAfgUfccaucsasu		AUGAUGGACUUUUAAGUUGUUUC	
AD-	usgscuu(Uda)UfuUfCfAfcuuaauaas		VPusAfsuuaUfuAfAfgugaAfaAfaagcasgs		CCUGCUUUUUUCACUUAAUA	

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:
1735059	usa		g		AUA	
AD-1735060	ascsaua(Ada)UfaAfCfUfacugcauasa		VPusUfsuauGfcAfGfuaguUfaUfuaugusgsg		CCACAUAAUAACUACUGCAUAAU	
AD-1735061	usascua(Gda)UfgUfCfAfcuuucugasgsa		VPusCfsucaGfaAfAfgugaCfaCfuaguasusu		AAUACUAGUGUCACUUUCUGAGU	
AD-1735062	csasauc(Ada)GfaUfGfCfaaaagcucsusa		VPusAfsgagCfuUfUfugcaUfcUfgauugsusu		AACAAUCAGAUGCAAAAGCUCUU	
AD-1735063	usasaga(Gda)UfaAfUfUfgccuaacususa		VPusAfsaguUfaGfGfcaauUfaCfucuuasusa		UAUAAGAGUAAUUGCCUAACUUG	
AD-1735064	gsgscuu(Gda)UfuUfAfUfgaacauuasasa		VPusUfsuaaUfgUfUfcauaAfaCfaagccsasu		AUGGCUUGUUUAUGAACAUUAAA	
AD-1735065	ususuuu(Gda)CfuAfCfUfgcaaacgasusa		VPusAfsucgUfuUfGfcaguAfgCfaaaaasasg		CUUUUUUGCUACUGCAAACGAUG	
AD-1735066	asascga(Uda)GfcUfAfUfaauaaaugsusa		VPusAfscauUfuAfUfuauaGfcAfucguususg		CAAACGAUGCUAUAAUAAAUGUC	
AD-1735067	usgsguu(Gda)UfuAfCfUfauaagagusasa		VPusUfsacuCfuUfAfuaguAfaCfaaccasasg		CUUGGUUGUUACUAUAAGAGUAA	
AD-1735068	csusgau(Gda)AfaCfAfUfccucugausgsa		VPusCfsaucAfgAfGfgaugUfuCfaucagsasg		CUCUGAUGAACAUCCUCUGAUGA	
AD-1735069	csusgcg(Gda)AfuAfAfAfAfuauuugccsasa		VPusUfsggcAfaAfUfauuuAfuCfcgcagsasg		CUCUGCGGAUAAAUAUUUGCCAC	
AD-1735070	cscsaaa(Ada)UfuCfAfGfauucugccsusa		VPusAfsggcAfgAfAfucugAfaUfuuuggsasa		UUCCAAAAUUCAGAUUCUGCCUC	
AD-1735071	asasgga(Uda)GfuGfUfGfucuuucucsusa		VPusGfsgagAfaAfGfacacAfcAfucccuusus		AAAAGGAUGUGUGUCUUUCUCCC	
AD-1735072	usgscga(Ada)UfgCfUfUfccagaagascsa		VPusGfsucuUfcUfGfgaagCfaUfucgcasgsg		CCUGCGAAUGCUUCCAGAAGACC	
AD-1735073	csgsaau(Gda)AfgUfAfAfcuccugucsasa		VPusUfsgacAfgGfAfguuaCfuCfauucgsusg		CACGAAUGAGUAACUCCUGUCAC	
AD-1735074	usgsggu(Gda)UfuUfAfUfuuaaaauassa		VPusGfsuauUfuUfAfaauaAfaCfacccasasg		CUUGGGUGUUUAUUUAAAAUACU	
AD-1735075	csasaaa(Gda)AfuAfUfUfugaccguususa		VPusAfsaacGfgUfCfaaauAfuCfuuuugsgsc		GCCAAAAGAUAUUUGACCGUUUC	
AD-1735076	asusaca(Gda)CfuUfGfGfagagauuususa		VPusAfsaaaUfcUfCfuccaAfgCfuguaususa		UAAUACAGCUUGGAGAGAUUUUU	

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-1735077	asasaug(Cda)AfuUfCfAfuacaauuasc sa		VPusGfsuaaUfuGfUfaugaAfuGfcauuusus c		GAAAAUGCAUUCAUACAAUU ACA	
AD-1735078	uscscca(Cda)UfcGfCfUfcuuuuugasu sa		VPusAfsucaAfaAfAfgagcGfaGfugggasus u		AAUCCCACUCGCUCUUUUUGA UG	
AD-1735079	gscsuug(Uda)GfuUfUfAfcacaagcus gsa		VPusCfsagcUfuGfUfguaaAfcAfcaagcsgsg		CCGCUUGUGUUUACACAAGC UGU	
AD-1735080	cscsugc(Cda)UfuAfCfAfuggcuugus usa		VPusAfsacaAfgCfCfauguAfaGfgcaggsus g		CACCUGCCUUACAUGGCUUGU UU	
AD-1735081	gsasgau(Uda)UfuUfGfUfaucacauus asa		VPusUfsaauGfuGfAfuacaAfaAfaucucsusc		GAGAGAUUUUUGUAUCACAU UAU	
AD-1735082	asgscac(Uda)UfcAfGfAfcaagguccsu sa		VPusAfsggaCfcUfUfgucuGfaAfgugcuscs g		CGAGCACUUCAGACAAGGUCC UG	
AD-1735083	uscsacu(Cda)UfcAfGfAfgccaguuus usa		VPusAfsaaaCfuGfGfcucuGfaGfagugasasg		CUUCACUCUCAGAGCCAGUUU UU	
AD-1735084	ascsuga(Ada)CfuCfCfUfcugugaucsu sa		VPusAfsgauCfaCfAfgaggAfgUfucagusgs c		GCACUGAACUCCUCUGUGAUC UA	
AD-1735085	usasguu(Cda)CfcUfAfAfugauggacs usa		VPusAfsgucCfaUfCfauuaGfgGfaacuasgsu		ACUAGUUCCCUAAUGAUGGA CUU	
AD-1735086	gsgscgu(Uda)AfcUfGfAfcaacguggs usa		VPusAfsccaCfgUfUfgucaGfuAfacgccscsu		AGGGCGUUACUGACAACGUG GUG	
AD-1735087	usgsauc(Uda)AfgGfAfUfgaucuguus csa		VPusGfsaacAfgAfUfcaucCfuAfgaucascsa		UGUGAUCUAGGAUGAUCUGU UCC	
AD-1735088	gsusgau(Gda)AfuAfUfAfuagacuuus asa		VPusUfsaaaGfuCfUfauauAfuCfaucacscsa		UGGUGAUGAUAUAUAGACUU UAU	
AD-1735089	gsgscua(Cda)UfuUfGfAfagggaacasa sa		VPusUfsuguUfcCfCfuucaAfaGfuagccsus g		CAGGCUACUUUGAAGGGAAC AAU	
AD-1735090	csusgcu(Cda)UfgAfUfUfcuauggcus usa		VPusAfsagcCfaUfAfgaauCfaGfagcgsgsc		GCCUGCUCUGAUUCUAUGGC UUG	
AD-1735091	asgsauu(Gda)CfuUfCfUfgagcugaas gsa		VPusCfsuucAfgCfUfcagaAfgCfaaucususu		AAAGAUUGCUUCUGAGCUGA AGG	
AD-1735092	gscscau(Cda)UfcUfUfGfguauugcas gsa		VPusCfsugcAfuAfCfacaaGfaGfauggcsasc		GUGCCAUCUCUUGUGUAUGC AGG	
AD-1735093	asgscca(Cda)AfuUfUfCfcauuugcasu sa		VPusAfsugcAfaAfUfggaaAfuGfuggcusgs u		ACAGCCACAUUUCCAUUUGCA UC	
AD-	uscscag(Ada)CfaGfAfAfggguuuugas		VPusGfsucaAfaAfCfcuucUfgUfcuggascsc		GGUCCAGACAGAAGGUUUUG	

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:
1735094	csa				ACA	
AD-1735095	csuscuc(Gda)AfuAfCfAfccgugcagsasa		VPusUfscugCfaCfGfguguAfuCfgagagsasg		CUCUCUCGAUACACCGUGCAGAC	
AD-1735096	gsgscgc(Ada)CfuUfUfUfUfuauuuuuas		VPusAfsuaaAfaAfUfaaaaAfgUfgcgccsusu		AAGGCGCACUUUUUUAUUUUUAUU	
AD-1735097	gsasgcg(Uda)UfgCfCfAfcuuucaaasg		VPusCfsuuuGfaAfAfguggCfaAfcgcucsgsc		GCGAGCGUUGCCACUUUCAAAGU	
AD-1735098	ususgca(Uda)CfaUfUfAfcugccuucsa		VPusUfsgaaGfgCfAfguaaUfgAfugcaasasu		AUUUGCAUCAUUACUGCCUUCAC	
AD-1735099	gscsgca(Ada)GfaAfGfAfgcugagucs		VPusCfsgacUfcAfGfcucuUfcUfugcgcsasg		CUGCGCAAGAAGAGCUGAGUCGC	
AD-1735100	usgscgg(Ada)AfuUfUfGfcugccaacs		VPusUfsguuGfgCfAfgcaaAfuUfccgcasgsu		ACUGCGGAAUUUGCUGCCAACAC	
AD-1735101	gsusgug(Cda)AfaUfGfCfcuaugagas		VPusUfsucuCfaUfAfggcaUfuGfcacacsasg		CUGUGUGCAAUGCCUAUGAGAAG	
AD-1735102	gsasauu(Cda)AfaAfUfAfuugcaaaasg		VPusCfsuuuUfgCfAfauauUfuGfaauucsusg		CAGAAUUCAAAUAUUGCAAAAGG	
AD-1735103	cscsugu(Gda)UfgCfUfUfuguagagcs		VPusGfsgcuCfuAfCfaaagCfaCfacaggscsc		GGCCUGUGUGCUUUGUAGAGCCA	
AD-1735104	uscscag(Ada)CfaAfGfGfgaagagucasg		VPusCfsugaCfuCfUfuccuUfgUfcuggasgsg		CCUCCAGACAAGGAAGAGUCAGC	
AD-1735105	usgscca(Gda)AfaAfCfAfgcaucagcsg		VPusCfsgcuGfaUfGfcuguUfuCfuggcascsu		AGUGCCAGAAACAGCAUCAGCGU	
AD-1735106	gscsaua(Ada)UfaUfGfGfgauacgccusu		VPusAfsaggCfgUfAfuccaUfaUfuaugcsasg		CUGCAUAAUAUGGAUACGCCUUA	
AD-1735107	asgsccu(Cda)AfuCfCfUfgaugaugcsua		VPusAfsgcaUfcAfUfcaggAfuGfaggcusgsa		UCAGCCUCAUCCUGAUGAUGCUG	
AD-1735108	asasgcc(Uda)CfuUfGfAfgcaggguus		VPusCfsaacCfcUfGfcucaAfgAfggcuusgsg		CCAAGCCUCUUGAGCAGGGGUUGG	
AD-1735109	usasaag(Gda)GfaAfGfAfaguugaags		VPusGfscuuCfaAfCfuucuUfcCfcuuuasasu		AUUAAAGGGAAGAAGUUGAAGCU	
AD-1735110	gsgscag(Cda)AfuUfGfAfgaagguggs		VPusAfsccaCfcUfUfcucaAfuGfcugccscsa		UGGGCAGCAUUGAGAAGGUGGUG	
AD-1735111	gsuscag(Cda)GfaCfAfGfcuucuuccsg		VPusCfsggaAfgAfAfgcugUfcGfcugacscsc		GGGUCAGCGACAGCUUCUUCCGG	

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-1735112	csusgcu(Gda)UfcUfCfCfucaaccaasg sa		VPusCfsuugGfuUfGfaggaGfaCfagcagsgs g		CCCUGCUGUCUCCUCAACCAA GG	
AD-1735113	asgsgag(Gda)AfaGfAfAfAfuuggagacs usa		VPusAfsgucUfcCfAfauucUfuCfcuccuscsc		GGAGGAGGAAGAAUUGGAGA CUG	
AD-1735114	cscsugu(Cda)AfcCfAfCfucugaaggsu sa		VPusAfsccuUfcAfGfagugGfuGfacaggsas g		CUCCUGUCACCACACUCUGAAGG UC	
AD-1735115	asgsacu(Uda)UfaUfGfUfauagccacsa sa		VPusUfsgugGfcUfAfuacaUfaAfagucusas u		AUAGACUUUAUGUAUAGCCA CAG	
AD-1735116	gsusuac(Gda)CfaUfGfCfcugcuuuus usa		VPusAfsaaaAfgCfAfggcaUfgCfguaacsasc		GUGUUACGCAUGCCUGCUUU UUU	
AD-1735117	cscsagu(Uda)CfaCfAfGfcugccaausg sa		VPusCfsauuGfgCfAfgcugUfgAfacuggsgs u		ACCCAGUUCACAGCUGCCAAU GA	
AD-1735118	csasggc(Ada)CfgUfGfUfguaugcacs usa		VPusAfsgugCfaUfAfcacaCfgUfgccugscsa		UGCAGGCACGUGUGUAUGCA CUC	
AD-1735119	asusggc(Ada)GfuCfAfAfcaaaggccsu sa		VPusAfsggcCfuUfUfguugAfcUfgccauscs c		GGAUGGCAGUCAACAAAGGC CUC	
AD-1735120	csasaac(Uda)UfgUfGfGfccaaaagasu sa		VPusAfsucuUfuUfGfgccaCfaAfguuugsgs u		ACCAAACUUGUGGCCAAAAG AUA	
AD-1735121	uscsuga(Cda)CfaAfCfAfcccucucusc sa		VPusGfsagaGfaGfGfguguUfgGfucagasgs c		GCUCUGACCAACACCCUCUCU CG	
AD-1735122	uscsaca(Uda)UfaUfAfAfaucccacusc sa		VPusGfsaguGfgGfAfuuuaUfaAfugugasus a		UAUCACAUUAUAAAUCCCAC UCG	
AD-1735123	gsasgga(Gda)AfaCfAfAfguucagugs asa		VPusUfscacUfgAfAfcuugUfuCfuccucsas g		CUGAGGAGAACAAGUUCAGU GAG	
AD-1735124	gsasgca(Gda)GfaGfAfAfugugcugcs asa		VPusUfsgcaGfcAfCfauucUfcCfugcucsasg		CUGAGCAGGAGAAUGUGCUG CAG	
AD-1735125	gsasaga(Cda)CfuAfCfAfccagcacusa sa		VPusUfsaguGfcUfGfguguAfgGfucuucsus g		CAGAAGACCUACACCAGCACU AA	
AD-1735126	asgsgcc(Uda)CfaCfCfUfugcuggausg sa		VPusCfsaucCfaGfCfaaggUfgAfggccususu		AAAGGCCUCACCUUGCUGGA UGG	
AD-1735127	asgscca(Gda)CfuGfCfUfugcucacasg sa		VPusCfsuguGfaGfCfaagcAfgCfuggcuscs u		AGAGCCAGCUGCUUGCUCACA GC	
AD-1735128	gsgsgcu(Cda)UfgUfGfAfgacugaggs usa		VPusAfsccuCfaGfUfcucaCfaGfagcccsasg		CUGGGCUCUGUGAGACUGAG GUG	
AD-	csgsaga(Gda)CfgAfAfUfuccgggacsa		VPusUfsgucCfcGfGfaauuCfgCfucucgsgs		CCCGAGAGCGAAUUCCGGGAC	

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:
1735129	sa		g		AU	
AD-1735130	gsusggc(Ada)CfaUfAfCfccugcagasasa		VPusUfsucuGfcAfGfgguaUfgUfgccacsasc		GUGUGGCACAUACCCUGCAGAAG	
AD-1735131	gsusgga(Cda)AfcAfGfUfggugcauusasa		VPusUfsaauGfcAfCfcacuGfuGfuccacscsa		UGGUGGACACAGUGGUGCAUUAC	
AD-1735132	asasgcc(Cda)AfgAfAfGfucucccaasgsa		VPusCfsuugGfgAfGfacuuCfuGfggcuusgsc		GCAAGCCCAGAAGUCUCCCAAGG	
AD-1735133	gsgscca(Uda)GfuCfCfCfuaucagausgsa		VPusCfsaucUfgAfUfagggAfcAfuggccscsu		AGGGCCAUGUCCCUAUCAGAUGC	
AD-1735134	gscscgg(Cda)GfgGfUfUfucucuaacsasa		VPusUfsguuAfgAfGfaaacCfcGfccggcscsc		GGGCCGGCGGGUUUCUCUAACAA	
AD-1735135	csusgaa(Gda)GfaCfAfCfcaucuccascsa		VPusGfsuggAfgAfUfggugUfcCfuucagscsu		AGCUGAAGGACACCAUCUCCACC	
AD-1735136	gsascca(Cda)CfaUfCfUfCfggcugugsasa		VPusUfscacAfgCfCfgagaUfgGfuggucsusg		CAGACCACCAUCUCGGCUGUGAC	
AD-1735137	cscsagu(Uda)UfuUfAfAfgggacaccsasa		VPusUfsgguGfuCfCfcuuaAfaAfacuggscsu		AGCCAGUUUUUAAGGGACACCAG	
AD-1735138	gsgscca(Gda)AfgAfCfAfcugcggaasusa		VPusAfsuucCfgCfAfguguCfuCfuggccsasc		GUGGCCAGAGACACUGCGGAAUU	
AD-1735139	csgsuuc(Cda)CfaUfCfGfcgagcacususa		VPusAfsaguGfcUfCfgcgaUfgGfgaacgscsu		AGCGUUCCCAUCGCGAGCACUUC	
AD-1735140	cscsggg(Ada)CfaUfCfCfGfacaacccascsa		VPusGfsuggGfuUfGfucgaUfgUfcccggsasa		UUCCGGGACAUCGACAACCCACC	
AD-1735141	uscsuga(Uda)GfaUfCfUfaggcucccsasa		VPusUfsgggAfgCfCfuagaUfcAfucagasgsg		CCUCUGAUGAUCUAGGCUCCCAG	
AD-1735142	csusgca(Gda)AfaGfAfCfccuccagascsa		VPusGfsucuGfgAfGfggucUfuCfugcagsgsg		CCCUGCAGAAGACCCUCCAGACC	
AD-1735143	csgscca(Gda)UfaGfCfUfuggcugccsusa		VPusAfsggcAfgCfCfaagcUfaCfuggcgscsu		AGCGCCAGUAGCUUGGCUGCCUG	
AD-1735144	csgscuu(Cda)AfcAfGfGfcugaguccsasa		VPusUfsggaCfuCfAfgccuGfuGfaagcgsgsc		GCCGCUUCACAGGCUGAGUCCAG	
AD-1735145	ususuuu(Uda)UfaGfCfAfucuuuuugsgsa		VPusCfscaaAfaGfGfaugcUfaAfaaaaasasa		UUUUUUUUUAGCAUCCUUUUGGG	
AD-1735146	gsasagc(Cda)AfaAfGfCfcgagggucsasa		VPusUfsgacCfcUfGfcgcuUfuGfgcuucsusc		GAGAAGCCAAAGGCGCAGGGUCAG	

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-1735147	gsasgga(Gda)GfaUfCfAfugaggaccsa		VPusUfsgguCfcUfCfaugaUfcCfuccucscsu		AGGAGGAGGAUCAUGAGGAC	
AD-1735148	gscsacg(Cda)AfuUfAfCfagccagcusg		VPusCfsagcUfgGfCfuguaAfuGfcgugcsgs g		CCGCACGCAUUACAGCCAGCU GC	
AD-1735149	csusuca(Uda)UfgAfAfAfaccaccacsg		VPusCfsgugGfuGfGfuuuuCfaAfugaagsgs g		CCCUUCAUUGAAAACCACCAC GG	
AD-1735150	ususuuu(Gda)AfuGfGfCfcacauaaus asa		VPusUfsauuAfuGfUfggccAfuCfaaaaasgsa		UCUUUUUGAUGGCCACAUAA UAA	
AD-1735151	cscsacc(Uda)GfgAfGfGfaaaagaucsc		VPusGfsgauCfuUfUfuccuCfcAfgguggsus c		GACCACCUGGAGGAAAAGAU CCC	
AD-1735152	csasagg(Cda)CfaAfGfCfcaagccucsu sa		VPusAfsgagGfcUfUfggcuUfgGfccuugsgs g		CCCAAGGCCAAGCCAAGCCUC UU	
AD-1735153	gsasgga(Cda)CfaGfAfCfagacacggsa sa		VPusUfsccgUfgUfCfugucUfgGfuccucsas u		AUGAGGACCAGACAGACACG GAG	
AD-1735154	gsasugc(Cda)CfuGfAfAfgggcguuas csa		VPusGfsuaaCfgCfCfcuucAfgGfgcaucsusg		CAGAUGCCCUGAAGGGCGUU ACU	
AD-1735155	cscsaac(Ada)CfuCfGfAfgcuggccgsa sa		VPusUfscggCfcAfGfcucgAfgUfguuggscs a		UGCCAACACUCGAGCUGGCCG AC	
AD-1735156	csasggg(Cda)UfaUfUfGfCfaccugcagsg sa		VPusCfscugCfaGfGfugcaUfaGfcccugscsa		UGCAGGGCUAUGCACCUGCA GGC	
AD-1735157	asasggu(Gda)GfuGfGfAfguaccucs usa		VPusAfsggaGfgUfAfcuccAfcCfaccuuscsu		AGAAGGUGGUGGAGUACCUC CUC	
AD-1735158	ususgaa(Gda)CfuUfGfAfggagcgags gsa		VPusCfscucGfcUfCfcucaAfgCfuucaascsu		AGUUGAAGCUUGAGGAGCGA GGA	
AD-1735159	csgsugg(Cda)CfaUfGfUfggaucccasg sa		VPusCfsuggGfaUfCfcacaUfgGfccacgsgsu		ACCGUGGCCAUGUGGAUCCCA GG	
AD-1735160	csasgca(Cda)UfaAfGfGfaagcccacsc sa		VPusGfsgugGfgCfUfuccuUfaGfugcugsgs u		ACCAGCACUAAGGAAGCCCAC CC	
AD-1735161	gsuscgc(Uda)GfaUfGfGfagcccgagsa sa		VPusUfscucGfgGfCfuccaUfcAfgcgacsasg		CUGUCGCUGAUGGAGCCCGA GAG	
AD-1735162	ususcuu(Cda)CfgGfCfCfcagcgucasu sa		VPusAfsugaCfgCfUfgggcCfgGfaagaasgsc		GCUUCUUCCGGCCCAGCGUCA UG	
AD-1735163	csusgcu(Cda)CfuGfGfAfcaccagcasa sa		VPusUfsugcUfgGfUfguccAfgGfagcagsgs g		CCCUGCUCCUGGACACCAGCA AG	
AD-	ususucu(Gda)AfgUfAfCfccgccgcus		VPusAfsagcGfgCfGfgguaCfuCfagaaasgsu		ACUUUCUGAGUACCCGCCGCU	

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:
1735164	usa				UC	
AD-1735165	csgscag(Gda)CfuGfUfCfcacccagususa		VPusAfsacuGfgGfUfggacAfgCfcugcgsgsa		UCCGCAGGCUGUCCACCCAGUUC	
AD-1735166	gsgscug(Uda)GfaCfAfUfgggcaccusgsa		VPusCfsaggUfgCfCfcaugUfcAfcagccsgsa		UCGGCUGUGACAUGGGCACCUGC	
AD-1735167	uscsagu(Gda)AfgGfUfAfgcagcccusgsa		VPusCfsaggGfcUfGfcuacCfuCfacugasasc		GUUCAGUGAGGUAGCAGCCCUGC	
AD-1735168	asgscgu(Cda)AfuGfGfAfgcccauccsusa		VPusAfsggaUfgGfGfcuccAfuGfacgcusgsg		CCAGCGUCAUGGAGCCCAUCCUG	
AD-1735169	csusgga(Uda)GfgAfGfAfcccuccugsasa		VPusUfscagGfgAfGfgucuCfcAfuccagscsa		UGCUGGAUGGAGACCUCCCUGAG	
AD-1735170	uscsagc(Cda)GfgAfGfUfgaguuugsgsa		VPusCfscaaCfaCfUfcacuCfcGfgcugascsc		GGUCAGCCGGAGUGAGUGUUGGG	
AD-1735171	csusggc(Cda)GfaCfUfUfGfgcuucuggsasa		VPusUfsccaGfaAfGfccagUfcGfgccagscsu		AGCUGGCCGACUGGCUUCUGGAG	
AD-1735172	gsgsugc(Uda)GfcAfCfCfucacaccasgsa		VPusCfsuggUfgUfUfGfagguGfcAfgcaccscsu		AGGGUGCUGCACCUCACACCAGC	
AD-1735173	gsgscug(Cda)CfuGfGfAfgcauggagscsa		VPusGfscucCfaUfGfcuccAfgGfcagccsasa		UUGGCUGCCUGGAGCAUGGAGCC	
AD-1735174	cscsugc(Ada)GfcUfGfUfGfcuggggcasusa		VPusAfsugcCfcAfGfcacaGfcUfgcaggsusg		CACCUGCAGCUGUGCUGGGGCAUG	
AD-1735175	asgsugg(Cda)CfaUfGfCfCfaggcggugsusa		VPusAfscacCfgCfCfugcaUfgGfccacusgsa		UCAGUGGCCAUGCAGGCGGUGUC	
AD-1735176	gsascuu(Gda)GfcCfUfUfUfgggcagcasusa		VPusAfsugcUfgCfCfcaagGfcCfaagucsgsg		CCGACUUGGCCUUGGGCAGCAUU	
AD-1735177	gsasgcg(Ada)AfgUfGfCfCfggguaccssusa		VPusAfsgggUfaCfCfcgcaCfuUfcgcucscsu		AGGAGCGAAGUGCGGGUACCCUG	
AD-1735178	csusggu(Gda)GfcCfUfUfCfugugugcasasa		VPusUfsugcAfcAfCfagagGfcCfaccagsgsg		CCCUGGUGGCCUCUGUGUGCAAU	
AD-1735179	asasccc(Ada)CfcAfGfUfCfcgaggucgsasa		VPusUfscgaCfcUfCfggcuGfgUfggguusgsu		ACAACCCACCAGCCGAGGUCGAG	
AD-1735180	usgsaug(Cda)UfgCfCfAfaggcgcacsusa		VPusAfsgugCfgCfCfuuggCfaGfcaucasusc		GAUGAUGCUGCCAAGGCGCACUU	
AD-1735181	cscsaau(Gda)AfgCfUfGfgccugccgsasa		VPusUfscggCfaGfGfccagCfuCfauugggscsa		UGCCAAUGAGCUGGCCUGCCGAG	

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-1735182	gsusgcu(Gda)CfaGfCfGfgguccugcsasa		VPusUfsgcaGfgAfCfccgcUfgCfagcacsasu		AUGUGCUGCAGCGGGUCCUGCAG	
AD-1735183	gsgsgcg(Uda)GfcAfGfAfgcgccagusasa		VPusUfsacuGfgCfGfcucuGfcAfcgcccsusu		AAGGGCGUGCAGAGCGCCAGUAG	
AD-1735184	gsgsuga(Gda)UfgGfCfAfccugcgaasusa		VPusAfsuucGfcAfGfgugcCfaCfucaccsasc		GUGGUGAGUGGCACCUGCGAAUG	
AD-1735185	ascsgga(Gda)GfgAfGfAfggacacggsasa		VPusUfsccgUfgUfCfcucuCfcCfuccgusgsu		ACACGGAGGGAGAGGACACGGAG	

Table 10. Unmodified Sense and Antisense Strand Sequences of PLIN1 dsRNA Agents Comprising a GalNAc Derivative Targeting Ligand

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002666.5	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002666.5
AD-1735186	CAUCUCUUUAACCAAACUUGA		1995-2015	UCAAGUUUGGUUAAAGAGAUGAA		1993-2015
AD-1735187	CUCUAACAAAUAAACAGAACA		1740-1760	UGUUCUGUUUAUUUGUUAGAGAA		1738-1760
AD-1735188	UGCAUAGUCACUCUUUUGAUA		2390-2410	UAUCAAAAGAGUGACUAUGCAGG		2388-2410
AD-1735189	AACUUGAUUUUUCAUCUCUUA		1983-2003	UAAGAGAUGAAAAAUCAAGUUAG		1981-2003
AD-1735190	GACACAUUCUUAGCACUGAAA		2128-2148	UUUCAGUGCUAAGAAUGUGUCAA		2126-2148
AD-1735191	ACGCCUUAUUUGAUUUAACUA		2807-2827	UAGUUAAAUCAAAUAAGGCGUAU		2805-2827
AD-1735192	UAGUCUUCGAAAUGUUAAUAA		2474-2494	UUAUUAACAUUUCGAAGACUAGG		2472-2494
AD-1735193	GAUGGACUUUUAAGUUGUUUA		2838-2858	UAAACAACUUAAAAGUCCAUCAU		2836-2858
AD-1735194	UGCUUUUUUCACUUAAUAAUA		2702-2722	UAUUAUUAAGUGAAAAAAGCAGG		2700-2722
AD-1735195	ACAUAAUAACUACUGCAUAAA		2780-2800	UUUAUGCAGUAGUUAUUAUGUG		2778-2800

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002666.5	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002666.5
				G		
AD-1735196	UACUAGUGUCACUUUCUGAGA		2271-2291	UCUCAGAAAGUGACACUAGUAU U		2269-2291
AD-1735197	CAAUCAGAUGCAAAAGCUCUA		2234-2254	UAGAGCUUUUGCAUCUGAUUGU U		2232-2254
AD-1735198	UAAGAGUAAUUGCCUAACUUA		1968-1988	UAAGUUAGGCAAUUACUCUUAU A		1966-1988
AD-1735199	GGCUUGUUUAUGAACAUUAAA		82-102	UUUAAUGUUCAUAAACAAGCCA U		80-102
AD-1735200	UUUUUGCUACUGCAAACGAUA		2871-2891	UAUCGUUUGCAGUAGCAAAAAA G		2869-2891
AD-1735201	AACGAUGCUAUAAUAAAUGUA		2885-2905	UACAUUUAUUAUAGCAUCGUUU G		2883-2905
AD-1735202	UGGUUGUUACUAUAAGAGUAA		1956-1976	UUACUCUUAUAGUAACAACCAA G		1954-1976
AD-1735203	CUGAUGAACAUCCUCUGAUGA		2181-2201	UCAUCAGAGGAUGUUCAUCAGA G		2179-2201
AD-1735204	CUGCGGAUAAAAUAUUUGCCAA		2059-2079	UUGGCAAAUAUUUAUCCGCAGA G		2057-2079
AD-1735205	CCAAAAUUCAGAUUCUGCCUA		2039-2059	UAGGCAGAAUCUGAAUUUUGGA A		2037-2059
AD-1735206	AAGGAUGUGUGUCUUUCUCCA		2547-2567	UGGAGAAAGACACACAUCCUUU U		2545-2567
AD-1735207	UGCGAAUGCUUCCAGAAGACA		231-251	UGUCUUCUGGAAGCAUUCGCAG G		229-251
AD-1735208	CGAAUGAGUAACUCCUGUCAA		2079-2099	UUGACAGGAGUUACUCAUUCGU G		2077-2099
AD-1735209	UGGGUGUUUAUUUAAAAUACA		2254-2274	UGUAUUUUAAAUAAACACCCAA G		2252-2274
AD-1735210	CAAAAGAUAUUUGACCGUUUA		2019-2039	UAAACGGUCAAAUAUCUUUUGG C		2017-2039
AD-1735211	AUACAGCUUGGAGAGAUUUUA		2720-2740	UAAAAUCUCUCCAAGCUGUAUU A		2718-2740

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002666.5	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002666.5
AD-1735212	AAAUGCAUUCAUACAAUUACA		2509-2529	UGUAAUUGUAUGAAUGCAUUUU C		2507-2529
AD-1735213	UCCCACUCGCUCUUUUUGAUA		2756-2776	UAUCAAAAAGAGCGAGUGGGAU U		2754-2776
AD-1735214	GCUUGUGUUUACACAAGCUGA		2664-2684	UCAGCUUGUGUAAACACAAGCG G		2662-2684
AD-1735215	CCUGCCUUACAUGGCUUGUUA		70-90	UAACAAGCCAUGUAAGGCAGGU G		68-90
AD-1735216	GAGAUUUUUGUAUCACAUUAA		2732-2752	UUAAUGUGAUACAAAAAUCUCU C		2730-2752
AD-1735217	AGCACUUCAGACAAGGUCCUA		540-560	UAGGACCUUGUCUGAAGUGCUC G		538-560
AD-1735218	UCACUCUCAGAGCCAGUUUUA		1895-1915	UAAAACUGGCUCUGAGAGUGAA G		1893-1915
AD-1735219	ACUGAACUCCUCUGUGAUCUA		2142-2162	UAGAUCACAGAGGAGUUCAGUG C		2140-2162
AD-1735220	UAGUUCCCUAAUGAUGGACUA		2826-2846	UAGUCCAUCAUUAGGGAACUAG U		2824-2846
AD-1735221	GGCGUUACUGACAACGUGGUA		1296-1316	UACCACGUUGUCAGUAACGCCC U		1294-1316
AD-1735222	UGAUCUAGGAUGAUCUGUUCA		2156-2176	UGAACAGAUCAUCCUAGAUCAC A		2154-2176
AD-1735223	GUGAUGAUAUAUAGACUUUAA		2427-2447	UUAAAGUCUAUAUAUCAUCACC A		2425-2447
AD-1735224	GGCUACUUUGAAGGGAACAAA		2217-2237	UUUGUUCCCUUCAAAGUAGCCU G		2215-2237
AD-1735225	CUGCUCUGAUUCUAUGGCUUA		1937-1957	UAAGCCAUAGAAUCAGAGCAGG C		1935-1957
AD-1735226	AGAUUGCUUCUGAGCUGAAGA		463-483	UCUUCAGCUCAGAAGCAAUCUU U		461-483
AD-1735227	GCCAUCUCUUGUGUAUGCAGA		2607-2627	UCUGCAUACACAAGAGAUGGCA C		2605-2627
AD-1735228	AGCCACAUUUCCAUUUGCAUA		2354-2374	UAUGCAAAUGGAAAUGUGGCUG		2352-2374

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002666.5	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002666.5
				U		
AD-1735229	UCCAGACAGAAGGUUUUGACA		2111-2131	UGUCAAAACCUUCUGUCUGGAC C		2109-2131
AD-1735230	CUCUCGAUACACCGUGCAGAA		818-838	UUCUGCACGGUGUAUCGAGAGA G		816-838
AD-1735231	GGCGCACUUUUUAUUUUUAUA		1838-1858	UAUAAAAAAUAAAAAGUGCGCCU U		1836-1858
AD-1735232	GAGCGUUGCCACUUUCAAAGA		1775-1795	UCUUUGAAAGUGGCAACGCUCG C		1773-1795
AD-1735233	UUGCAUCAUUACUGCCUUCAA		2368-2388	UUGAAGGCAGUAAUGAUGCAAA U		2366-2388
AD-1735234	GCGCAAGAAGAGCUGAGUCGA		1685-1705	UCGACUCAGCUCUUCUUGCGCA G		1683-1705
AD-1735235	UGCGGAAUUUGCUGCCAACAA		611-631	UUGUUGGCAGCAAAUUCCGCAG U		609-631
AD-1735236	GUGUGCAAUGCCUAUGAGAAA		291-311	UUUCUCAUAGGCAUUGCACACA G		289-311
AD-1735237	GAAUUCAAAUAUUGCAAAAGA		2530-2550	UCUUUUGCAAUAUUUGAAUUCU G		2528-2550
AD-1735238	CCUGUGUGCUUUGUAGAGCCA		2320-2340	UGGCUCUACAAAGCACACAGGC C		2318-2340
AD-1735239	UCCAGACAAGGAAGAGUCAGA		710-730	UCUGACUCUUCCUUGUCUGGAG G		708-730
AD-1735240	UGCCAGAAACAGCAUCAGCGA		509-529	UCGCUGAUGCUGUUUCUGGCAC U		507-529
AD-1735241	GCAUAAUAUGGAUACGCCUUA		2794-2814	UAAGGCGUAUCCAUAUUAUGCA G		2792-2814
AD-1735242	AGCCUCAUCCUGAUGAUGCUA		1813-1833	UAGCAUCAUCAGGAUGAGGCUG A		1811-1833
AD-1735243	AAGCCUCUUGAGCAGGGUUGA		779-799	UCAACCCUGCUCAAGAGGCUUG G		777-799
AD-1735244	UAAAGGGAAGAAGUUGAAGCA		99-119	UGCUUCAACUUCUUCCCUUUAA U		97-119

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002666.5	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002666.5
AD-1735245	GGCAGCAUUGAGAAGGUGGUA		675-695	UACCACCUUCUCAAUGCUGCCC A		673-695
AD-1735246	GUCAGCGACAGCUUCUUCCGA		1617-1637	UCGGAAGAAGCUGUCGCUGACC C		1615-1637
AD-1735247	CUGCUGUCUCCUCAACCAAGA		1243-1263	UCUUGGUUGAGGAGACAGCAGG G		1241-1263
AD-1735248	AGGAGGAAGAAUUGGAGACUA		1054-1074	UAGUCUCCAAUUCUUCCUCCUC C		1052-1074
AD-1735249	CCUGUCACCACUCUGAAGGUA		2092-2112	UACCUUCAGAGUGGUGACAGGA G		2090-2112
AD-1735250	AGACUUUAUGUAUAGCCACAA		2439-2459	UUGUGGCUAUACAUAAAGUCUA U		2437-2459
AD-1735251	GUUACGCAUGCCUGCUUUUUA		2690-2710	UAAAAAGCAGGCAUGCGUAACA C		2688-2710
AD-1735252	CCAGUUCACAGCUGCCAAUGA		377-397	UCAUUGGCAGCUGUGAACUGGG U		375-397
AD-1735253	CAGGCACGUGUGUAUGCACUA		2640-2660	UAGUGCAUACACACGUGCCUGC A		2638-2660
AD-1735254	AUGGCAGUCAACAAAGGCCUA		132-152	UAGGCCUUUGUUGACUGCCAUC C		130-152
AD-1735255	CAAACUUGUGGCCAAAAGAUA		2007-2027	UAUCUUUUGGCCACAAGUUUGG U		2005-2027
AD-1735256	UCUGACCAACACCCUCUCUCA		803-823	UGAGAGAGGGUGUUGGUCAGAG C		801-823
AD-1735257	UCACAUUAUAAAAUCCCACUCA		2744-2764	UGAGUGGGAUUUAUAAUGUGAU A		2742-2764
AD-1735258	GAGGAGAACAAGUUCAGUGAA		1074-1094	UUCACUGAACUUGUUCUCCUCA G		1072-1094
AD-1735259	GAGCAGGAGAAUGUGCUGCAA		177-197	UUGCAGCACAUUCUCCUGCUCA G		175-197
AD-1735260	GAAGACCUACACCAGCACUAA		245-265	UUAGUGCUGGUGUAGGUCUUCU G		243-265
AD-1735261	AGGCCUCACCUUGCUGGAUGA		146-166	UCAUCCAGCAAGGUGAGGCCUU		144-166

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002666.5	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002666.5
				U		
AD-1735262	AGCCAGCUGCUUGCUCACAGA		2336-2356	UCUGUGAGCAAGCAGCUGGCUC U		2334-2356
AD-1735263	GGGCUCUGUGAGACUGAGGUA		13-33	UACCUCAGUCUCACAGAGCCCA G		11-33
AD-1735264	CGAGAGCGAAUUCCGGGACAA		1367-1387	UUGUCCCGGAAUUCGCUCUCGG G		1365-1387
AD-1735265	GUGGCACAUACCCUGCAGAAA		1134-1154	UUUCUGCAGGGUAUGUGCCACA C		1132-1154
AD-1735266	GUGGACACAGUGGUGCAUUAA		1314-1334	UUAAUGCACCACUGUGUCCACC A		1312-1334
AD-1735267	AAGCCCAGAAGUCUCCCAAGA		751-771	UCUUGGGAGACUUCUGGGCUUG C		749-771
AD-1735268	GGCCAUGUCCCUAUCAGAUGA		1268-1288	UCAUCUGAUAGGGACAUGGCCC U		1266-1288
AD-1735269	GCCGGCGGGUUUCUCUAACAA		1728-1748	UUGUUAGAGAAACCCGCCGGCC C		1726-1748
AD-1735270	CUGAAGGACACCAUCUCCACA		477-497	UGUGGAGAUGGUGUCCUUCAGC U		475-497
AD-1735271	GACCACCAUCUCGGCUGUGAA		1163-1183	UUCACAGCCGAGAUGGUGGUCU G		1161-1183
AD-1735272	CCAGUUUUUAAGGGACACCAA		1907-1927	UUGGUGUCCCUUAAAAACUGGC U		1905-1927
AD-1735273	GGCCAGAGACACUGCGGAAUA		599-619	UAUUCCGCAGUGUCUCUGGCCA C		597-619
AD-1735274	CGUUCCCAUCGCGAGCACUUA		527-547	UAAGUGCUCGCGAUGGGAACGC U		525-547
AD-1735275	CCGGGACAUCGACAACCCACA		1379-1399	UGUGGGUUGUCGAUGUCCCGGA A		1377-1399
AD-1735276	UCUGAUGAUCUAGGCUCCCAA		2194-2214	UUGGGAGCCUAGAUCAUCAGAG G		2192-2214
AD-1735277	CUGCAGAAGACCCUCCAGACA		1146-1166	UGUCUGGAGGGUCUUCUGCAGG G		1144-1166

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002666.5	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002666.5
AD-1735278	CGCCAGUAGCUUGGCUGCCUA		323-343	UAGGCAGCCAAGCUACUGGCGC U		321-343
AD-1735279	CGCUUCACAGGCUGAGUCCAA		2298-2318	UUGGACUCAGCCUGUGAAGCGG C		2296-2318
AD-1735280	UUUUUUUAGCAUCCUUUUGGA		1871-1891	UCCAAAAGGAUGCUAAAAAAAA A		1869-1891
AD-1735281	GAAGCCAAAGCGCAGGGUCAA		1601-1621	UUGACCCUGCGCUUUGGCUUCU C		1599-1621
AD-1735282	GAGGAGGAUCAUGAGGACCAA		1005-1025	UUGGUCCUCAUGAUCCUCCUCC U		1003-1025
AD-1735283	GCACGCAUUACAGCCAGCUGA		1666-1686	UCAGCUGGCUGUAAUGCGUGCG G		1664-1686
AD-1735284	CUUCAUUGAAAACCACCACGA		2585-2605	UCGUGGUGGUUUUCAAUGAAGG G		2583-2605
AD-1735285	UUUUUGAUGGCCACAUAAUAA		2768-2788	UUAUUAUGUGGCCAUCAAAAAG A		2766-2788
AD-1735286	CCACCUGGAGGAAAAGAUCCA		419-439	UGGAUCUUUUCCUCCAGGUGGU C		417-439
AD-1735287	CAAGGCCAAGCCAAGCCUCUA		767-787	UAGAGGCUUGGCUUGGCCUUGG G		765-787
AD-1735288	GAGGACCAGACAGACACGGAA		1017-1037	UUCCGUGUCUGUCUGGUCCUCA U		1015-1037
AD-1735289	GAUGCCCUGAAGGGCGUUACA		1284-1304	UGUAACGCCCUUCAGGGCAUCU G		1282-1304
AD-1735290	CCAACACUCGAGCUGGCCGAA		625-645	UUCGGCCAGCUCGAGUGUUGGC A		623-645
AD-1735291	CAGGGCUAUGCACCUGCAGGA		2624-2644	UCCUGCAGGUGCAUAGCCCUGC A		2622-2644
AD-1735292	AAGGUGGUGGAGUACCUCCUA		687-707	UAGGAGGUACUCCACCACCUUC U		685-707
AD-1735293	UUGAAGCUUGAGGAGCGAGGA		112-132	UCCUCGCUCCUCAAGCUUCAAC U		110-132
AD-1735294	CGUGGCCAUGUGGAUCCCAGA		869-889	UCUGGGAUCCACAUGGCCACGG		867-889

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002666.5	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002666.5
				U		
AD-1735295	CAGCACUAAGGAAGCCCACCA		257-277	UGGUGGGCUUCCUUAGUGCUGGU		255-277
AD-1735296	GUCGCUGAUGGAGCCCGAGAA		1352-1372	UUCUCGGGCUCCAUCAGCGACAG		1350-1372
AD-1735297	UUCUUCCGGCCCAGCGUCAUA		1629-1649	UAUGACGCUGGGCCGGAAGAAGC		1627-1649
AD-1735298	CUGCUCCUGGACACCAGCAAA		733-753	UUUGCUGGUGUCCAGGAGCAGGG		731-753
AD-1735299	UUUCUGAGUACCCGCCGCUUA		2283-2303	UAAGCGGCGGGUACUCAGAAAGU		2281-2303
AD-1735300	CGCAGGCUGUCCACCCAGUUA		363-383	UAACUGGGUGGACAGCCUGCGGA		361-383
AD-1735301	GGCUGUGACAUGGGCACCUGA		1175-1195	UCAGGUGCCCAUGUCACAGCCGA		1173-1195
AD-1735302	UCAGUGAGGUAGCAGCCCUGA		1087-1107	UCAGGGCUGCUACCUCACUGAAC		1085-1107
AD-1735303	AGCGUCAUGGAGCCCAUCCUA		1641-1661	UAGGAUGGGCUCCCAUGACGCUGG		1639-1661
AD-1735304	CUGGAUGGAGACCUCCCUGAA		159-179	UUCAGGGAGGUCUCCAUCCAGCA		157-179
AD-1735305	UCAGCCGGAGUGAGUGUUGGA		38-58	UCCAACACUCACUCCGGCUGACC		36-58
AD-1735306	CUGGCCGACUGGCUUCUGGAA		637-657	UUCCAGAAGCCAGUCGGCCAGCU		635-657
AD-1735307	GGUGCUGCACCUCACACCAGA		1220-1240	UCUGGUGUGAGGUGCAGCACCCU		1218-1240
AD-1735308	GGCUGCCUGGAGCAUGGAGCA		335-355	UGCUCCAUGCUCCAGGCAGCCAA		333-355
AD-1735309	CCUGCAGCUGUGCUGGGCAUA		1191-1211	UAUGCCCAGCACAGCUGCAGGUG		1189-1211
AD-1735310	AGUGGCCAUGCAGGCGGUGUA		929-949	UACACCGCCUGCAUGGCCACUGA		927-949

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002666.5	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_002666.5
AD-1735311	GACUUGGCCUUGGGCAGCAUA		663-683	UAUGCUGCCCAAGGCCAAGUCGG		661-683
AD-1735312	GAGCGAAGUGCGGGUACCCUA		959-979	UAGGGUACCCGCACUUCGCUCCU		957-979
AD-1735313	CUGGUGGCCUCUGUGUGCAAA		279-299	UUUGCACACAGAGGCCACCAGGG		277-299
AD-1735314	AACCCACCAGCCGAGGUCGAA		1392-1412	UUCGACCUCGGCUGGUGGGUUGU		1390-1412
AD-1735315	UGAUGCUGCCAAGGCGCACUA		1826-1846	UAGUGCGCCUUGGCAGCAUCAUC		1824-1846
AD-1735316	CCAAUGAGCUGGCCUGCCGAA		391-411	UUCGGCAGGCCAGCUCAUUGGCA		389-411
AD-1735317	GUGCUGCAGCGGGUCCUGCAA		189-209	UUGCAGGACCCGCUGCAGCACAU		187-209
AD-1735318	GGGCGUGCAGAGCGCCAGUAA		311-331	UUACUGGCGCUCUGCACGCCCUU		309-331
AD-1735319	GGUGAGUGGCACCUGCGAAUA		218-238	UAUUCGCAGGUGCCACUCACCAC		216-238
AD-1735320	ACGGAGGGAGAGGACACGGAA		1032-1052	UUCCGUGUCCUCUCCCUCCGUGU		1030-1052

Table 11. Modified Sense and Antisense Strand Sequences of PLIN1 dsRNA Agents Comprising a GalNAc Derivative Targeting Ligand

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-1735186	csasucucUfuUfAfAfccaaacuusgsa		VPusCfsaagUfuUfGfguuaAfaGfagaugsasa		UUCAUCUCUUUAACCAAACUUGU	
AD-1735187	csuscuaaCfaAfAfUfaaacagaascsa		VPusGfsuucUfgUfUfuauuUfgUfuagagsasa		UUCUCUAACAAAUAAACAGAACC	
AD-1735188	usgscauaGfuCfAfCfucuuuugasusa		VPusAfsucaAfaAfGfagugAfcUfaugcasgsg		CCUGCAUAGUCACUCUUUUGAUG	

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-1735189	asascuugAfuUfUfUfucaucucu susa		VPusAfsagaGfaUfGfaaaaAfuCfaagu usasg		CUAACUUGAUUUUUCAUCUC UUU	
AD-1735190	gsascacaUfuCfUfUfagcacuga sasa		VPusUfsucaGfuGfCfuaagAfaUfgugu csasa		UUGACACAUUCUUAGCACUG AAC	
AD-1735191	ascsgccuUfaUfUfUfgauuuaac susa		VPusAfsguuAfaAfUfcaaaUfaAfggcg usasu		AUACGCCUUAUUUGAUUUAA CUA	
AD-1735192	usasgucuUfcGfAfAfauguuaau sasa		VPusUfsauuAfaCfAfuuucGfaAfgacu asgsg		CCUAGUCUUCGAAAUGUUAA UAU	
AD-1735193	gsasuggaCfuUfUfUfaaguuguu susa		VPusAfsaacAfaCfUfuaaaAfgUfccau csasu		AUGAUGGACUUUUAAGUUGU UUC	
AD-1735194	usgscuuuUfuUfCfAfcuuaauaa susa		VPusAfsuuaUfuAfAfgugaAfaAfaagc asgsg		CCUGCUUUUUUCACUUAAUA AUA	
AD-1735195	ascsauaaUfaAfCfUfacugcauas asa		VPusUfsuauGfcAfGfuaguUfaUfuaug usgsg		CCACAUAAUAACUACUGCAU AAU	
AD-1735196	usascuagUfgUfCfAfcuuucuga sgsa		VPusCfsucaGfaAfAfgugaCfaCfuagu asusu		AAUACUAGUGUCACUUUCUG AGU	
AD-1735197	csasaucaGfaUfGfCfaaaagcucs usa		VPusAfsgagCfuUfUfugcaUfcUfgauu gsusu		AACAAUCAGAUGCAAAAGCU CUU	
AD-1735198	usasagagUfaAfUfUfgccuaacu susa		VPusAfsaguUfaGfGfcaauUfaCfucuu asusa		UAUAAGAGUAAUUGCCUAAC UUG	
AD-1735199	gsgscuugUfuUfAfUfgaacauua sasa		VPusUfsuaaUfgUfUfcauaAfaCfaagc csasu		AUGGCUUGUUUAUGAACAUU AAA	
AD-1735200	ususuuugCfuAfCfUfgcaaacga susa		VPusAfsucgUfuUfGfcaguAfgCfaaaa asasg		CUUUUUUGCUACUGCAAACG AUG	
AD-1735201	asascgauGfcUfAfUfaauaaaug susa		VPusAfscauUfuAfUfuauaGfcAfucgu ususg		CAAACGAUGCUAUAAUAAAU GUC	
AD-1735202	usgsguugUfuAfCfUfauaagagu sasa		VPusUfsacuCfuUfAfuaguAfaCfaacc asasg		CUUGGUUGUUACUAUAAGAG UAA	
AD-1735203	csusgaugAfaCfAfUfccucugau sgsa		VPusCfsaucAfgAfGfgaugUfuCfauca gsasg		CUCUGAUGAACAUCCUCUGA UGA	
AD-1735204	csusgcggAfuAfAfAfuauuugcc sasa		VPusUfsggcAfaAfUfauuuAfuCfcgca gsasg		CUCUGCGGAUAAAUAUUUGC CAC	
AD-	cscsaaaaUfuCfAfGfauucugcc		VPusAfsggcAfgAfAfucugAfaUfuuu		UUCCAAAAUUCAGAUUCUGC	

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:
1735205	susa		ggsasa		CUC	
AD-1735206	asasggauGfuGfUfGfucuuucuc scsa		VPusGfsgagAfaAfGfacacAfcAfuccu ususu		AAAAGGAUGUGUGUCUUUCU CCC	
AD-1735207	usgscgaaUfgCfUfUfccagaaga scsa		VPusGfsucuUfcUfGfgaagCfaUfucgc asgsg		CCUGCGAAUGCUUCCAGAAG ACC	
AD-1735208	csgsaaugAfgUfAfAfcuccuguc sasa		VPusUfsgacAfgGfAfguuaCfuCfauuc gsusg		CACGAAUGAGUAACUCCUGU CAC	
AD-1735209	usgsggugUfuUfAfUfuuaaaaua scsa		VPusGfsuauUfuUfAfaauaAfaCfaccc asasg		CUUGGGUGUUUAUUUAAAAU ACU	
AD-1735210	csasaaagAfuAfUfUfugaccguu susa		VPusAfsaacGfgUfCfaaauAfuCfuuuu gsgsc		GCCAAAAGAUAUUUGACCGU UUC	
AD-1735211	asusacagCfuUfGfGfagagauuu susa		VPusAfsaaaUfcUfCfuccaAfgCfugua ususa		UAAUACAGCUUGGAGAGAUU UUU	
AD-1735212	asasaugcAfuUfCfCfAfuacaauua scsa		VPusGfsuaaUfuGfUfUfaugaAfuGfcauu ususc		GAAAAUGCAUUCAUACAAUU ACA	
AD-1735213	uscsccacUfcGfCfUfcuuuuuga susa		VPusAfsucaAfaAfAfgagcGfaGfuggg asusu		AAUCCCACUCGCUCUUUUUG AUG	
AD-1735214	gscsuuguGfuUfUfAfcacaagcu sgsa		VPusCfsagcUfuGfUfguaaAfcAfcaag csgsg		CCGCUUGUGUUUACACAAGC UGU	
AD-1735215	cscsugccUfuAfCfAfuggcuugu susa		VPusAfsacaAfgCfCfauguAfaGfgcag gsusg		CACCUGCCUUACAUGGCUUG UUU	
AD-1735216	gsasgauuUfuUfGfUfaucacauu sasa		VPusUfsaauGfuGfAfuacaAfaAfaucu csusc		GAGAGAUUUUUGUAUCACAU UAU	
AD-1735217	asgscacuUfcAfGfAfcaaggucc susa		VPusAfsggaCfcUfUfgucuGfaAfgugc uscsg		CGAGCACUUCAGACAAGGUC CUG	
AD-1735218	uscsacucUfcAfGfAfgccaguuu susa		VPusAfsaaaCfuGfGfcucuGfaGfagug asasg		CUUCACUCUCAGAGCCAGUU UUU	
AD-1735219	ascsugaaCfuCfCfUfcugugauc susa		VPusAfsgauCfaCfAfgaggAfgUfucag usgsc		GCACUGAACUCCUCUGUGAU CUA	
AD-1735220	usasguucCfcUfAfAfuguggac susa		VPusAfsgucCfaUfCfauuaGfgGfaacu asgsu		ACUAGUUCCCUAAUGAUGGA CUU	
AD-1735221	ggsgscguuAfcUfGfAfcaacgugg susa		VPusAfsccaCfgUfUfgucaGfuAfacgc cscsu		AGGGCGUUACUGACAACGUG GUG	

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-1735222	usgsaucuAfgGfAfUfgaucugu uscsa		VPusGfsaacAfgAfUfcaucCfuAfgauc ascsa		UGUGAUCUAGGAUGAUCUGU UCC	
AD-1735223	gsusgaugAfuAfUfAfuagacuu usasa		VPusUfsaaaGfuCfUfauauAfuCfauca cscsa		UGGUGAUGAUAUAUAGACUU UAU	
AD-1735224	gsgscuacUfuUfGfAfagggaaca sasa		VPusUfsuguUfcCfCfuucaAfaGfuagc csusg		CAGGCUACUUUGAAGGGAAC AAU	
AD-1735225	csusgcucUfgAfUfUfcuauggcu susa		VPusAfsagcCfaUfAfgaauCfaGfagca gsgsc		GCCUGCUCUGAUUCUAUGGC UUG	
AD-1735226	asgsauugCfuUfCfUfgagcugaa sgsa		VPusCfsuucAfgCfUfcagaAfgCfaauc ususu		AAAGAUUGCUUCUGAGCUGA AGG	
AD-1735227	gscscaucUfcUfUfGfuguaugca sgsa		VPusCfsugcAfuAfCfacaaGfaGfaugg csasc		GUGCCAUCUCUUGUGUAUGC AGG	
AD-1735228	asgsccacAfuUfUfCfcauuugca susa		VPusAfsugcAfaAfUfggaaAfuGfuggc usgsu		ACAGCCACAUUUCCAUUUGC AUC	
AD-1735229	uscscagaCfaGfAfAfgguuuuga scsa		VPusGfsucaAfaAfCfcuucUfgUfcugg ascsc		GGUCCAGACAGAAGGUUUUG ACA	
AD-1735230	csuscucgAfuAfCfAfccgugcag sasa		VPusUfscugCfaCfGfguguAfuCfgaga gsasg		CUCUCUCGAUACACCGUGCA GAC	
AD-1735231	gsgscgcaCfuUfUfUfuauuuuua susa		VPusAfsuaaAfaAfUfUfaaaaAfgUfgcgc csusu		AAGGCGCACUUUUUAUUUUU AUU	
AD-1735232	gsasgcguUfgCfCfCfAfcuuucaaa sgsa		VPusCfsuuuGfaAfAfguggCfaAfcgcu csgsc		GCGAGCGUUGCCACUUUCAA AGU	
AD-1735233	ususgcauCfaUfUfUfAfcugccuuc sasa		VPusUfsgaaGfgCfAfguaaUfgAfugca asasu		AUUUGCAUCAUUACUGCCUU CAC	
AD-1735234	gscsgcaaGfaAfGfGfAfgcugaguc sgsa		VPusCfsgacUfcAfGfcucuUfcUfugcg csasg		CUGCGCAAGAAGAGCUGAGU CGC	
AD-1735235	usgscggaAfuUfUfGfcugccaac sasa		VPusUfsguuGfgCfAfgcaaAfuUfccgc asgsu		ACUGCGGAAUUUGCUGCCAA CAC	
AD-1735236	gsusgugcAfaUfGfCfcuaugaga sasa		VPusUfsucuCfaUfAfggcaUfuGfcaca csasg		CUGUGUGCAAUGCCUAUGAG AAG	
AD-1735237	gsasauucAfaAfUfAfuuugcaaaa sgsa		VPusCfsuuuUfgCfAfauauUfuGfaauu csusg		CAGAAUUCAAAUAUUGCAAA AGG	
AD-	cscsugugUfgCfUfUfuguagagc		VPusGfsgcuCfuAfCfaaagCfaCfacag		GGCCUGUGUGCUUUGUAGAG	

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:
1735238	scsa		gscsc		CCA	
AD-1735239	uscscagaCfaAfGfGfaagaguca sgsa		VPusCfsugaCfuCfUfuccuUfgUfcugg asgsg		CCUCCAGACAAGGAAGAGUC AGC	
AD-1735240	usgsccagAfaAfCfAfgcaucagc sgsa		VPusCfsgcuGfaUfGfcuguUfuCfuggc ascsu		AGUGCCAGAAACAGCAUCAG CGU	
AD-1735241	gscsauaaUfaUfGfGfauacgccu susa		VPusAfsaggCfgUfAfuccaUfaUfuaug csasg		CUGCAUAAUAUGGAUACGCC UUA	
AD-1735242	asgsccucAfuCfCfUfgaugaugc susa		VPusAfsgcaUfcAfUfcaggAfuGfaggc usgsa		UCAGCCUCAUCCUGAUGAUG CUG	
AD-1735243	asasgccuCfuUfGfAfgcaggguu sgsa		VPusCfsaacCfcUfGfcucaAfgAfggcu usgsg		CCAAGCCUCUUGAGCAGGGU UGG	
AD-1735244	usasaaggGfaAfGfAfaguugaag scsa		VPusGfscuuCfaAfCfuucuUfcCfcuuu asasu		AUUAAAGGGAAGAAGUUGAA GCU	
AD-1735245	gsgscagcAfuUfGfAfgaaggugg susa		VPusAfsccaCfcUfUfcucaAfuGfcugc cscsa		UGGGCAGCAUUGAGAAGGUG GUG	
AD-1735246	gsuscagcGfaCfAfGfcuucuucc sgsa		VPusCfsggaAfgAfAfgcugUfcGfcuga cscsc		GGGUCAGCGACAGCUUCUUC CGG	
AD-1735247	csusgcugUfcUfCfCfucaaccaas gsa		VPusCfsuugGfuUfGfaggaGfaCfagca ggsgg		CCCUGCUGUCUCCUCAACCAA GG	
AD-1735248	asgsgaggAfaGfAfAfuuggagac susa		VPusAfsgucUfcCfAfauucUfuCfcucc uscsc		GGAGGAGGAAGAAUUGGAGA CUG	
AD-1735249	cscsugucAfcCfAfCfucugaagg susa		VPusAfsccuUfcAfGfagugGfuGfacag gsasg		CUCCUGUCACCACUCUGAAG GUC	
AD-1735250	asgsacuuUfaUfGfUfauagccac sasa		VPusUfsgugGfcUfAfuacaUfaAfaguc usasu		AUAGACUUUAUGUAUAGCCA CAG	
AD-1735251	gsusuacgCfaUfGfCfcugcuuuu susa		VPusAfsaaaAfgCfAfggcaUfgCfguaa csasc		GUGUUACGCAUGCCUGCUUU UUU	
AD-1735252	cscsaguuCfaCfAfGfcugccaau sgsa		VPusCfsauuGfgCfAfgcugUfgAfacug gsgsu		ACCCAGUUCACAGCUGCCAA UGA	
AD-1735253	csasggcaCfgUfGfUfguaugcac susa		VPusAfsgugCfaUfAfcacaCfgUfgccu gscsa		UGCAGGCACGUGUGUAUGCA CUC	
AD-1735254	asusggcaGfuCfAfAfcaaaggcc susa		VPusAfsggcCfuUfUfguugAfcUfgcca uscsc		GGAUGGCAGUCAACAAAGGC CUC	

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-1735255	csasaacuUfgUfGfGfccaaaagas usa		VPusAfsucuUfuUfGfgccaCfaAfguuu gsgsu		ACCAAACUUGUGGCCAAAAG AUA	
AD-1735256	uscsugacCfaAfCfAfcccucucu scsa		VPusGfsagaGfaGfGfguguUfgGfucag asgsc		GCUCUGACCAACACCCUCUCU CG	
AD-1735257	uscsacauUfaUfAfAfauccacu scsa		VPusGfsaguGfgGfAfuuuaUfaAfugu gasusa		UAUCACAUUAUAAAUCCCAC UCG	
AD-1735258	gsasggagAfaCfAfAfguucagug sasa		VPusUfscacUfgAfAfcuugUfuCfuccu csasg		CUGAGGAGAACAAGUUCAGU GAG	
AD-1735259	gsasgcagGfaGfAfAfugugcugc sasa		VPusUfsgcaGfcAfCfauucUfcCfugcu csasg		CUGAGCAGGAGAAUGUGCUG CAG	
AD-1735260	gsasagacCfuAfCfAfccagcacus asa		VPusUfsaguGfcUfGfguguAfgGfucu ucsusg		CAGAAGACCUACACCAGCAC UAA	
AD-1735261	asgsgccuCfaCfCfUfugcuggau sgsa		VPusCfsaucCfaGfCfaaggUfgAfggcc ususu		AAAGGCCUCACCUUGCUGGA UGG	
AD-1735262	asgsccagCfuGfCfUfugcucaca sgsa		VPusCfsuguGfaGfCfaagcAfgCfuggc uscsu		AGAGCCAGCUGCUUGCUCAC AGC	
AD-1735263	gsgsgcucUfgUfGfAfgacugagg susa		VPusAfsccuCfaGfUfcucaCfaGfagccc sasg		CUGGGCUCUGUGAGACUGAG GUG	
AD-1735264	csgsagagCfgAfAfUfuccgggac sasa		VPusUfsgucCfcGfGfaauuCfgCfucuc gsgsg		CCCGAGAGCGAAUUCCGGGA CAU	
AD-1735265	gsusggcaCfaUfAfCfccugcaga sasa		VPusUfsucuGfcAfGfgguaUfgUfgcca csasc		GUGUGGCACAUACCCUGCAG AAG	
AD-1735266	gsusggacAfcAfGfUfgggugcauu sasa		VPusUfsaauGfcAfCfcacuGfuGfucca cscsa		UGGUGGACACAGUGGGUGCAU UAC	
AD-1735267	asasgcccAfgAfAfGfucucccaa sgsa		VPusCfsuugGfgAfGfacuuCfuGfggcu usgsc		GCAAGCCCAGAAGUCUCCCA AGG	
AD-1735268	gsgsccauGfuCfCfCfuaucagau sgsa		VPusCfsaucUfgAfUfagggAfcAfuggc cscsu		AGGGCCAUGUCCCUAUCAGA UGC	
AD-1735269	gscscggcGfgGfUfUfucucuaac sasa		VPusUfsguuAfgAfGfaaacCfcGfccgg cscsc		GGGCCGGCGGGUUUCUCUAA CAA	
AD-1735270	csusgaagGfaCfAfCfcaucuccas csa		VPusGfsuggAfgAfUfggugUfcCfuuca gscsu		AGCUGAAGGACACCAUCUCC ACC	
AD-	gsasccacCfaUfCfUfcggcugug		VPusUfscacAfgCfCfgagaUfgGfuggu		CAGACCACCAUCUCGGCUGU	

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:
1735271	sasa		csusg		GAC	
AD-1735272	cscsaguuUfuUfAfAfgggacacc sasa		VPusUfsgguGfuCfCfcuuaAfaAfacug gscsu		AGCCAGUUUUUAAGGGACAC CAG	
AD-1735273	gsgsccagAfgAfCfAfcugcggaa susa		VPusAfsuucCfgCfAfguguCfuCfuggc csasc		GUGGCCAGAGACACUGCGGA AUU	
AD-1735274	csgsuuccCfaUfCfGfcgagcacu susa		VPusAfsaguGfcUfCfgcgaUfgGfgaac gscsu		AGCGUUCCCAUCGCGAGCAC UUC	
AD-1735275	cscsgggaCfaUfCfGfacaacccas csa		VPusGfsuggGfuUfGfucgaUfgUfcccg gsasa		UUCCGGGACAUCGACAACCC ACC	
AD-1735276	uscsugauGfaUfCfUfaggcuccc sasa		VPusUfsgggAfgCfCfuagaUfcAfucag asgsg		CCUCUGAUGAUCUAGGCUCC CAG	
AD-1735277	csusgcagAfaGfAfCfccuccaga scsa		VPusGfsucuGfgAfGfggucUfuCfugca gsgsg		CCCUGCAGAAGACCCUCCAGA CC	
AD-1735278	csgsccagUfaGfCfUfuggcugcc susa		VPusAfsggcAfgCfCfaagcUfaCfuggc gscsu		AGCGCCAGUAGCUUGGCUGC CUG	
AD-1735279	csgscuucAfcAfGfGfcugagucc sasa		VPusUfsggaCfuCfAfgccuGfuGfaagc gsgsc		GCCGCUUCACAGGCUGAGUC CAG	
AD-1735280	ususuuuuUfaGfCfAfuccuuuu gsgsa		VPusCfscaaAfaGfGfaugcUfaAfaaaaa sasa		UUUUUUUUUAGCAUCCUUUU GGG	
AD-1735281	gsasagccAfaAfGfCfcgaggguc sasa		VPusUfsgacCfcUfGfcgcuUfuGfgcuu csusc		GAGAAGCCAAAGCGCAGGGU CAG	
AD-1735282	gsasggagGfaUfCfAfugaggacc sasa		VPusUfsgguCfcUfCfaugaUfcCfuccu cscsu		AGGAGGAGGAUCAUGAGGAC CAG	
AD-1735283	gscsacgcAfuUfAfCfagccagcu sgsa		VPusCfsagcUfgGfCfuguaAfuGfcgug csgsg		CCGCACGCAUUACAGCCAGCU GC	
AD-1735284	csusucauUfgAfAfAfaccaccac sgsa		VPusCfsgugGfuGfGfuuuuCfaAfugaa gsgsg		CCCUUCAUUGAAAACCACCAC GG	
AD-1735285	ususuuugAfuGfGfCfcacauaau sasa		VPusUfsauuAfuGfUfggccAfuCfaaaa asgsa		UCUUUUUGAUGGCCACAUAA UAA	
AD-1735286	cscsaccuGfgAfGfGfaaaagauc scsa		VPusGfsgauCfuUfUfuccuCfcAfggug gsusc		GACCACCUGGAGGAAAAGAU CCC	
AD-1735287	csasaggcCfaAfGfCfcaagccucs usa		VPusAfsgagGfcUfUfggcuUfgGfccuu gsgsg		CCCAAGGCCAAGCCAAGCCUC UU	

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-1735288	gsasggacCfaGfAfCfagacacgg sasa		VPusUfsccgUfgUfCfugucUfgGfuccu csasu		AUGAGGACCAGACAGACACG GAG	
AD-1735289	gsasugccCfuGfAfAfgggcguua scsa		VPusGfsuaaCfgCfCfcuucAfgGfgcau csusg		CAGAUGCCCUGAAGGGCGUU ACU	
AD-1735290	cscsaacaCfuCfGfAfgcuggccg sasa		VPusUfscggCfcAfGfcucgAfgUfguug gscsa		UGCCAACACUCGAGGCUGGCC GAC	
AD-1735291	csasgggcUfaUfGfCfaccugcag sgsa		VPusCfscugCfaGfGfugcaUfaGfcccu gscsa		UGCAGGGCUAUGCACCUGCA GGC	
AD-1735292	asasggugGfuGfGfAfguaccucc susa		VPusAfsggaGfgUfAfcuccAfcCfaccu uscsu		AGAAGGUGGUGGAGUACCUC CUC	
AD-1735293	ususgaagCfuUfGfAfggagcgag sgsa		VPusCfscucGfcUfCfcucaAfgCfuuca ascsu		AGUUGAAGCUUGAGGAGCGA GGA	
AD-1735294	csgsuggcCfaUfGfUfggauccca sgsa		VPusCfsuggGfaUfCfcacaUfgGfccac gsgsu		ACCGUGGCCAUGUGGAUCCC AGG	
AD-1735295	csasgcacUfaAfGfGfaagcccacs csa		VPusGfsgugGfgCfUfuccuUfaGfugcu ggsgsu		ACCAGCACUAAGGAAGCCCA CCC	
AD-1735296	gsuscgcuGfaUfGfGfagcccgag sasa		VPusUfscucGfgGfCfuccaUfcAfgcga csasg		CUGUCGCUGAUGGAGCCCGA GAG	
AD-1735297	ususcuucCfgGfCfCfCfcagcguca susa		VPusAfsugaCfgCfUfgggcCfgGfaaga asgsc		GCUUCUUCCGGCCCAGCGUCA UG	
AD-1735298	csusgcucCfuGfGfAfcaccagca sasa		VPusUfsugcUfgGfUfguccAfgGfagca gsgsg		CCCUGCUCCUGGACACCAGCA AG	
AD-1735299	ususucugAfgUfAfCfccgccgcu susa		VPusAfsagcGfgCfGfgguaCfuCfagaa asgsu		ACUUUCUGAGUACCCGCCGC UUC	
AD-1735300	csgscaggCfuGfUfCfcacccagu susa		VPusAfsacuGfgGfUfggacAfgCfcugc gsgsa		UCCGCAGGCUGUCCACCCAGU UC	
AD-1735301	gsgscuguGfaCfAfUfgggcaccu sgsa		VPusCfsaggUfgCfCfcaugUfcAfcagc csgsa		UCGGCUGUGACAUGGGCACC UGC	
AD-1735302	uscsagugAfgGfUfAfgcagcccu sgsa		VPusCfsaggGfcUfGfcuacCfuCfacug asasc		GUUCAGUGAGGUAGCAGCCC UGC	
AD-1735303	asgscgucAfuGfGfAfgcccaucc susa		VPusAfsggaUfgGfGfcuccAfuGfacgc usgsg		CCAGCGUCAUGGAGCCCAUCC UG	
AD-	csusggauGfgAfGfAfccucccug		VPusUfscagGfgAfGfgucuCfcAfucca		UGCUGGAUGGAGACCUCCCU	

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:
1735304	sasa		gscsa		GAG	
AD-1735305	uscsagccGfgAfGfUfgaguguug sgsa		VPusCfscaaCfaCfUfcacuCfcGfgcuga scsc		GGUCAGCCGGAGUGAGUGUU GGG	
AD-1735306	csusggccGfaCfUfGfgcuucugg sasa		VPusUfsccaGfaAfGfccagUfcGfgcca gscsu		AGCUGGCCGACUGGCUUCUG GAG	
AD-1735307	gsgsugcuGfcAfCfCfcfucacacca sgsa		VPusCfsuggUfgUfGfagguGfcAfgcac cscsu		AGGGUGCUGCACCUCACACC AGC	
AD-1735308	gsgscugcCfuGfGfAfgcauggag scsa		VPusGfscucCfaUfGfcuccAfgGfcagc csasa		UUGGCUGCCUGGAGCAUGGA GCC	
AD-1735309	cscsugcaGfcUfGfUfUfgcugggca susa		VPusAfsugcCfcAfGfcacaGfcUfgcag gsusg		CACCUGCAGCUGUGCUGGGC AUG	
AD-1735310	asgsuggcCfaUfGfCfaggcggug susa		VPusAfscacCfgCfCfugcaUfgGfccac usgsa		UCAGUGGCCAUGCAGGCGGU GUC	
AD-1735311	gsascuugGfcCfUfUfgggcagca susa		VPusAfsugcUfgCfCfcaagGfcCfaagu csgsg		CCGACUUGGCCUUGGGCAGC AUU	
AD-1735312	gsasgcgaAfgUfGfCfggguaccc susa		VPusAfsgggUfaCfCfcgcaCfuUfcgcu cscsu		AGGAGCGAAGUGCGGGUACC CUG	
AD-1735313	csusggugGfcCfUfCfugugugca sasa		VPusUfsugcAfcAfCfagagGfcCfacca ggsgg		CCCUGGUGGCCUCUGUGUGC AAU	
AD-1735314	asascccaCfcAfGfCfcgaggucgs asa		VPusUfscgaCfcUfCfggcuGfgUfgggu usgsu		ACAACCCACCAGCCGAGGUCG AG	
AD-1735315	usgsaugcUfgCfCfAfaggcgcac susa		VPusAfsgugCfgCfCfuuggCfaGfcauc asusc		GAUGAUGCUGCCAAGGCGCA CUU	
AD-1735316	cscsaaugAfgCfUfGfgccugccg sasa		VPusUfscggCfaGfGfccagCfuCfauug gscsa		UGCCAAUGAGCUGGCCUGCC GAG	
AD-1735317	gsusgcugCfaGfCfCfGfgguccugc sasa		VPusUfsgcaGfgAfCfccgcUfgCfagca csasu		AUGUGCUGCAGCGGGUCCUG CAG	
AD-1735318	gsgsgcguGfcAfGfAfgcgccagu sasa		VPusUfsacuGfgCfGfcucuGfcAfcgcc csusu		AAGGGCGUGCAGAGCGCCAG UAG	
AD-1735319	gsgsugagUfgGfCfAfccugcgaa susa		VPusAfsuucGfcAfGfgugcCfaCfucac csasc		GUGGUGAGUGGCACCUGCGA AUG	
AD-1735320	ascsggagGfgAfGfAfggacacgg sasa		VPusUfsccgUfgUfCfcucuCfcCfuccg usgsu		ACACGGAGGGAGAGGACACG GAG	

Table 12. Unmodified Sense and Antisense Strand Sequences of PDE3B dsRNA Agents Comprising an Unsaturated C22 Hydrocarbon Chain Conjugated to Position 6 on the Sense Strand, Counting from the 5'-end of the Sense Strand

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4
AD-1735321	UUCCUUCUUCAUCUUGAUCAA		2880-2900	UUGAUCAAGAUGAAGAAGGAAGU		2878-2900
AD-1735322	CACUCUAAAACUGAUGUUCAA		4621-4641	UUGAACAUCAGUUUUAGAGUGAA		4619-4641
AD-1735323	UCUUCUGUAUCACUGACUCAA		1752-1772	UUGAGUCAGUGAUACAGAAGAUG		1750-1772
AD-1735324	CAGAUCUUCUGACUGAUCCAA		1363-1383	UUGGAUCAGUCAGAAGAUCUGAC		1361-1383
AD-1735325	UGACACAUUUUUCUCCAUAAA		5958-5978	UUUAUGGAGAAAAAUGUGUCAGU		5956-5978
AD-1735326	GGAAACUCAUUUUUACAUAAA		5617-5637	UUUAUGUAAAAAUGAGUUUCCAG		5615-5637
AD-1735327	AUCAGCAACUUAGAAAUUCUA		1966-1986	UAGAAUUUCUAAGUUGCUGAUAA		1964-1986
AD-1735328	CUUAUAUUUCUCUAGAGUACA		5351-5371	UGUACUCUAGAGAAAUAUAAGGA		5349-5371
AD-1735329	AACUCCAAGAAUCUUUUAUCA		3229-3249	UGAUAAAAGAUUCUUGGAGUUUU		3227-3249
AD-1735330	CUUCAAACAUUCCUGCAUUAA		2680-2700	UUAAUGCAGGAAUGUUUGAAGAC		2678-2700
AD-1735331	UCGUUCUUCUCCUCAACUAGA		3206-3226	UCUAGUUGAGGAGAAGAACGAUC		3204-3226
AD-1735332	AAAGAUUAAUCCUCUCACACA		1460-1480	UGUGUGAGAGGAUUAAUCUUUGG		1458-1480
AD-1735333	ACUAACCUCAUCAAAGAUACA		4501-4521	UGUAUCUUUGAUGAGGUUAGUUU		4499-4521
AD-1735334	CACCACUUAUUACUAAUAAAA		5283-5303	UUUUAUUAGUAAUAAGUGGUGGG		5281-5303
AD-1735335	UGGUACUAGAAAUAUUCUUUA		5915-5935	UAAAGAAUAUUUCUAGUACCAGC		5913-5935

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4
AD-1735336	GCUGUCAUUUGUUCACUCUA A		4608-4628	UUAGAGUGAACAAAUGACAGCU A		4606-4628
AD-1735337	ACUCAACAAUUUAUGAACUA A		2421-2441	UUAGUUCAUAAAUUGUUGAGUG G		2419-2441
AD-1735338	AGUAUGACUCAUUAAUAGAA A		2269-2289	UUUCUAUUAAUGAGUCAUACUC U		2267-2289
AD-1735339	CUGCUGAUUUUCUUAAUAAG A		1891-1911	UCUUAUUAAGAAAAUCAGCAGU A		1889-1911
AD-1735340	UAUCUUUAGAUCCACAUCUU A		4587-4607	UAAGAUGUGGAUCUAAAGAUAA C		4585-4607
AD-1735341	CGAGACAUUCCUUAUCACAAA		2466-2486	UUUGUGAUAAGGAAUGUCUCGA U		2464-2486
AD-1735342	UACUGAAUCAGAUUAAUUUC A		5850-5870	UGAAAUUAAUCUGAUUCAGUAA C		5848-5870
AD-1735343	CUUACUUAAAUCCUUCACUGA		3855-3875	UCAGUGAAGGAUUUAAGUAAGG G		3853-3875
AD-1735344	UCGAAAGAAUCAUUCAAACU A		2100-2120	UAGUUUGAAUGAUUCUUUCGAG A		2098-2120
AD-1735345	AAAUGACCUAUCACUACUUA A		4682-4702	UUAAGUAGUGAUAGGUCAUUUC U		4680-4702
AD-1735346	CAAGUCAUUUCCUCUCUACGA		1395-1415	UCGUAGAGAGGAAAUGACUUGU G		1393-1415
AD-1735347	AUGCAGUUUCUUACUUAUCU A		5079-5099	UAGAUAAGUAAGAAACUGCAUG C		5077-5099
AD-1735348	UCAAUGCAAUACACUGUUCA A		4124-4144	UUGAACAGUGUAUUGCAUUGAG C		4122-4144
AD-1735349	UCUAUGUACCUACUGACACAA		5945-5965	UUGUGUCAGUAGGUACAUAGAU A		5943-5965
AD-1735350	UGAAUUCCAGUCUUAUCUUA A		4312-4332	UUAAGAUAAGACUGGAAUUCAA A		4310-4332
AD-1735351	UUGCUGUAAUACCAAAACUA A		4485-4505	UUAGUUUUGGUAUUACAGCAAA U		4483-4505
AD-1735352	GGAUCACUUCUUUCAAAUCA		1061-1081	UUGAUUUGAAAGAAGUGAUCCA		1059-1081

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4
	A			A		
AD-1735353	GAACUAGAAAACUAUUCUUA A		3795-3815	UUAAGAAUAGUUUUCUAGUUCC U		3793-3815
AD-1735354	ACAUUUCCAUACUGUCUGUU A		5484-5504	UAACAGACAGUAUGGAAAUGUG A		5482-5504
AD-1735355	UGAUCCUUCACAGUGUCAAU A		5158-5178	UAUUGACACUGUGAAGGAUCAA A		5156-5178
AD-1735356	GAUUUCUGAGAACAAGUAAA A		4729-4749	UUUUACUUGUUCUCAGAAAUCA G		4727-4749
AD-1735357	CCUACUUGUGAAAUACAUUU A		4906-4926	UAAAUGUAUUUCACAAGUAGGG U		4904-4926
AD-1735358	CAACUGGAAUUUUCCAAUUU A		2297-2317	UAAAUUGGAAAAUUCCAGUUGC U		2295-2317
AD-1735359	UCUAAUCCUGAUGAGAGUUA A		2649-2669	UUAACUCUCAUCAGGAUUAGAG C		2647-2669
AD-1735360	AGCCUCAUUAUCAAAAUUCU A		1288-1308	UAGAAUUUUGAUAAUGAGGCUU A		1286-1308
AD-1735361	AAUUUCUGAUGCUUUUUACU A		4220-4240	UAGUAAAAAAGCAUCAGAAAUUG A		4218-4240
AD-1735362	UACCAUUAGAUGAAAUCUUA A		5788-5808	UUAAGAUUUCAUCUAAUGGUAC A		5786-5808
AD-1735363	CUGUGAAUUCUUCCAACCAUA		1816-1836	UAUGGUUGGAAGAAUUCACAGG A		1814-1836
AD-1735364	CUAAUACUCCCAGAUUUUUAU A		1948-1968	UAUAAAAAAUCUGGAGUAUUAGG U		1946-1968
AD-1735365	GGACACAUACAUUGAAUAAA A		4550-4570	UUUUAUUCAAUGUAUGUGUCCU U		4548-4570
AD-1735366	UUUGUCAUAAUGCUGCUUUG A		3887-3907	UCAAAGCAGCAUUAUGACAAAG U		3885-3907
AD-1735367	UUCAUCUUUCUGUUAAUUUC A		4637-4657	UGAAAUUAACAGAAAGAUGAAC A		4635-4657
AD-1735368	CAGUGAAACCAUUAAUUUUC A		5028-5048	UGAAAAUUAAUGGUUUCACUGU G		5026-5048

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4
AD-1735369	UAACUGCAAGACUGAUUUCUA		4716-4736	UAGAAAUCAGUCUUGCAGUUAG		4714-4736
AD-1735370	AGAAUUCCUCCUUACCUCAAA		3547-3567	UUUGAGGUAAGGAGGAAUUCUC		3545-3567
AD-1735371	UAUUACAGAUCUUACUUUGU		5830-5850	UACAAAGUAAGAUCUGUAAUAU		5828-5850
AD-1735372	UUAUCUGAAAGAUAUCAAUU		5111-5131	UAAUUGAUAUCUUUCAGAUAAG		5109-5131
AD-1735373	AGAUCUGUUCUGGAAAAUCA		2811-2831	UUGAUUUUCCAGAACAGAUCUG		2809-2831
AD-1735374	CCCAGAAUACAACUUCCUUCA		2867-2887	UGAAGGAAGUUGUAUUCUGGGC		2865-2887
AD-1735375	GUUGAUCUUUCAGUGCUAAA		1323-1343	UUUUAGCACUGAAAGAUCAACU		1321-1343
AD-1735376	CUAAGCUUUAUUUAUUAGAC		5191-5211	UGUCUAAUAAAUAAAGCUUAGU		5189-5211
AD-1735377	AGCUUGGAAUCUAUAUCUUU		2843-2863	UAAAGAUAUAGAUUCCAAGCUG		2841-2863
AD-1735378	UUAUUAUUUCUGAAGCCUAA		4699-4719	UUUAGGCUUCAGAAAUAAUAAG		4697-4719
AD-1735379	CCUUUGUUGUAUUUAACAAA		4187-4207	UUUUGUUAAAUACAACAAAGGU		4185-4207
AD-1735380	GCUCUCUAACUAAUCGAUCAA		1852-1872	UUGAUCGAUUAGUUAGAGAGCC		1850-1872
AD-1735381	AAAGACUACAUGACAGAAAU		4666-4686	UAUUUCUGUCAUGUAGUCUUUA		4664-4686
AD-1735382	CAGGAUUCGUAUUUUUAAAG		4418-4438	UCUUUAAAAAUACGAAUCCUGA		4416-4438
AD-1735383	CCUUGCUAAGUAAUUGACAU		5659-5679	UAUGUCAAUUACUUAGCAAGGG		5657-5679
AD-1735384	CCUAUGCACUUUCACAGGAAA		3778-3798	UUUCCUGUGAAAGUGCAUAGGA		3776-3798
AD-1735385	AUGCUGAAAUAUGUUUCAAC		2019-2039	UGUUGAAACAUAUUUCAGCAUU		2017-2039

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4
	A			U		
AD-1735386	CCUUUUAAUUCAAAUCUACUA		1710-1730	UAGUAGAUUUGAAUUAAAAGGCC		1708-1730
AD-1735387	ACUGGACUUAUUGGAUUUAAA		5577-5597	UUUAAAUCCAAUAAGUCCAGUAU		5575-5597
AD-1735388	CAUCUGAAUCAGAUGGUACAA		2038-2058	UUGUACCAUCUGAUUCAGAUGU		2036-2058
AD-1735389	AAUUCUGAUAGCAAUCUGUGA		1980-2000	UCACAGAUUGCUAUCAGAAUUC		1978-2000
AD-1735390	UCAAGUCAAGGAUGCUAUCUA		1683-1703	UAGAUAGCAUCCUUGACUUGAA		1681-1703
AD-1735391	UCACUGAAAACCACAAGAUAA		3466-3486	UUAUCUUGUGGUUUUCAGUGAG		3464-3486
AD-1735392	ACCUGUUGAACAGUCUUCAAA		1616-1636	UUUGAAGACUGUUCAACAGGUA		1614-1636
AD-1735393	UCAAGUGACAUAUUUCAGUUA		3957-3977	UAACUGAAAUAUGUCACUUGAG		3955-3977
AD-1735394	UCAGGAACUUCAGGAUUGCUA		1596-1616	UAGCAAUCCUGAAGUUCCUGAG		1594-1616
AD-1735395	ACGGAGUAUUAGUAGCUUAAA		1412-1432	UUUAAGCUACUAAUACUCCGUA		1410-1432
AD-1735396	AUUGUCAAUGAAUUUUAUGAA		3135-3155	UUCAUAAAAUUCAUUGACAAUG		3133-3155
AD-1735397	GAACAGCAAACAAAUAUUGAA		2214-2234	UUCAAUAUUUGUUUGCUGUUCA		2212-2234
AD-1735398	UGAACUAUUUUCGUGCAUUAA		2434-2454	UUAAUGCACGAAAAUAGUUCAU		2432-2454
AD-1735399	ACUGGAAUACUUAUUUUUCAA		4751-4771	UUGAAAAAUAAGUAUUCCAGUU		4749-4771
AD-1735400	UUAUCUUGCAGAGAUCUCUGA		1918-1938	UCAGAGAUCUCUGCAAGAUAAC		1916-1938
AD-1735401	GAAGUGUUAGAAUUUUUGAUA		5142-5162	UAUCAAAAAUUCUAACACUUCC		5140-5162

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4
AD-1735402	UCAAUUUAAGAUCUCUGGAA A		5125-5145	UUUCCAGAGAUCUUAAAUUGAU A		5123-5145
AD-1735403	UGGACCAUAUUUACAAUGUU A		4856-4876	UAACAUUGUAAAUAUGGUCCAU U		4854-4876
AD-1735404	UAGUCAUUGAAGCAAUCCUU A		2926-2946	UAAGGAUUGCUUCAAUGACUAA A		2924-2946
AD-1735405	AGCUGUUUAGGUUUAACAAU A		4353-4373	UAUUGUUAAACCUAAACAGCUU U		4351-4373
AD-1735406	CAAGGCAAAUGAUGUAAAUA A		2993-3013	UUAUUUACAUCAUUUGCCUUGG C		2991-3013
AD-1735407	AUCCAAUUACUACUGGAAAC A		5603-5623	UGUUUCCAGUAGUAAUUGGAUU U		5601-5623
AD-1735408	ACUUACAAUAUAUAUAUCCU A		5328-5348	UAGGAUAUAUAUAUUGUAAGUG C		5326-5348
AD-1735409	AUGCAGUUUGGUAUCUGACA A		2512-2532	UUGUCAGAUACCAAACUGCAUG U		2510-2532
AD-1735410	CCUUAUUUCAAGACACUGGU A		2377-2397	UACCAGUGUCUUGAAAUAAGGU A		2375-2397
AD-1735411	GAAGGGAUUUAUUCUUUAGU A		4373-4393	UACUAAAGAAUAAAUCCCUUCA U		4371-4393
AD-1735412	AUCCUUGCUACGGAUCUUAA A		2940-2960	UUUAAGAUCCGUAGCAAGGAUU G		2938-2960
AD-1735413	ACUGACUAUCCCGAAGCAAAA		1727-1747	UUUUGCUUCGGGAUAGUCAGUA G		1725-1747
AD-1735414	UGUAUUUCUGCUAUUAUUUC A		5390-5410	UGAAAUAAUAGCAGAAAUACAC U		5388-5410
AD-1735415	UGUAACAAUAACUAGCCUAA A		5680-5700	UUUAGGCUAGUUAUUGUUACAU A		5678-5700
AD-1735416	GUUGUUUUUACUCUAGCUCA A		4400-4420	UUGAGCUAGAGUAAAAACAACA A		4398-4420
AD-1735417	CAGGCAGUUUUAUACAAUGA A		2790-2810	UUCAUUGUAUAAAACUGCCUGA G		2788-2810
AD-1735418	AGGAUUCUCAGUCAGGUUAU		2352-2372	UAUAACCUGACUGAGAAUCCUU		2350-2372

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4
	A			C		
AD-1735419	AUUUUCCAUCAUGUUUAAGUA		5371-5391	UACUUAAACAUGAUGGAAAAUGU		5369-5391
AD-1735420	UGCCACUUUUGUUACCAUUGA		5238-5258	UCAAUGGUAACAAAAGUGGCAGC		5236-5258
AD-1735421	ACUUGCUAGUGUGUGGAUAUA		4882-4902	UAUAUCCACACACUAGCAAGUUU		4880-4902
AD-1735422	AAUCUUACUUGAGAAAUUGCA		5801-5821	UGCAAUUUCUCAAGUAAGAUUUC		5799-5821
AD-1735423	AGUUCGAGACUUGCAUUUGAA		3101-3121	UUCAAAUGCAAGUCUCGAACUU		3099-3121
AD-1735424	CCAUAGAAUUUCCUGAUACUA		1873-1893	UAGUAUCAGGAAAUUCUAUGGG		1871-1893
AD-1735425	AGGUAAUUCCUUUAGAAUAUA		5050-5070	UAUAUUCUAAAGGAAUUACCUUG		5048-5070
AD-1735426	CUUAUGGAAACUCAACAAGAA		2118-2138	UUCUUGUUGAGUUUCCAUAAGUU		2116-2138
AD-1735427	AAGCAGCAUUUUAAAUUACGA		5554-5574	UCGUAAUUUAAAAUGCUGCUUUU		5552-5574
AD-1735428	UGACUCUCAACUGACCAUUCA		3699-3719	UGAAUGGUCAGUUGAGAGUCAGC		3697-3719
AD-1735429	AGGUUUAUCCAUGAAGGACUA		4161-4181	UAGUCCUUCAUGGAUAAACCUAG		4159-4181
AD-1735430	ACCAAGAAUUUUGGCAUUUCA		1666-1686	UUGAAAUGCCAAAUUCUUGGUGA		1664-1686
AD-1735431	UAUCUAGAAUAUUUGGCUUAA		5094-5114	UUAAGCCAAAUAUUCUAGAUAAG		5092-5114
AD-1735432	CUCCUGCAGAAUACAUACAAA		5412-5432	UUUGUAUGUAUUCUGCAGGAGAG		5410-5432
AD-1735433	UCACACCAUUUCCUGGAUUUA		1474-1494	UAAAUCCAGGAAAUGGUGUGAGG		1472-1494
AD-1735434	AUGUGGAAUUCAAGCGCUUUA		2899-2919	UAAAGCGCUUGAAUUCCACAUGA		2897-2919

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4
AD-1735435	AUUGUGUAUUAUCUACUAUGA		4240-4260	UCAUAGUAGAUAAUACACAAUAG		4238-4260
AD-1735436	AAUGGAGUAAUGAAAAUGAUA		3025-3045	UAUCAUUUUCAUUACUCCAUUCU		3023-3045
AD-1735437	ACUGGUUUAUUGGAAAUAUUA		2391-2411	UAAUAUUUCCAAUAAACCAGUG		2389-2411
AD-1735438	CAAGUGUAUGUGUAUAAAGUA		5429-5449	UACUUUAUACACAUACACUUGU		5427-5449
AD-1735439	UACAAGCAUGCAUAUUGAGA		5457-5477	UUCUCAAUAUGCAUGCUUGUAC		5455-5477
AD-1735440	UGUGUCUUUUAUGUCUUUGA		4036-4056	UUCAAAGACAUAAAAGACACAC		4034-4056
AD-1735441	AUUUUCUCGCAGAAUUCAAU		2971-2991	UAUUGAAUUCUGCGAGAAAAUC		2969-2991
AD-1735442	UAGCGACAGUUUGAGUAAAA		3609-3629	UUUUUACUCAAACUGUCGCUAU		3607-3629
AD-1735443	CUGGUGUAUGAAUACUUUGU		3872-3892	UACAAAGUAUUCAUACACCAGU		3870-3892
AD-1735444	GUGAUAAGUGGGCUAACAGAA		2182-2202	UUUCUGUUAGCCACUUAUCACC		2180-2202
AD-1735445	GUAGGCUAAUAUUUUCUAUU		4962-4982	UAAUAGAAAAUAUUAGCCUACC		4960-4982
AD-1735446	CCUCUUCAUCCUCGACUGUCA		1089-1109	UGACAGUCGAGGAUGAAGAGGC		1087-1109
AD-1735447	AAUUGCCAUAAGCCAUAUUA		5815-5835	UUAAUAUGGCUUAUGGCAAUUU		5813-5835
AD-1735448	GCGAAUAUUUUGUCAGCUAA		3437-3457	UUUAGCUGACAAAAUAUUCGCC		3435-3457
AD-1735449	AUCCAGUGUUGCCUUUCUGA		4093-4113	UUCAGAAAGGCAACACUGGAUU		4091-4113
AD-1735450	AAAGUCUAUGCCUGUCUAAA		4068-4088	UUUUAGACAGGCAUAGACUUUU		4066-4088
AD-1735451	GGACAUCAGAAGUUUGAAUU		4298-4318	UAAUUCAAACUUCUGAUGUCCA		4296-4318

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4
	A			U		
AD-1735452	GGCGAAUUGCUUAUAUUUCU A		2617-2637	UAGAAAUAUAAGCAAUUCGCCC A		2615-2637
AD-1735453	CACACUAUGUGUAAACCAGU A		5261-5281	UACUGGUUUACACAUAGUGUGU G		5259-5281
AD-1735454	CAGGUGAAGAAGAAAACAUU A		2077-2097	UAAUGUUUUCUUCUUCACCUGA U		2075-2097
AD-1735455	GUGAGCUCUUAUUUUUCACU A		3914-3934	UAGUGAAAAAUAAGAGCUCACU A		3912-3934
AD-1735456	AAAGCUGAUGGGAAUAAACU A		3519-3539	UAGUUUAUUCCCAUCAGCUUUA C		3517-3539
AD-1735457	GUGUCGUUAGGAGAAACUGC A		1164-1184	UGCAGUUUCUCCUAACGACACG C		1162-1184
AD-1735458	GGGACUUAAAACAAUGGUAU A		1267-1287	UAUACCAUUGUUUUAAGUCCCA A		1265-1287
AD-1735459	CUGAUGGUAGAAUUAACCAU A		2596-2616	UAUGGUUAAUUCUACCAUCAGA A		2594-2616
AD-1735460	ACUAUGUGUGUUUUAUUUCU A		4254-4274	UAGAAAUAAAAACACACAUAGUA G		4252-4274
AD-1735461	CUGAUAAUUUAUAUUUGCAC A		5310-5330	UGUGCAAAUAUAAAUUAUCAGU C		5308-5330
AD-1735462	GUCCUUAAAUUAUUUAACCC A		5641-5661	UGGGUUAAAUAAUUUAAGGACU A		5639-5661
AD-1735463	CGCAAUAUGGUGUCAGAUCU A		1350-1370	UAGAUCUGACACCAUAUUGCGA G		1348-1370
AD-1735464	UUCGAAGAGCUGCUCUAAUC A		2636-2656	UGAUUAGAGCAGCUCUUCGAAG A		2634-2656
AD-1735465	UUUCUGCUGAGAGUAUUCAG A		4269-4289	UCUGAAUACUCUCAGCAGAAAU A		4267-4289
AD-1735466	UUGAACAGGAAGUAUCACUG A		2230-2250	UCAGUGAUACUUCCUGUUCAAU A		2228-2250
AD-1735467	UGCCUUGUAUUUCCAGAGAA A		1228-1248	UUUCUCUGGAAAUACAAGGCAA C		1226-1248

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4
AD-1735468	GUUACUAUGGCAGUUGCAAA A		1189-1209	UUUUGCAACUGCCAUAGUAACU G		1187-1209
AD-1735469	AUGGCUGAAUUUUAAAGCUG A		4338-4358	UCAGCUUUAAAAUUCAGCCAUG G		4336-4358
AD-1735470	GUCCAUUCAUGGAUCGUUCU A		3193-3213	UAGAACGAUCCAUGAAUGGACU G		3191-3213
AD-1735471	UGUGUAACUCCUAUGAUGCU A		3268-3288	UAGCAUCAUAGGAGUUACACAG G		3266-3288
AD-1735472	UGGCAGUUUCCCACUCCUAUA		3763-3783	UAUAGGAGUGGGAAACUGCCAG C		3761-3783
AD-1735473	CCUCAAGCAGAUGAGAUUCA A		3561-3581	UUGAAUCUCAUCUGCUUGAGGU A		3559-3581
AD-1735474	AUGUUGUUUUCUCAAAAGCA A		5539-5559	UUGCUUUUGAGAAAACAACAUA A		5537-5559
AD-1735475	GAGGGAUUUCUGCUCAAUGC A		4111-4131	UGCAUUGAGCAGAAAUCCCUCA G		4109-4131
AD-1735476	GCCUUCUUCUUCCUCACCUGA		654-674	UCAGGUGAGGAAGAAGAAGGCA C		652-674
AD-1735477	UUGAGAUUGAAUCACAUUUC A		5471-5491	UGAAAUGUGAUUCAAUCUCAAU A		5469-5491
AD-1735478	CUGUUCAGUGCUAUUCUCCCA		4137-4157	UGGGAGAAUAGCACUGAACAGU G		4135-4157
AD-1735479	CCUGGCUUACAGCAGAUCCAA		2544-2564	UUGGAUCUGCUGUAAGCCAGGA A		2542-2564
AD-1735480	GACAGCAGAAAAUUAUUUUCA A		2157-2177	UUGAAAUAAUUUUCUGCUGUCU U		2155-2177
AD-1735481	UUGGGUUUCUUUAGUUUAUG A		5522-5542	UCAUAAACUAAAGAAACCCAAU A		5520-5542
AD-1735482	CACCAUGUAGGUCUCAGAAG A		1770-1790	UCUUCUGAGACCUACAUGGUGA G		1768-1790
AD-1735483	GUUGUGGAACAGGAAAUGAA A		2569-2589	UUUCAUUUCCUGUUCCACAACC A		2567-2589
AD-1735484	GGAGAACAUAUCAUAUUUUG		4988-5008	UCAAAAUAUGAUAUGUUCUCCA		4986-5008

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4
	A			A		
AD-1735485	CAGCCAAAAAUGAUGGCAAAA A		4940-4960	UUUUUGCCAUCAUUUUGGCUGC U		4938-4960
AD-1735486	CCAAUUUUUGAACUUGUAGA A		2310-2330	UUCUACAAGUUCAAAAAUUGGA A		2308-2330
AD-1735487	AUAGGAAUAGUUUGCCAACU A		1558-1578	UAGUUGGCAAACUAUUCCUAUU U		1556-1578
AD-1735488	UUUGAAUGUUUUGGAGAAAA A		4051-4071	UUUUUCUCCAAAACAUUCAAAG A		4049-4071
AD-1735489	GUCAAUAUUUAAUGAAUCAC A		5172-5192	UGUGAUUCAUUAAAUAUUGACA C		5170-5192
AD-1735490	UGAGAAUAUAUUAAAUGCAC A		5764-5784	UGUGCAUUUAAUAUAUUCUCAC A		5762-5784
AD-1735491	UAACAAGGGACUAAAUAGGA A		1544-1564	UUCCUAUUUAGUCCCUUGUUAA G		1542-1564
AD-1735492	GGCUUCUUCUUCCACCUCUGA		408-428	UCAGAGGUGGAAGAAGAAGCCG C		406-428
AD-1735493	UUGGAACAUGUGGUUAUCUU A		4573-4593	UAAGAUAACCACACAUGUUCCAAU U		4571-4593
AD-1735494	CAGAGAACAGAUGAUCUUU A		1241-1261	UAAAGAAUCAUCUGUUCUCUGG A		1239-1261
AD-1735495	CUGUUAUUUUAUUGGGUUUU A		5499-5519	UAAAACCCAAUAAAAUAACAGA C		5497-5519
AD-1735496	AUGAAGAAGCAAAUCUUGGU A		3163-3183	UACCAAGAUUUGCUUCUUCAUC U		3161-3183
AD-1735497	UUUGGAAUCAUGCAAUUUUG A		5004-5024	UCAAAAUUGCAUGAUUCCAAAA U		5002-5024
AD-1735498	CAAUGUUUUGUAAACUUGCU A		4869-4889	UAGCAAGUUUACAAAACAUUGU A		4867-4889
AD-1735499	GGAUCGUAAUAAUGGCAAAA A		1640-1660	UUUUUGCCAUUAUUACGAUCCC A		1638-1660
AD-1735500	GUGCUUUCUCAGGUUCCUGU A		1435-1455	UACAGGAACCUGAGAAAGCACC C		1433-1455

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4
AD-1735501	AUGAUACUGAAAGUGGUGAUA		3331-3351	UAUCACCACUUUCAGUAUCAUUA		3329-3351
AD-1735502	UCACUGGACCUGAUUUUUAGUA		2244-2264	UACUAAAAAUCAGGUCCAGUGAUA		2242-2264
AD-1735503	GAACUUUUUGCUUUUAUGAAA		3991-4011	UUUCAUAAAAGCAAAAAGUUCCU		3989-4011
AD-1735504	GAACACAGCACAGAUUUGUUA		4451-4471	UAACAAAUCUGUGCUGUGUUCAU		4449-4471
AD-1735505	AUAUGGAAGGAAAUCGUAGAA		3483-3503	UUCUACGAUUUCCUUCCAUAUCU		3481-3503
AD-1735506	GCUAUCUAAAUGGGCCUUUUA		1696-1716	UAAAAGGCCCAUUUAGAUAGCAU		1694-1716
AD-1735507	CAAAACCACCAAGAAGGAAAA		3409-3429	UUUUCCUUCUUGGUGGUUUUGG		3407-3429
AD-1735508	CCACAGAUGUGCUACAUGCAA		2497-2517	UUGCAUGUAGCACAUCUGUGGC		2495-2517
AD-1735509	AAAGUCAUACAUGUACAAGCA		5444-5464	UGCUUGUACAUGUAUGACUUUA		5442-5464
AD-1735510	UAGAAGCAGAAGAGGAUAAUA		3313-3333	UAUUAUCCUCUUCUGCUUCUAAC		3311-3333
AD-1735511	CGUGUGUUCGCACAGCUUGAA		611-631	UUCAAGCUGUGCGAACACACGCU		609-631
AD-1735512	GCUGGUGUUUUGUCCAGUCUA		1791-1811	UAGACUGGACAAAACACCAGCUC		1789-1811
AD-1735513	AUGGAAAACAAUCUAAAUCCA		3390-3410	UGGAUUUAGAUUGUUUUCCAUU		3388-3410
AD-1735514	CAUUAGAAAAUGGCUAUCGAA		2449-2469	UUCGAUAGCCAUUUUCUAAUGC		2447-2469
AD-1735515	AUGGACAGAAGGCAUUGUCAA		3122-3142	UUGACAAUGCCUUCUGUCCAUU		3120-3142
AD-1735516	CAGAUUGCUGCAGUGGAAAAA		2056-2076	UUUUUCCACUGCAGCAAUCUGU		2054-2076
AD-1735517	AGGUGGAAAUGGAGUUGAUCA		1310-1330	UGAUCAACUCCAUUUCCACCUCC		1308-1330

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4
	A			C		
AD-1735518	CUGGGCAAUGCACCUAAUACA		1935-1955	UGUAUUAGGUGCAUUGCCCAGA G		1933-1955
AD-1735519	AUUUCCCCUCUGCCUAAAGACA		4652-4672	UGUCUUUAGGCAGAGGGAAAUU A		4650-4672
AD-1735520	CGCUUCUGCAACGUGGAGCUA		429-449	UAGCUCCACGUUGCAGAAGCGG C		427-449
AD-1735521	AGAUUCAUAUUGUAUUUCCC A		4014-4034	UGGGAAAUACAAUAUGAAUCUA U		4012-4034
AD-1735522	AGGACAAAUGCAUUUCUAGU A		2754-2774	UACUAGAAAUGCAUUUGUCCUC C		2752-2774
AD-1735523	UUAGACGUGUUGAGUGAGUG A		5205-5225	UCACUCACUCAACACGUCUAAU A		5203-5225
AD-1735524	CUGUGGACAUCAAAUGCUGA A		2006-2026	UUCAGCAUUUGAUGUCCACAGC U		2004-2026
AD-1735525	AGGCCUUAAUACUGUGAGAG A		3729-3749	UCUCUCACAGUAUUAAGGCCUG U		3727-3749
AD-1735526	AGAAAUCAUUGCCUAGUGUU A		3672-3692	UAACACUAGGCAAUGAUUUCUG C		3670-3692
AD-1735527	UGAGUGCUGAGUUCCUUGCU A		5219-5239	UAGCAAGGAACUCAGCACUCAC U		5217-5239
AD-1735528	GCCAUGCAUGAUUAUGAUCA A		2727-2747	UUGAUCAUAAUCAUGCAUGGCA G		2725-2747
AD-1735529	UGCUGCUGGUUUGCUACCAG A		3284-3304	UCUGGUAGCAAACCAGCAGCAU C		3282-3304
AD-1735530	CAGAUGAAGAGGAAUAGCGA A		3595-3615	UUCGCUAUUCCUCUUCAUCUGC C		3593-3615
AD-1735531	AUCCAGGUGCAUCAAUUUCU A		4207-4227	UAGAAAUUGAUGCACCUGGAUU U		4205-4227
AD-1735532	AAUAAGCCAAGCGUUAUCUU A		1905-1925	UAAGAUAACGCUUGGCUUAUUA A		1903-1925
AD-1735533	GAGAGGAUCCUUGCUCUGCU A		3744-3764	UAGCAGAGCAAGGAUCCUCUCA C		3742-3764

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4
AD-1735534	AUGAUGAAGACGGUGAAGAA A		3349-3369	UUUCUUCACCGUCUUCAUCAUC A		3347-3369
AD-1735535	UCGUAAGUGUAAGAAAGAAU A		5743-5763	UAUUCUUUCUUACACUUACGAA U		5741-5763
AD-1735536	AUCUGUGUAACAGCUGUGGA A		1993-2013	UUCCACAGCUGUUACACAGAUU G		1991-2013
AD-1735537	AUUUAAAAUUCCCACUCAACA		2408-2428	UGUUGAGUGGGAAUUUUAAAUA U		2406-2428
AD-1735538	GACCAGUGUCUACUGGCUCUA		1837-1857	UAGAGCCAGUAGACACUGGUCC A		1835-1857
AD-1735539	CGCUUUCGUUUUUUAGUCAU A		2913-2933	UAUGACUAAAAAACGAAAGCGC U		2911-2933
AD-1735540	UCCGUGUUGACCCAUGUUGCA		3829-3849	UGCAACAUGGGUCAACACGGAU G		3827-3849
AD-1735541	AUACAGAAGAUGAAGAAAUG A		3373-3393	UCAUUUCUUCAUCUUCUGUAUC U		3371-3393
AD-1735542	UCUCCCGAGCUGAAACUUAAA		5719-5739	UUUAAGUUUCAGCUCGGGAGAG A		5717-5739
AD-1735543	UGCAUCAAACUGGCAGAUAU A		3066-3086	UAUAUCUGCCAGUUUGAUGCAC A		3064-3086
AD-1735544	UUGCAAAAUAUUCAGGAGAC A		1202-1222	UGUCUCCUGAAUAUUUUGCAAC U		1200-1222
AD-1735545	ACAAUCGUAUACAUGCCACAA A		2482-2502	UUGUGGCAUGUAUACGAUUGUG A		2480-2502
AD-1735546	AAUAGAAAAGAUGAGCAACU A		2282-2302	UAGUUGCUCAUCUUUUCUAUUA A		2280-2302
AD-1735547	UAUCUUAUGUUCCAUGGCUG A		4325-4345	UCAGCCAUGGAACAUAAGAUAA G		4323-4345
AD-1735548	CUACGUGAAGAGCUGCGUGA A		362-382	UUCACGCAGCUCUUCACGUAGC C		360-382
AD-1735549	GAAUUGAUGGCUCUAUACGU A		2700-2720	UACGUAUAGAGCCAUCAAUUCU A		2698-2720
AD-1735550	UUCAGGUAAUUGAAGAGGCA		3577-3597	UUGCCUCUUCAAUUACCUGAAU		3575-3597

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4
	A			C		
AD-1735551	AAGGACUGAGUGACCUUUGUA		4174-4194	UACAAAGGUCACUCAGUCCUUCA		4172-4194
AD-1735552	CGAGAGUCUGAGGAACGGCUA		344-364	UAGCCGUUCCUCAGACUCUCGGG		342-364
AD-1735553	AUUCUUUGGGAUUGGGACUUA		1254-1274	UAAGUCCCAAUCCCAAAGAAUCA		1252-1274
AD-1735554	UACCAGGUCAGUGGUUAGAAA		3298-3318	UUUCUAACCACUGACCUGGUAGC		3296-3318
AD-1735555	AUUCAGGUUUGCCAUGGACAA		4283-4303	UUGUCCAUGGCAAACCUGAAUAC		4281-4303
AD-1735556	GCAGCUAAACUGGUCCUGGAA		34-54	UUCCAGGACCAGUUUAGCUGCCG		32-54
AD-1735557	AGUAAUGGCAUAGAAUGGAGA		3012-3032	UCUCCAUUCUAUGCCAUUACUAU		3010-3032
AD-1735558	AAUUGCAAGAAAAUGGACCAA		4843-4863	UUGGUCCAUUUUCUUGCAAUUAU		4841-4863
AD-1735559	CGGCACUGCGUUCUGGUGCUA		921-941	UAGCACCAGAACGCAGUGCCGGA		919-941
AD-1735560	AGUCAUAUUGAAGAAGCCCAA		3633-3653	UUGGGCUUCUUCAAUAUGACUUU		3631-3653
AD-1735561	UCAUCAUGCUGCGUCAGCUUA		2828-2848	UAAGCUGACGCAGCAUGAUGAUU		2826-2848
AD-1735562	AAAUGAUCGCCUCUUGGUAUA		3038-3058	UAUACCAAGAGGCGAUCAUUUUC		3036-3058
AD-1735563	AUUUGAAGAUAUAAAGAGCAA		4922-4942	UUGCUCUUUAUAUCUUCAAAUGU		4920-4942
AD-1735564	GGUCUCCUUCACCAGCCUCGA		965-985	UCGAGGCUGGUGAAGGAGACCCA		963-985
AD-1735565	GAAACAGAGAAGAAAGACAGA		2142-2162	UCUGUCUUUCUUCUCUGUUUCCU		2140-2162
AD-1735566	UUCUAGUGGCUACAAAUGCCA		2767-2787	UGGCAUUUGUAGCCACUAGAAAU		2765-2787

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4
AD-1735567	GGAGAGAAAUCAGGAAGGAU A		2337-2357	UAUCCUUCCUGAUUUCUCUCCC A		2335-2357
AD-1735568	AUAUAGUGAGCCCUAAAGGA A		4533-4553	UUCCUUUAGGGCUCACUAUAUU U		4531-4553
AD-1735569	GCUGCCUUUGUCCUCGCCCUA		528-548	UAGGGCGAGGACAAAGGCAGCC A		526-548
AD-1735570	GGCAAAAGACCUCACCAAGAA		1653-1673	UUCUUGGUGAGGUCUUUUGCCA U		1651-1673
AD-1735571	UUCAGCAUCGCCUGUGCCUUA		639-659	UAAGGCACAGGCGAUGCUGAAG A		637-659
AD-1735572	GCUAAAUGAGGCUCGCAAUA A		1337-1357	UUAUUGCGAGCCUCAUUUAGCA C		1335-1357
AD-1735573	CAGCUUCGUCUGGUGGGUCU A		950-970	UAGACCCACCAGACGAAGCUGG C		948-970
AD-1735574	AUAUGGUAUUGGCAUGCAGU A		5066-5086	UACUGCAUGCCAAUACCAUAUU C		5064-5086
AD-1735575	AAACUGCAGGUGGAGAAUUC A		3534-3554	UGAAUUCUCCACCUGCAGUUUA U		3532-3554
AD-1735576	UAUGGCUGCCUGUCUUCAAA A		2667-2687	UUUUGAAGACAGGCAGCCAUAA C		2665-2687
AD-1735577	CUGUUCUGAAAUAGAGGACC A		1499-1519	UGGUCCUCUAUUUCAGAACAGG G		1497-1519
AD-1735578	UCUAUUUUUAAAGCCGCUGG A		5898-5918	UCCAGCGGCUUUAAAAAUAGAA A		5896-5918
AD-1735579	GCUGAGGAGAAGCUCAGGAA A		1583-1603	UUUCCUGAGCUUCUCCUCAGCU G		1581-1603
AD-1735580	CAAGCCUUCCACCACAAGUCA		1381-1401	UGACUUGUGGUGGAAGGCUUGG A		1379-1401
AD-1735581	UUCAGUUACCAAAGUGGCCA A		3970-3990	UUGGCCACUUUGGUAACUGAAA U		3968-3990
AD-1735582	CACCUGCUUCCUCACCCGGAA		668-688	UUCCGGGUGAGGAAGCAGGUGA G		666-688
AD-1735583	UUUUAUCACCCACAUAGUGG		3242-3262	UCCACUAUGUGGGUGAUAAAAG		3240-3262

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4
	A			A		
AD-1735584	AGGAGACCGUCGUUGCCUUGA		1215-1235	UCAAGGCAACGACGGUCUCCUGA		1213-1235
AD-1735585	AUGGCCCAGCAAAAGUUCGAA		3088-3108	UUCGAACUUUUGCUGGGCCAUUU		3086-3108
AD-1735586	AGACGCCAAAGCCAUGCGGUA		290-310	UACCGCAUGGCUUUGGCGUCUCG		288-310
AD-1735587	CAGCUAAUGCACCACCUCACA		3450-3470	UGUGAGGUGGUGCAUUAGCUGAC		3448-3470
AD-1735588	GGAAAAGCAGACGGCGAAUAA		3424-3444	UUAUUCGCCGUCUGCUUUUCCUU		3422-3444
AD-1735589	GCUUUGCUGGGUAGUGAGCUA		3901-3921	UAGCUCACUACCCAGCAAAGCAG		3899-3921

Table 13. Modified Sense and Antisense Strand Sequences of PDE3B dsRNA Agents Comprising an Unsaturated C22 Hydrocarbon Chain Conjugated to Position 6 on the Sense Strand, Counting from the 5'-end of the Sense Strand

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-1735321	ususccu(Uda)CfuUfCfAfucuugaucsasa		VPusUfsgauCfaAfGfaugaAfgAfaggaasgsu		ACUUCCUUCUUCAUCUUGAUCAU	
AD-1735322	csascuc(Uda)AfaAfAfCfugauguucsasa		VPusUfsgaaCfaUfCfaguuUfuAfgagugsasa		UUCACUCUAAAACUGAUGUUCAU	
AD-1735323	uscsuuc(Uda)GfuAfUfCfacugacucsasa		VPusUfsgagUfcAfGfugauAfcAfgaagasusg		CAUCUUCUGUAUCACUGACUCAC	
AD-1735324	csasgau(Cda)UfuCfUfGfacugauccsasa		VPusUfsggaUfcAfGfucagAfaGfaucugsasc		GUCAGAUCUUCUGACUGAUCCAA	
AD-1735325	usgsaca(Cda)AfuUfUfUfucuccauasasa		VPusUfsuauGfgAfGfaaaaAfuGfugucasgsu		ACUGACACAUUUUUCUCCAUAAA	
AD-1735326	gsgsaaa(Cda)UfcAfUfUfuuuacauasasa		VPusUfsuauGfuAfAfaaauGfaGfuuuccsasg		CUGGAAACUCAUUUUUACAUAAU	
AD-	asuscag(Cda)AfaCfUfUfagaaauuc		VPusAfsgaaUfuUfCfuaagUfuGfcugaus		UUAUCAGCAACUUAGAAAU	

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:
1735327	susa		asa		UCUG	
AD-1735328	csusuau(Ada)UfuUfCfUfcuagagua scsa		VPusGfsuacUfcUfAfgagaAfaUfauaags gsa		UCCUUAUAUUUCUCUAGAG UACA	
AD-1735329	asascuc(Cda)AfaGfAfAfcuuuuuau scsa		VPusGfsauaAfaAfGfauucUfuGfgaguus usu		AAAACUCCAAGAAUCUUUU AUCA	
AD-1735330	csusuca(Ada)AfcAfUfUfccugcauu sasa		VPusUfsaauGfcAfGfgaauGfuUfugaags asc		GUCUUCAAACAUUCCUGCA UUAG	
AD-1735331	uscsguu(Cda)UfuCfUfCfcucaacua sgsa		VPusCfsuagUfuGfAfggagAfaGfaacgas usc		GAUCGUUCUUCUCCUCAAC UAGC	
AD-1735332	asasaga(Uda)UfaAfUfCfcucucaca scsa		VPusGfsuguGfaGfAfggauUfaAfucuuu sgsg		CCAAAGAUUAAUCCUCUCA CACC	
AD-1735333	ascsuaa(Cda)CfuCfAfUfcaaagaua scsa		VPusGfsuauCfuUfUfgaugAfgGfuuagu susu		AAACUAACCUCAUCAAAGA UACA	
AD-1735334	csascca(Cda)UfuAfUfUfUfacuaauaa sasa		VPusUfsuuaUfuAfUfGfuaauAfaGfuggug sgsg		CCCACCACUUAUUACUAAU AAAA	
AD-1735335	usgsgua(Cda)UfaGfAfAfauauucu ususa		VPusAfsaagAfaUfAfuuucUfaGfuaccas gsc		GCUGGUACUAGAAAUAUUC UUUU	
AD-1735336	gscsugu(Cda)AfuUfUfUfGfuucacuc usasa		VPusUfsagaGfuGfAfacaaAfuGfacagcs usa		UAGCUGUCAUUUGUUCACU CUAA	
AD-1735337	ascsuca(Ada)CfaAfUfUfUfuaugaacu sasa		VPusUfsaguUfcAfUfaaauUfgUfugagus gsg		CCACUCAACAAUUUAUGAA CUAU	
AD-1735338	asgsuau(Gda)AfcUfCfAfuuaauaga sasa		VPusUfsucuAfuUfAfaugaGfuCfauacus csu		AGAGUAUGACUCAUUAAUA GAAA	
AD-1735339	csusgcu(Gda)AfuUfUfUfcuuaauaa sgsa		VPusCfsuuaUfuAfAfgaaaAfuCfagcags usa		UACUGCUGAUUUUCUUAAU AAGC	
AD-1735340	usasucu(Uda)UfaGfAfUfccacaucu susa		VPusAfsagaUfgUfGfgaucUfaAfagauas asc		GUUAUCUUUAGAUCCACAU CUUA	
AD-1735341	csgsaga(Cda)AfuUfCfCfcuuaucaca sasa		VPusUfsuguGfaUfAfaggaAfuGfucucg sasu		AUCGAGACAUUCCUUAUCA CAAU	
AD-1735342	usascug(Ada)AfuCfAfGfauuaauu uscsa		VPusGfsaaaUfuAfAfucugAfuUfcaguas asc		GUUACUGAAUCAGAUUAAU UUCU	
AD-1735343	csusuac(Uda)UfaAfAfUfccuucacu sgsa		VPusCfsaguGfaAfGfgauuUfaAfguaags gsg		CCCUUACUUAAAUCCUUCA CUGG	
AD-1735344	uscsgaa(Ada)GfaAfUfCfauucaaac susa		VPusAfsguuUfgAfAfugauUfcUfuucga sgsa		UCUCGAAAGAAUCAUUCAA ACUU	

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-1735345	asasaug(Ada)CfcUfAfUfcacuacuusasa		VPusUfsaagUfaGfUfgauaGfgUfcauuuscsu		AGAAAUGACCUAUCACUACUUAU	
AD-1735346	csasagu(Cda)AfuUfUfUfCfcucucuacsgsa		VPusCfsguaGfaGfAfggaaAfuGfacuugsusg		CACAAGUCAUUUCCUCUCUACGG	
AD-1735347	asusgca(Gda)UfuUfCfUfUfuacuuaucsusa		VPusAfsgauAfaGfUfaagaAfaCfugcausgsc		GCAUGCAGUUUCUUACUUAUCUA	
AD-1735348	uscsaau(Gda)CfaAfUfAfcacuguucsasa		VPusUfsgaaCfaGfUfguauUfgCfauugasgsc		GCUCAAUGCAAUACACUGUUCAG	
AD-1735349	uscsuau(Gda)UfaCfCfUfUfacugacacsasa		VPusUfsgugUfcAfGfuaggUfaCfauagasusa		UAUCUAUGUACCUACUGACACAU	
AD-1735350	usgsaau(Uda)CfcAfGfUfUfcuuaucuusasa		VPusUfsaagAfuAfAfgacuGfgAfauucasasa		UUUGAAUUCCAGUCUUAUCUUAU	
AD-1735351	ususgcu(Gda)UfaAfUfAfUfccaaaacusasa		VPusUfsaguUfuUfGfguauUfaCfagcaasasu		AUUUGCUGUAAUACCAAAACUAA	
AD-1735352	gsgsauc(Ada)CfuUfCfUfUfuucaaaucsasa		VPusUfsgauUfuGfAfaagaAfgUfgauccsasa		UUGGAUCACUUCUUUCAAAUCAG	
AD-1735353	gsasacu(Ada)GfaAfAfAfAfcuauucuusasa		VPusUfsaagAfaUfAfguuuUfcUfaguucscsu		AGGAACUAGAAAACUAUUCUUAA	
AD-1735354	ascsauu(Uda)CfcAfUfAfcugucugususa		VPusAfsacaGfaCfAfguauGfgAfaaugusgsa		UCACAUUUCCAUACUGUCUGUUA	
AD-1735355	usgsauc(Cda)UfuCfAfCfagugucaasusa		VPusAfsuugAfcAfCfugugAfaGfgaucasasa		UUUGAUCCUUCACAGUGUCAAUA	
AD-1735356	gsasuuu(Cda)UfgAfGfAfacaaguaasasa		VPusUfsuuaCfuUfGfuucuCfaGfaaaucsasg		CUGAUUUCUGAGAACAAGUAAAG	
AD-1735357	cscsuac(Uda)UfgUfGfAfaauacauususa		VPusAfsaauGfuAfUfuucaCfaAfguaggsgsu		ACCCUACUUGUGAAAUACAUUUG	
AD-1735358	csasacu(Gda)GfaAfUfUfuuccaauususa		VPusAfsaauUfgGfAfaaauUfcCfaguugscsu		AGCAACUGGAAUUUUCCAAUUUU	
AD-1735359	uscsuaa(Uda)CfcUfGfAfugagaguusasa		VPusUfsaacUfcUfCfaucaGfgAfuuagasgsc		GCUCUAAUCCUGAUGAGAGUUAU	
AD-1735360	asgsccu(Cda)AfuUfAfUfUfcaaaauucususa		VPusAfsgaaUfuUfUfgauaAfuGfaggcususa		UAAGCCUCAUUAUCAAAAUUCUG	
AD-1735361	asasuuu(Cda)UfgAfUfGfcuuuuuasusa		VPusAfsguaAfaAfAfgcauCfaGfaaauusgsa		UCAAUUUCUGAUGCUUUUUACUA	
AD-	usascca(Uda)UfaGfAfUfgaaaucuu		VPusUfsaagAfuUfUfcaucUfaAfugguas		UGUACCAUUAGAUGAAAUC	

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:
1735362	sasa		csa		UUAC	
AD-1735363	csusgug(Ada)AfuUfCfUfuccaacca susa		VPusAfsuggUfuGfGfaagaAfuUfcacags gsa		UCCUGUGAAUUCUUCCAAC CAUG	
AD-1735364	csusaau(Ada)CfuCfCfCfAfgauuuuua susa		VPusAfsuaaAfaAfUfcuggAfgUfauuags gsu		ACCUAAUACUCCAGAUUUU UAUC	
AD-1735365	gsgsaca(Cda)AfuAfCfAfuugaauaa sasa		VPusUfsuuaUfuCfAfauguAfuGfugucc susu		AAGGACACAUACAUUGAAU AAAU	
AD-1735366	usususgu(Cda)AfuAfAfUfgcugcuu usgsa		VPusCfsaaaGfcAfGfcauuAfuGfacaaas gsu		ACUUUGUCAUAAUGCUGCU UUGC	
AD-1735367	ususcau(Cda)UfuUfCfUfguuaauu uscsa		VPusGfsaaaUfuAfAfcagaAfaGfaugaas csa		UGUUCAUCUUUCUGUUAAU UUCC	
AD-1735368	csasgug(Ada)AfaCfCfAfuuaauuuu scsa		VPusGfsaaaAfuUfAfauggUfuUfcacugs usg		CACAGUGAAACCAUUAAUU UUCC	
AD-1735369	usasacu(Gda)CfaAfGfAfcugauuuc susa		VPusAfsgaaAfuCfAfgucuUfgCfaguuas gsg		CCUAACUGCAAGACUGAUU UCUG	
AD-1735370	asgsaau(Uda)CfcUfCfCfuuaccuca sasa		VPusUfsugaGfgUfAfaggaGfgAfauucu scsc		GGAGAAUUCCUCCUUACCU CAAG	
AD-1735371	usasuua(Cda)AfgAfUfCfuuacuuu gsusa		VPusAfscaaAfgUfAfagauCfuGfuaauas usg		CAUAUUACAGAUCUUACUU UGUU	
AD-1735372	ususauc(Uda)GfaAfAfGfauaucaau susa		VPusAfsauuGfaUfAfucuuUfcAfgauaas gsc		GCUUAUCUGAAAGAUAUCA AUUU	
AD-1735373	asgsauc(Uda)GfuUfCfUfggaaaauc sasa		VPusUfsgauUfuUfCfcagaAfcAfgaucus gsu		ACAGAUCUGUUCUGGAAAA UCAU	
AD-1735374	cscscag(Ada)AfuAfCfAfacuuccuu scsa		VPusGfsaagGfaAfGfuuguAfuUfcuggg scsg		CGCCCAGAAUACAACUUCC UUCU	
AD-1735375	gsusuga(Uda)CfuUfUfCfagugcuaa sasa		VPusUfsuuaGfcAfCfugaaAfgAfucaacs usc		GAGUUGAUCUUUCAGUGCU AAAU	
AD-1735376	csusaag(Cda)UfuUfAfUfuauuuaga scsa		VPusGfsucuAfaUfAfaauaAfaGfcuuags usg		CACUAAGCUUUAUUUAUUA GACG	
AD-1735377	asgscuu(Gda)GfaAfUfCfuauaucuu susa		VPusAfsaagAfuAfUfagauUfcCfaagcus gsa		UCAGCUUGGAAUCUAUAUC UUUC	
AD-1735378	ususauu(Ada)UfuUfCfUfgaagccua sasa		VPusUfsuagGfcUfUfcagaAfaUfaauaas gsu		ACUUAUUAUUUCUGAAGCC UAAC	
AD-1735379	cscsuuu(Gda)UfuGfUfAfuuuaacaa sasa		VPusUfsuugUfuAfAfauacAfaCfaaaggs usc		GACCUUUGUUGUAUUUAAC AAAA	

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-1735380	gscsucu(Cda)UfaAfCfUfaaucgauc sasa		VPusUfsgauCfgAfUfuaguUfaGfagagcs csa		UGGCUCUCUAACUAAUCGA UCAC	
AD-1735381	asasaga(Cda)UfaCfAfUfgacagaaa susa		VPusAfsuuuCfuGfUfcaugUfaGfucuuu sasg		CUAAAGACUACAUGACAGA AAUG	
AD-1735382	csasgga(Uda)UfcGfUfAfuuuuuaaa sgsa		VPusCfsuuuAfaAfAfauacGfaAfuccugs asg		CUCAGGAUUCGUAUUUUUA AAGA	
AD-1735383	cscsuug(Cda)UfaAfGfUfaauugaca susa		VPusAfsuguCfaAfUfuacuUfaGfcaaggs gsu		ACCCUUGCUAAGUAAUUGA CAUA	
AD-1735384	cscsuau(Gda)CfaCfUfUfucacagga sasa		VPusUfsuccUfgUfGfaaagUfgCfauaggs asg		CUCCUAUGCACUUUCACAG GAAC	
AD-1735385	asusgcu(Gda)AfaAfUfAfuguuuca ascsa		VPusGfsuugAfaAfCfauauUfuCfagcaus usu		AAAUGCUGAAAUAUGUUUC AACA	
AD-1735386	cscsuuu(Uda)AfaUfUfCfaaaucuac susa		VPusAfsguaGfaUfUfugaaUfuAfaaaggs csc		GGCCUUUUAAUUCAAAUCU ACUG	
AD-1735387	ascsugg(Ada)CfuUfAfUfuggauuu asasa		VPusUfsuaaAfuCfCfaauaAfgUfccagus asu		AUACUGGACUUAUUGGAUU UAAU	
AD-1735388	csasucu(Gda)AfaUfCfAfgaugguac sasa		VPusUfsguaCfcAfUfcugaUfuCfagaugs usu		AACAUCUGAAUCAGAUGGU ACAG	
AD-1735389	asasuuc(Uda)GfaUfAfGfcaaucugu sgsa		VPusCfsacaGfaUfUfgcuaUfcAfgaauus usc		GAAAUUCUGAUAGCAAUCU GUGU	
AD-1735390	uscsaag(Uda)CfaAfGfGfaugcuauc susa		VPusAfsgauAfgCfAfuccuUfgAfcuugas asa		UUUCAAGUCAAGGAUGCUA UCUA	
AD-1735391	uscsacu(Gda)AfaAfAfCfcacaagau sasa		VPusUfsaucUfuGfUfgguuUfuCfaguga sgsg		CCUCACUGAAAACCACACAAG AUAU	
AD-1735392	ascscug(Uda)UfgAfAfCfagucuuca sasa		VPusUfsugaAfgAfCfuguuCfaAfcaggus asg		CUACCUGUUGAACAGUCUU CAAG	
AD-1735393	uscsaag(Uda)GfaCfAfUfauuucagu susa		VPusAfsacuGfaAfAfuaugUfcAfcuugas gsu		ACUCAAGUGACAUAUUUCA GUUA	
AD-1735394	uscsagg(Ada)AfcUfUfCfaggauugc susa		VPusAfsgcaAfuCfCfugaaGfuUfccugas gsc		GCUCAGGAACUUCAGGAUU GCUA	
AD-1735395	ascsgga(Gda)UfaUfUfAfguagcuua sasa		VPusUfsuaaGfcUfAfcuaaUfaCfuccgus asg		CUACGGAGUAUUAGUAGCU UAAU	
AD-1735396	asusugu(Cda)AfaUfGfAfauuuuau gsasa		VPusUfscauAfaAfAfauucaUfuGfacaaus gsc		GCAUUGUCAAUGAAUUUUA UGAG	
AD-	gsasaca(Gda)CfaAfAfCfaaauauug		VPusUfscaaUfaUfUfuguuUfgCfuguucs		GUGAACAGCAAACAAAUAU	

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:
1735397	sasa		asc		UGAA	
AD-1735398	usgsaac(Uda)AfuUfUfUfcgugcau usasa		VPusUfsaauGfcAfCfgaaaAfuAfguucas usa		UAUGAACUAUUUUCGUGCA UUAG	
AD-1735399	ascsugg(Ada)AfuAfCfUfuauuuuu csasa		VPusUfsgaaAfaAfUfaaguAfuUfccagus usc		GAACUGGAAUACUUAUUUU UCAU	
AD-1735400	ususauc(Uda)UfgCfAfGfagaucucu sgsa		VPusCfsagaGfaUfCfucugCfaAfgauaas csg		CGUUAUCUUGCAGAGAUCU CUGG	
AD-1735401	gsasagu(Gda)UfuAfGfAfauuuuug asusa		VPusAfsucaAfaAfAfuucuAfaCfacuucs csa		UGGAAGUGUUAGAAUUUU UGAUC	
AD-1735402	uscsaau(Uda)UfaAfGfAfucucugga sasa		VPusUfsuccAfgAfGfaucuUfaAfauugas usa		UAUCAAUUUAAGAUCUCUG GAAG	
AD-1735403	usgsgac(Cda)AfuAfUfUfuacaaugu susa		VPusAfsacaUfuGfUfaaauAfuGfguccas usu		AAUGGACCAUAUUUACAAU GUUU	
AD-1735404	usasguc(Ada)UfuGfAfAfgcaauccu susa		VPusAfsaggAfuUfGfcuucAfaUfgacuas asa		UUUAGUCAUUGAAGCAAUC CUUG	
AD-1735405	asgscug(Uda)UfuAfGfGfuuuaacaa susa		VPusAfsuugUfuAfAfaccuAfaAfcagcus usu		AAAGCUGUUUAGGUUUAAC AAUG	
AD-1735406	csasagg(Cda)AfaAfUfUfGfauguaaau sasa		VPusUfsauuUfaCfAfucauUfuGfccuugs gsc		GCCAAGGCAAAUGAUGUAA AUAG	
AD-1735407	asuscca(Ada)UfuAfCfUfacuggaaa scsa		VPusGfsuuuCfcAfGfuaguAfaUfuggau susu		AAAUCCAAUUACUACUGGA AACU	
AD-1735408	ascsuua(Cda)AfaUfAfUfauauaucc susa		VPusAfsggaUfaUfAfuauaUfuGfuaagus gsc		GCACUUACAAUAUAUAUAU CCUG	
AD-1735409	asusgca(Gda)UfuUfGfGfuaucugac sasa		VPusUfsgucAfgAfUfaccaAfaCfugcaus gsu		ACAUGCAGUUUGGUAUCUG ACAA	
AD-1735410	cscsuua(Uda)UfuCfAfAfgacacugg susa		VPusAfsccaGfuGfUfcuugAfaAfuaaggs usa		UACCUUAUUUCAAGACACU GGUU	
AD-1735411	gsasagg(Gda)AfuUfUfUfAfuucuuua gsusa		VPusAfscuaAfaGfAfauaaAfuCfccuucs asu		AUGAAGGGAUUUAUUCUUU AGUC	
AD-1735412	asusccu(Uda)GfcUfAfCfggaucuua sasa		VPusUfsuaaGfaUfCfcguaGfcAfaggaus usg		CAAUCCUUGCUACGGAUCU UAAA	
AD-1735413	ascsuga(Cda)UfaUfCfCfcgaagcaa sasa		VPusUfsuugCfuUfCfgggaUfaGfucagus asg		CUACUGACUAUCCCGAAGC AAAG	
AD-1735414	usgsuau(Uda)UfcUfGfCfuauuauu uscsa		VPusGfsaaaUfaAfUfagcaGfaAfauacas csu		AGUGUAUUUCUGCUAUUAU UUCC	

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-1735415	usgsuaa(Cda)AfaUfAfAfcuagccua sasa		VPusUfsuagGfcUfAfguuaUfuGfuuacas usa		UAUGUAACAAUAACUAGCC UAAA	
AD-1735416	gsusugu(Uda)UfuUfAfCfucuagcu csasa		VPusUfsgagCfuAfGfaguaAfaAfacaacs asa		UUGUUGUUUUUACUCUAGC UCAG	
AD-1735417	csasggc(Ada)GfuUfUfUfUfauacaaug sasa		VPusUfscauUfgUfAfuaaaAfcUfgccugs asg		CUCAGGCAGUUUUAUACAA UGAC	
AD-1735418	asgsgau(Uda)CfuCfAfGfucagguua susa		VPusAfsuaaCfcUfGfacugAfgAfauccus usc		GAAGGAUUCUCAGUCAGGU UAUG	
AD-1735419	asusuuu(Cda)CfaUfCfAfuguuuaag susa		VPusAfscuuAfaAfCfaugaUfgGfaaaaus gsu		ACAUUUUCCAUCAUGUUUA AGUG	
AD-1735420	usgscca(Cda)UfuUfUfUfGfuuaccauu sgsa		VPusCfsaauGfgUfAfacaaAfaGfuggcas gsc		GCUGCCACUUUUGUUACCA UUGU	
AD-1735421	ascsuug(Cda)UfaGfUfUfGfuguggau asusa		VPusAfsuauCfcAfCfacacUfaGfcaagus usu		AAACUUGCUAGUGUGUGGA UAUG	
AD-1735422	asasucu(Uda)AfcUfUfUfGfagaaauug scsa		VPusGfscaaUfuUfCfucaaGfuAfagauus usc		GAAAUCUUACUUGAGAAAU UGCC	
AD-1735423	asgsuuc(Gda)AfgAfCfUfUfugcauuu gsasa		VPusUfscaaAfuGfCfaaguCfuCfgaacus usu		AAAGUUCGAGACUUGCAUU UGAA	
AD-1735424	cscsaua(Gda)AfaUfUfUfUfccugauac susa		VPusAfsguaUfcAfGfgaaaUfuCfuauggs gsu		ACCCAUAGAAUUUCCUGAU ACUG	
AD-1735425	asgsgua(Ada)UfuCfCfUfUfuagaaua susa		VPusAfsuauUfcUfUfAfaggAfaUfuaccus usg		CAAGGUAAUUCCUUUAGAA UAUG	
AD-1735426	csusuau(Gda)GfaAfAfCfucaacaag sasa		VPusUfscuuGfuUfGfaguuUfcCfauaags usu		AACUUAUGGAAACUCAACA AGAA	
AD-1735427	asasgca(Gda)CfaUfUfUfUfuaaauuac sgsa		VPusCfsguaAfuUfUfUfaaaaUfgCfugcuus usu		AAAAGCAGCAUUUUAAAUU ACGA	
AD-1735428	usgsacu(Cda)UfcAfAfCfUfgaccauu scsa		VPusGfsaauGfgUfCfaguuGfaGfagucas gsc		GCUGACUCUCAACUGACCA UUCC	
AD-1735429	asgsguu(Uda)AfuCfCfCfAfugaaggac susa		VPusAfsgucCfuUfUfCfauggAfuAfaaccus asg		CUAGGUUUAUCCAUGAAGG ACUG	
AD-1735430	ascscaa(Gda)AfaUfUfUfUfggcauuuc sasa		VPusUfsgaaAfuGfCfcaaaUfuCfuuggus gsa		UCACCAAGAAUUUGGCAUU UCAA	
AD-1735431	usasucu(Ada)GfaAfUfAfAfuuuggcu usasa		VPusUfsaagCfcAfAfauauUfcUfagauas asg		CUUAUCUAGAAUAUUUGGC UUAU	
AD-	csusccu(Gda)CfaGfAfAfuacauaca		VPusUfsuguAfuGfUfauucUfgCfaggag		CUCUCCUGCAGAAUACAUA	

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:
1735432	sasa		sasg		CAAG	
AD-1735433	uscsaca(Cda)CfaUfUfUfccuggauu susa		VPusAfsaauCfcAfGfgaaaUfgGfugugas gsa		UCUCACACCAUUUCCUGGA UUUU	
AD-1735434	asusgug(Gda)AfaUfUfCfaagcgcuu susa		VPusAfsaagCfgCfUfugaaUfuCfcacaus gsa		UCAUGUGGAAUUCAAGCGC UUUC	
AD-1735435	asusugu(Gda)UfaUfUfAfucuacua usgsa		VPusCfsauaGfuAfGfauaaUfaCfacaaus asg		CUAUUGUGUAUUAUCUACU AUGU	
AD-1735436	asasugg(Ada)GfuAfAfUfgaaaauga susa		VPusAfsucaUfuUfUfcauuAfcUfccauus csu		AGAAUGGAGUAAUGAAAA UGAUC	
AD-1735437	ascsugg(Uda)UfuAfUfUfUfggaaaua ususa		VPusAfsauaUfuUfUfCfcaauAfaAfccagus gsu		ACACUGGUUUAUUGGAAAU AUUU	
AD-1735438	csasagu(Gda)UfaUfGfUfUfguauaaag susa		VPusAfscuuUfaUfAfcacaUfaCfacuugs usa		UACAAGUGUAUGUGUAUAA AGUC	
AD-1735439	usascaa(Gda)CfaUfGfCfCfauauugag sasa		VPusUfscucAfaUfAfugcaUfgCfuuguas csa		UGUACAAGCAUGCAUAUUG AGAU	
AD-1735440	usgsugu(Cda)UfuUfUfUfAfugucuuu gsasa		VPusUfscaaAfgAfCfauaaAfaGfacacas csu		AGUGUGUCUUUUAUGUCUU UGAA	
AD-1735441	asusuuu(Cda)UfcGfCfAfgaauucaa susa		VPusAfsuugAfaUfUfcugcGfaGfaaaaus csa		UGAUUUUCUCGCAGAAUUC AAUG	
AD-1735442	usasgcg(Ada)CfaGfUfUfUfugaguaaa sasa		VPusUfsuuuAfcUfCfaaacUfgUfcgcuas usu		AAUAGCGACAGUUUGAGUA AAAG	
AD-1735443	csusggu(Gda)UfaUfGfGfAfauacuuu gsusa		VPusAfscaaAfgUfAfuucaUfaCfaccags usg		CACUGGUGUAUGAAUACUU UGUC	
AD-1735444	gsusgau(Ada)AfgUfGfGfGfcuaacaga sasa		VPusUfsucuGfuUfAfgccaCfuUfaucacs csu		AGGUGAUAAGUGGGCUAACA GAAG	
AD-1735445	gsusagg(Cda)UfaAfUfAfAfuuuucua ususa		VPusAfsauaGfaAfAfauauUfaGfccuacs csa		UGGUAGGCUAAUAUUUUCU AUUA	
AD-1735446	cscsucu(Uda)CfaUfCfCfCfucgacugu scsa		VPusGfsacaGfuCfGfaggaUfgAfagaggs csg		CGCCUCUUCAUCCUCGACU GUCC	
AD-1735447	asasuug(Cda)CfaUfAfAfAfgccauauu sasa		VPusUfsaauAfuGfGfCfcuuaUfgGfcaauus usc		GAAAUUGCCAUAAGCCAUA UUAC	
AD-1735448	gscsgaa(Uda)AfuUfUfUfUfgucagcua sasa		VPusUfsuagCfuGfAfcaaaAfuAfuucgcs csg		CGGCGAAUAUUUUGUCAGC UAAU	
AD-1735449	asuscca(Gda)UfgUfUfGfCfccuuucug sasa		VPusUfscagAfaAfGfgcaaCfaCfuggaus usc		GAAUCCAGUGUUGCCUUUC UGAG	

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-1735450	asasagu(Cda)UfaUfGfCfcugucuaasasa		VPusUfsuuaGfaCfAfggcaUfaGfacuuususc		GAAAAGUCUAUGCCUGUCUAAAA	
AD-1735451	gsgsaca(Uda)CfaGfAfAfAfguuugaaususa		VPusAfsauuCfaAfAfcuucUfgAfuguccsasu		AUGGACAUCAGAAGUUUGAAUUC	
AD-1735452	gsgscga(Ada)UfuGfCfUfuauauuucsusa		VPusAfsgaaAfuAfUfaagcAfaUfucgccscsa		UGGGCGAAUUGCUUAUAUUUCUU	
AD-1735453	csascac(Uda)AfuGfUfGfuaaaccagsusa		VPusAfscugGfuUfUfacacAfuAfgugugsusg		CACACACUAUGUGUAAACCAGUC	
AD-1735454	csasggu(Gda)AfaGfAfAfAfgaaaacaususa		VPusAfsaugUfuUfUfcuucUfuCfaccugsasu		AUCAGGUGAAGAAGAAAACAUUU	
AD-1735455	gsusgag(Cda)UfcUfUfUfAfuuuuucaususa		VPusAfsgugAfaAfAfauaaGfaGfcucacsusa		UAGUGAGCUCUUAUUUUUCACUG	
AD-1735456	asasagc(Uda)GfaUfGfUfGfgaauaaacsusa		VPusAfsguuUfaUfUfcccaUfcAfgcuuussasc		GUAAAGCUGAUGGGAAUAAACUG	
AD-1735457	gsusguc(Gda)UfuAfGfGfGfagaaacusgscsa		VPusGfscagUfuUfUfCfuccuAfaCfgacacsgsc		GCGUGUCGUUAGGAGAAACUGCA	
AD-1735458	gsgsgac(Uda)UfaAfAfAfAfcaaugguasusa		VPusAfsuacCfaUfUfguuuUfaAfgucccsasa		UUGGGACUUAAAACAAUGGUAUA	
AD-1735459	csusgau(Gda)GfuAfGfAfAfauuaaccasusa		VPusAfsuggUfuAfAfuucuAfcCfaucagsasa		UUCUGAUGGUAGAAUUAACCAUG	
AD-1735460	ascsuau(Gda)UfgUfGfUfUfuuauuususa		VPusAfsgaaAfuAfAfaacaCfaCfauagusasg		CUACUAUGUGUGUUUUAUUUCUG	
AD-1735461	csusgau(Ada)AfuUfUfUfAfuauuugcascsa		VPusGfsugcAfaAfUfauaaAfuUfaucagsusc		GACUGAUAAUUUAUAUUUGCACU	
AD-1735462	gsusccu(Uda)AfaAfUfUfUfauuuaaccscsa		VPusGfsggUfaAfAfuaauUfuAfaggacsusa		UAGUCCUUAAAUUAUUUAACCCU	
AD-1735463	csgscaa(Uda)AfuGfGfUfUfgucagauscsusa		VPusAfsgauCfuGfAfcaccAfuAfuugcgsasg		CUCGCAAUAUGGUGUCAGAUCUU	
AD-1735464	ususcga(Ada)GfaGfCfUfUfgcucuaaausscsa		VPusGfsauuAfgAfGfcageUfcUfucgaasgsa		UCUUCGAAGAGCUGCUCUAAUCC	
AD-1735465	ususucu(Gda)CfuGfAfGfAfguauuucasgsa		VPusCfsugaAfuAfCfucucAfgCfagaaasusa		UAUUUCUGCUGAGAGUAUUCAGG	
AD-1735466	ususgaa(Cda)AfgGfAfAfAfguaucacusgsa		VPusCfsaguGfaUfAfcuucCfuGfuucaasusa		UAUUGAACAGGAAGUAUCACUGG	
AD-	usgsccu(Uda)GfuAfUfUfUfuccagagaa		VPusUfsucuCfuGfGfaaauAfcAfaggcas		GUUGCCUUGUAUUUCCAGA	

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:
1735467	sasa		asc		GAAC	
AD-1735468	gsusuac(Uda)AfuGfGfCfagugcaasasa		VPusUfsuugCfaAfCfugccAfuAfguaacsusg		CAGUUACUAUGGCAGUUGCAAAA	
AD-1735469	asusggc(Uda)GfaAfUfUfuaaagcusgsa		VPusCfsagcUfuUfAfaaauUfcAfgccausgsg		CCAUGGCUGAAUUUUAAAGCUGU	
AD-1735470	gsuscca(Uda)UfcAfUfGfgaucguucusa		VPusAfsgaaCfgAfUfccauGfaAfuggacsusg		CAGUCCAUUCAUGGAUCGUUCUU	
AD-1735471	usgsugu(Ada)AfcUfCfCfuaugaugcsusa		VPusAfsgcaUfcAfUfaggaGfuUfacacasgsg		CCUGUGUAACUCCUAUGAUGCUG	
AD-1735472	usgsgca(Gda)UfuUfCfCfcacuccuasusa		VPusAfsuagGfaGfUfgggaAfaCfugccasgsc		GCUGGCAGUUUCCCACUCCUAUG	
AD-1735473	cscsuca(Ada)GfcAfGfAfugagauucsasa		VPusUfsgaaUfcUfCfaucuGfcUfugaggsusa		UACCUCAAGCAGAUGAGAUUCAG	
AD-1735474	asusguu(Gda)UfuUfUfUfCfucaaaagcsasa		VPusUfsgcuUfuUfGfagaaAfaCfaacausasa		UUAUGUUGUUUUCUCAAAAGCAG	
AD-1735475	gsasggg(Ada)UfuUfCfCfUfgcucaaugscsa		VPusGfscauUfgAfGfcagaAfaUfcccucsasg		CUGAGGGAUUUCUGCUCAAUGCA	
AD-1735476	gscscuu(Cda)UfuCfUfUfCfccucaccusgsa		VPusCfsaggUfgAfGfgaagAfaGfaaggcsasc		GUGCCUUCUUCUUCCUCACCUGC	
AD-1735477	ususgag(Ada)UfuGfAfAfucacauuuscsa		VPusGfsaaaUfgUfGfauucAfaUfcucaasusa		UAUUGAGAUUGAAUCACAUUUCC	
AD-1735478	csusguu(Cda)AfgUfGfCfuauucucscsa		VPusGfsggaGfaAfUfagcaCfuGfaacagsusg		CACUGUUCAGUGCUAUUCUCCCA	
AD-1735479	cscsugg(Cda)UfuAfCfAfgcagauccsasa		VPusUfsggaUfcUfGfcuguAfaGfccaggsasa		UUCCUGGCUUACAGCAGAUCCAC	
AD-1735480	gsascag(Cda)AfgAfAfAfauauauucsasa		VPusUfsgaaAfuAfAfuuuuCfuGfcugucsusu		AAGACAGCAGAAAAUUAUUUCAG	
AD-1735481	ususggg(Uda)UfuCfUfUfuaguuuausgsa		VPusCfsauaAfaCfUfaaagAfaAfcccaasusa		UAUUGGGUUUCUUUAGUUUAUGU	
AD-1735482	csascca(Uda)GfuAfGfGfucucagaasgsa		VPusCfsuucUfgAfGfaccuAfcAfuggugsasg		CUCACCAUGUAGGUCUCAGAAGA	
AD-1735483	gsusugu(Gda)GfaAfCfAfggaaaugasasa		VPusUfsucaUfuUfCfcuguUfcCfacaacscsa		UGGUUGUGGAACAGGAAAUGAAA	
AD-1735484	ggsgaga(Ada)CfaUfAfUfcauauuuusgsa		VPusCfsaaaAfuAfUfgauaUfgUfucuccsasa		UUGGAGAACAUAUCAUAUUUUGG	

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-1735485	csasgcc(Ada)AfaAfUfGfauggcaaasasa		VPusUfsuuuGfcCfAfucauUfuUfggcugscsu		AGCAGCCAAAAUGAUGGCAAAAU	
AD-1735486	cscsaau(Uda)UfuUfGfAfacuuguagsasa		VPusUfscuaCfaAfGfuucaAfaAfauuggsasa		UUCCAAUUUUUGAACUUGUAGAA	
AD-1735487	asusagg(Ada)AfuAfGfUfuugccaacsusa		VPusAfsguuGfgCfAfaacuAfuUfccuaususu		AAAUAGGAAUAGUUUGCCAACUC	
AD-1735488	ususuga(Ada)UfgUfUfUfuggagaaasasa		VPusUfsuuuCfuCfCfaaaaCfaUfucaaasgsa		UCUUUGAAUGUUUUGGAGAAAAG	
AD-1735489	gsuscaa(Uda)AfuUfUfAfaugaaucascsa		VPusGfsugaUfuCfAfuuaaAfuAfuugacsasc		GUGUCAAUAUUUAAUGAAUCACU	
AD-1735490	usgsaga(Ada)UfaUfAfUfuaaaugcascsa		VPusGfsugcAfuUfUfaauaUfaUfucucascsa		UGUGAGAAUAUAUUAAAUGCACA	
AD-1735491	usasaca(Ada)GfgGfAfCfuaaauaggsasa		VPusUfsccuAfuUfUfagucCfcUfuguuasasg		CUUAACAAGGGACUAAAUAGGAA	
AD-1735492	gsgscuu(Cda)UfuCfUfUfccaccucusgsa		VPusCfsagaGfgUfGfgaagAfaGfaagccsgsc		GCGGCUUCUUCUUCCACCUCUGC	
AD-1735493	ususgga(Ada)CfaUfGfUfgguuaucususa		VPusAfsagaUfaAfCfcacaUfgUfuccaasusu		AAUUGGAACAUGUGGUUAUCUUU	
AD-1735494	csasgag(Ada)AfcAfGfAfugauucuususa		VPusAfsaagAfaUfCfaucuGfuUfcucugsgsa		UCCAGAGAACAGAUGAUUCUUUG	
AD-1735495	csusguu(Ada)UfuUfUfAfuuggguuususa		VPusAfsaaaCfcCfAfauaaAfaUfaacagsasc		GUCUGUUAUUUUAUUGGGUUUUA	
AD-1735496	asusgaa(Gda)AfaGfCfAfaaucuuggsusa		VPusAfsccaAfgAfUfuugcUfuCfuucauscsu		AGAUGAAGAAGCAAAUCUUGGUC	
AD-1735497	ususugg(Ada)AfuCfAfUfgcaauuuusgsa		VPusCfsaaaAfuUfGfcaugAfuUfccaaasasu		AUUUUGGAAUCAUGCAAUUUUGC	
AD-1735498	csasaug(Uda)UfuUfGfUfaaacuugcsusa		VPusAfsgcaAfgUfUfuacaAfaAfcauugsusa		UACAAUGUUUUGUAAACUUGCUA	
AD-1735499	gsgsauc(Gda)UfaAfUfAfauggcaaasasa		VPusUfsuuuGfcCfAfuuauUfaCfgauccscsa		UGGGAUCGUAAUAAUGGCAAAAG	
AD-1735500	gsusgcu(Uda)UfcUfCfAfgguuccugsusa		VPusAfscagGfaAfCfcugaGfaAfagcacscsc		GGGUGCUUUCUCAGGUUCCUGUA	
AD-1735501	asusgau(Ada)CfuGfAfAfaguggugasusa		VPusAfsucaCfcAfCfuuucAfgUfaucaususa		UAAUGAUACUGAAAGUGGUGAUG	
AD-	uscsacu(Gda)GfaCfCfUfgauuuuag		VPusAfscuaAfaAfUfcaggUfcCfagugas		UAUCACUGGACCUGAUUUU	

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:
1735502	susa		usa		AGUA	
AD-1735503	gsasacu(Uda)UfuUfGfCfuuuuaug asasa		VPusUfsucaUfaAfAfagcaAfaAfaguucs csu		AGGAACUUUUUGCUUUUAU GAAA	
AD-1735504	gsasaca(Cda)AfgCfAfCfagauuugu susa		VPusAfsacaAfaUfCfugugCfuGfuguucs asu		AUGAACACAGCACAGAUUU GUUA	
AD-1735505	asusaug(Gda)AfaGfGfAfaaucguag sasa		VPusUfscuaCfgAfUfuuccUfuCfcauaus csu		AGAUAUGGAAGGAAAUCGU AGAG	
AD-1735506	gscsuau(Cda)UfaAfAfUfgggccuu ususa		VPusAfsaaaGfgCfCfcauuUfaGfauagcs asu		AUGCUAUCUAAAUGGGCCU UUUA	
AD-1735507	csasaaa(Cda)CfaCfCfAfagaaggaas asa		VPusUfsuucCfuUfCfuuggUfgGfuuuug sgsa		UCCAAAACCACCAAGAAGG AAAA	
AD-1735508	cscsaca(Gda)AfuGfUfGfcuacaugc sasa		VPusUfsgcaUfgUfAfgcacAfuCfuguggs csa		UGCCACAGAUGUGCUACAU GCAG	
AD-1735509	asasagu(Cda)AfuAfCfAfuguacaag scsa		VPusGfscuuGfuAfCfauguAfuGfacuuu sasu		AUAAAGUCAUACAUGUACA AGCA	
AD-1735510	usasgaa(Gda)CfaGfAfAfgaggauaa susa		VPusAfsuuaUfcCfUfcuucUfgCfuucuas asc		GUUAGAAGCAGAAGAGGAU AAUG	
AD-1735511	csgsugu(Gda)UfuCfGfCfacagcuug sasa		VPusUfscaaGfcUfGfugcgAfaCfacacgs csu		AGCGUGUGUUCGCACAGCU UGAG	
AD-1735512	gscsugg(Uda)GfuUfUfUfguccagu csusa		VPusAfsgacUfgGfAfcaaaAfcAfccagcs usc		GAGCUGGUGUUUUGUCCAG UCUG	
AD-1735513	asusgga(Ada)AfaCfAfAfucuaaauc scsa		VPusGfsgauUfuAfGfauugUfuUfuccau susu		AAAUGGAAAACAAUCUAAA UCCA	
AD-1735514	csasuua(Gda)AfaAfAfUfggcuaucg sasa		VPusUfscgaUfaGfCfcauuUfuCfuaaugs csa		UGCAUUAGAAAAUGGCUAU CGAG	
AD-1735515	asusgga(Cda)AfgAfAfGfgcauugu csasa		VPusUfsgacAfaUfGfccuuCfuGfuccaus usu		AAAUGGACAGAAGGCAUUG UCAA	
AD-1735516	csasgau(Uda)GfcUfGfCfaguggaaa sasa		VPusUfsuuuCfcAfCfugcaGfcAfaucugs usa		UACAGAUUGCUGCAGUGGA AAAU	
AD-1735517	asgsgug(Gda)AfaAfUfGfgaguuga uscsa		VPusGfsaucAfaCfUfccauUfuCfcaccus csc		GGAGGUGGAAAUGGAGUU GAUCU	
AD-1735518	csusggg(Cda)AfaUfGfCfaccuaaua scsa		VPusGfsuauUfaGfGfugcaUfuGfcccags asg		CUCUGGGCAAUGCACCUAA UACU	
AD-1735519	asusuuc(Cda)CfuCfUfGfccuaaaga scsa		VPusGfsucuUfuAfGfgcagAfgGfgaaaus usa		UAAUUUCCCUCUGCCUAAA GACU	

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-1735520	csgscuu(Cda)UfgCfAfAfcguggagc susa		VPusAfsgcuCfcAfCfguugCfaGfaagcgs gsc		GCCGCUUCUGCAACGUGGA GCUG	
AD-1735521	asgsauu(Cda)AfuAfUfUfUfguauuuc cscsa		VPusGfsggaAfaUfAfcaauAfuGfaaucus asu		AUAGAUUCAUAUUGUAUUU CCCA	
AD-1735522	asgsgac(Ada)AfaUfGfCfCfauuucuag susa		VPusAfscuaGfaAfAfugcaUfuUfguccus csc		GGAGGACAAAUGCAUUUCU AGUG	
AD-1735523	ususaga(Cda)GfuGfUfUfUfgagugag usgsa		VPusCfsacuCfaCfUfcaacAfcGfucuaas usa		UAUUAGACGUGUUGAGUGA GUGC	
AD-1735524	csusgug(Gda)AfcAfUfCfCfaaaugcug sasa		VPusUfscagCfaUfUfugauGfuCfcacags csu		AGCUGUGGACAUCAAAUGC UGAA	
AD-1735525	asgsgcc(Uda)UfaAfUfUfAfcuguggaga sgsa		VPusCfsucuCfaCfAfguauUfaAfggccus gsu		ACAGGCCUUAAUACUGUGA GAGG	
AD-1735526	asgsaaaa(Uda)CfaUfUfGfCfcuagugu susa		VPusAfsacaCfuAfGfgcaaUfgAfuuucus gsc		GCAGAAAUCAUUGCCUAGU GUUC	
AD-1735527	usgsagu(Gda)CfuGfAfGfuucccuug csusa		VPusAfsgcaAfgGfAfacucAfgCfacucas csu		AGUGAGUGCUGAGUUCCUU GCUG	
AD-1735528	gscscau(Gda)CfaUfGfAfuuaugauc sasa		VPusUfsgauCfaUfAfaucaUfgCfauggcs asg		CUGCCAUGCAUGAUUAUGA UCAC	
AD-1735529	usgscug(Cda)UfgGfUfUfUfugcuacca sgsa		VPusCfsuggUfaGfCfaaacCfaGfcagcas usc		GAUGCUGCUGGUUUGCUAC CAGG	
AD-1735530	csasgau(Gda)AfaGfAfGfgaauagcg sasa		VPusUfscgcUfaUfUfccucUfuCfaucugs csc		GGCAGAUGAAGAGGAAUAG CGAC	
AD-1735531	asuscca(Gda)GfuGfCfAfucaauuuc susa		VPusAfsgaaAfuUfGfaugcAfcCfuggaus usu		AAAUCCAGGUGCAUCAAUU UCUG	
AD-1735532	asasuaa(Gda)CfcAfAfGfCfguuaucu susa		VPusAfsagaUfaAfCfgcuuGfgCfuuauus asa		UUAAUAAGCCAAGCGUUAU CUUG	
AD-1735533	gsasgag(Gda)AfuCfCfUfUfugcucugc susa		VPusAfsgcaGfaGfCfaaggAfuCfcucucs asc		GUGAGAGGAUCCUUGCUCU GCUG	
AD-1735534	asusgau(Gda)AfaGfAfCfggugaaga sasa		VPusUfsucuUfcAfCfcgucUfuCfaucaus csa		UGAUGAUGAAGACGGUGAA GAAU	
AD-1735535	uscsgua(Ada)GfuGfUfUfAfagaaagaa susa		VPusAfsuucUfuUfCfuuacAfcUfuacgas asu		AUUCGUAAGUGUAAGAAAG AAUG	
AD-1735536	asuscug(Uda)GfuAfAfCfagcugug gsasa		VPusUfsccaCfaGfCfuguuAfcAfcagaus usg		CAAUCUGUGUAACAGCUGU GGAC	
AD-	asusuua(Ada)AfaUfUfUfCfccacucaa		VPusGfsuugAfgUfGfggaaUfuUfuaaau		AUAUUUAAAAUUCCCACUC	

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:
1735537	scsa		sasu		AACA	
AD-1735538	gsascca(Gda)UfgUfCfUfacuggcuc susa		VPusAfsgagCfcAfGfuagaCfaCfuggucs csa		UGGACCAGUGUCUACUGGC UCUC	
AD-1735539	csgscuu(Uda)CfgUfUfUfuuuaguc asusa		VPusAfsugaCfuAfAfaaaaCfgAfaagcgs csu		AGCGCUUUCGUUUUUUAGU CAUU	
AD-1735540	uscscgu(Gda)UfuGfAfCfccauguu gscsa		VPusGfscaaCfaUfGfggucAfaCfacggas usg		CAUCCGUGUUGACCCAUGU UGCA	
AD-1735541	asusaca(Gda)AfaGfAfUfgaagaaau sgsa		VPusCfsauuUfcUfUfcaucUfuCfuguaus csu		AGAUACAGAAGAUGAAGAA AUGG	
AD-1735542	uscsucc(Cda)GfaGfCfUfgaaacuua sasa		VPusUfsuaaGfuUfUfcagcUfcGfggagas gsa		UCUCUCCCGAGCUGAAACU UAAA	
AD-1735543	usgscau(Cda)AfaAfCfUfggcagaua susa		VPusAfsuauCfuGfCfcaguUfuGfaugcas csa		UGUGCAUCAAACUGGCAGA UAUA	
AD-1735544	ususgca(Ada)AfaUfAfUfucaggaga scsa		VPusGfsucuCfcUfGfaauaUfuUfugcaas csu		AGUUGCAAAAUAUUCAGGA GACC	
AD-1735545	ascsaau(Cda)GfuAfUfAfcaugccac sasa		VPusUfsguGfcAfUfguauAfcGfauugu sgsa		UCACAAUCGUAUACAUGCC ACAG	
AD-1735546	asasuag(Ada)AfaAfGfAfugagcaac susa		VPusAfsguuGfcUfCfaucuUfuUfcuauus asa		UUAAUAGAAAAGAUGAGCA ACUG	
AD-1735547	usasucu(Uda)AfuGfUfUfccauggc usgsa		VPusCfsagcCfaUfGfgaacAfuAfagauas asg		CUUAUCUUAUGUUCCAUGG CUGA	
AD-1735548	csusacg(Uda)GfaAfGfAfgcugcgu gsasa		VPusUfscacGfcAfGfcucuUfcAfcguags csc		GGCUACGUGAAGAGCUGCG UGAG	
AD-1735549	gsasauu(Gda)AfuGfGfCfucuauacg susa		VPusAfscguAfuAfGfagccAfuCfaauucs usa		UAGAAUUGAUGGCUCUAUA CGUG	
AD-1735550	ususcag(Gda)UfaAfUfUfUfgaagaggc sasa		VPusUfsgccUfcUfUfcaauUfaCfcugaas usc		GAUUCAGGUAAUUGAAGAG GCAG	
AD-1735551	asasgga(Cda)UfgAfGfUfUfgaccuuug susa		VPusAfscaaAfgGfUfcacuCfaGfuccuus csa		UGAAGGACUGAGUGACCUU UGUU	
AD-1735552	csgsaga(Gda)UfcUfGfAfggaacggc susa		VPusAfsgccGfuUfCfcucaGfaCfucucgs ggg		CCCGAGAGUCUGAGGAACG GCUA	
AD-1735553	asususcu(Uda)UfgGfGfAfuugggac ususa		VPusAfsaguCfcCfAfauccCfaAfagaaus csa		UGAUUCUUUGGGAUUGGGA CUUA	
AD-1735554	usascca(Gda)GfuCfAfGfugguuaga sasa		VPusUfsucuAfaCfCfacugAfcCfugguas gsc		GCUACCAGGUCAGUGGUUA GAAG	

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-1735555	asusuca(Gda)GfuUfUfGfccauggac sasa		VPusUfsgucCfaUfGfgcaaAfcCfugaaus asc		GUAUUCAGGUUUGCCAUGG ACAU	
AD-1735556	gscsagc(Uda)AfaAfCfUfgguccugg sasa		VPusUfsccaGfgAfCfcaguUfuAfgcugcs csg		CGGCAGCUAAACUGGUCCU GGAG	
AD-1735557	asgsuaa(Uda)GfgCfAfUfagaaugga sgsa		VPusCfsuccAfuUfCfuaugCfcAfuuacus asu		AUAGUAAUGGCAUAGAAUG GAGU	
AD-1735558	asasuug(Cda)AfaGfAfAfaauggacc sasa		VPusUfsgguCfcAfUfuuucUfuGfcaauus asu		AUAAUUGCAAGAAAAUGGA CCAU	
AD-1735559	csgsgca(Cda)UfgCfGfUfucuggugc susa		VPusAfsgcaCfcAfGfaacgCfaGfugccgs gsa		UCCGGCACUGCGUUCUGGU GCUG	
AD-1735560	asgsuca(Uda)AfuUfGfAfagaagccc sasa		VPusUfsgggCfuUfCfuucaAfuAfugacus usu		AAAGUCAUAUUGAAGAAGC CCAG	
AD-1735561	uscsauc(Ada)UfgCfUfGfcgucagcu susa		VPusAfsagcUfgAfCfgcagCfaUfgaugas usu		AAUCAUCAUGCUGCGUCAG CUUG	
AD-1735562	asasaug(Ada)UfcGfCfCfucuuggua susa		VPusAfsuacCfaAfGfaggcGfaUfcauuus usc		GAAAAUGAUCGCCUCUUGG UAUG	
AD-1735563	asusuug(Ada)AfgAfUfAfuaaagag csasa		VPusUfsgcuCfuUfUfauauCfuUfcaaaus gsu		ACAUUUGAAGAUAUAAAGA GCAG	
AD-1735564	gsgsucu(Cda)CfuUfCfAfccagccuc sgsa		VPusCfsgagGfcUfGfgugaAfgGfagaccs csa		UGGGUCUCCUUCACCAGCC UCGG	
AD-1735565	gsasaac(Ada)GfaGfAfAfgaaagaca sgsa		VPusCfsuguCfuUfUfcuucUfcUfguuucs csu		AGGAAACAGAGAAGAAAGA CAGC	
AD-1735566	ususcua(Gda)UfgGfCfUfacaaaugc scsa		VPusGfsgcaUfuUfGfuagcCfaCfuagaas asu		AUUUCUAGUGGCUACAAAU GCCC	
AD-1735567	gsgsaga(Gda)AfaAfUfCfaggaagga susa		VPusAfsucuUfuCfCfugauUfuCfucuccs csa		UGGGAGAGAAAUCAGGAAG GAUU	
AD-1735568	asusaua(Gda)UfgAfGfCfccuaaagg sasa		VPusUfsccuUfuAfGfggcuCfaCfuauaus usu		AAAUAUAGUGAGCCCUAAA GGAC	
AD-1735569	gscsugc(Cda)UfuUfGfUfccucgccc susa		VPusAfsgggCfgAfGfgacaAfaGfgcagcs csa		UGGCUGCCUUUGUCCUCGC CCUG	
AD-1735570	gsgscaa(Ada)AfgAfCfCfcuccaaag sasa		VPusUfscuuGfgUfGfaggcUfuUfuugcc sasu		AUGGCAAAAGACCUCACCA AGAA	
AD-1735571	ususcag(Cda)AfuCfGfCfcfugugccu susa		VPusAfsaggCfaCfAfggcgAfuGfcugaas gsa		UCUUCAGCAUCGCCUGUGC CUUC	
AD-	gscsuaa(Ada)UfgAfGfGfcucgcaau		VPusUfsauuGfcGfAfgccuCfaUfuuagcs		GUGCUAAAUGAGGCUCGCA	

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:
1735572	sasa		asc		AUAU	
AD-1735573	csasgcu(Uda)CfgUfCfUfggugggu csusa		VPusAfsgacCfcAfCfcagaCfgAfagcugs gsc		GCCAGCUUCGUCUGGUGGG UCUC	
AD-1735574	asusaug(Gda)UfaUfUfUfGfgcaugcag susa		VPusAfscugCfaUfGfccaaUfaCfcauaus usc		GAAUAUGGUAUUGGCAUGC AGUU	
AD-1735575	asasacu(Gda)CfaGfGfUfggagaauu scsa		VPusGfsaauUfcUfCfcaccUfgCfaguuus asu		AUAAACUGCAGGUGGAGAA UUCC	
AD-1735576	usasugg(Cda)UfgCfCfUfgucuucaa sasa		VPusUfsuugAfaGfAfcaggCfaGfccauas asc		GUUAUGGCUGCCUGUCUUC AAAC	
AD-1735577	csusguu(Cda)UfgAfAfAfuagagga cscsa		VPusGfsgucCfuCfUfauuuCfaGfaacags gsg		CCCUGUUCUGAAAUAGAGG ACCC	
AD-1735578	uscsuau(Uda)UfuUfAfAfagccgcu ggsga		VPusCfscagCfgGfCfuuuaAfaAfauagas asa		UUUCUAUUUUUAAAGCCGC UGGU	
AD-1735579	gscsuga(Gda)GfaGfAfAfgcucagga sasa		VPusUfsuccUfgAfGfcuucUfcCfucagcs usg		CAGCUGAGGAGAAGCUCAG GAAC	
AD-1735580	csasagc(Cda)UfuCfCfAfccacaagu scsa		VPusGfsacuUfgUfGfguggAfaGfgcuug sgsa		UCCAAGCCUUCCACCACAA GUCA	
AD-1735581	ususcag(Uda)UfaCfCfAfaaguggcc sasa		VPusUfsggcCfaCfUfuuggUfaAfcugaas asu		AUUUCAGUUACCAAAGUGG CCAG	
AD-1735582	csasccu(Gda)CfuUfCfCfcfucacccgg sasa		VPusUfsccgGfgUfGfaggaAfgCfaggugs asg		CUCACCUGCUUCCUCACCC GGAC	
AD-1735583	ususuua(Uda)CfaCfCfCfCfacauagug sgsa		VPusCfscacUfaUfGfuggguUfgAfuaaaas gsa		UCUUUUAUCACCCACAUAG UGGG	
AD-1735584	asgsgag(Ada)CfcGfUfCfguuugccuu sgsa		VPusCfsaagGfcAfAfcgacGfgUfcuccus gsa		UCAGGAGACCGUCGUUGCC UUGU	
AD-1735585	asusggc(Cda)CfaGfCfCfAfaaaguucg sasa		VPusUfscgaAfcUfUfuugcUfgGfgccaus usu		AAAUGGCCCAGCAAAAGUU CGAG	
AD-1735586	asgsacg(Cda)CfaAfAfGfccaugcgg susa		VPusAfsccgCfaUfGfgcuuUfgGfcgucus csg		CGAGACGCCAAAGCCAUGC GGUC	
AD-1735587	csasgcu(Ada)AfuGfCfAfccaccuca scsa		VPusGfsugaGfgUfGfgugcAfuUfagcug sasc		GUCAGCUAAUGCACCACCU CACU	
AD-1735588	gsgsaaa(Ada)GfcAfGfAfcggcgaau sasa		VPusUfsauuCfgCfCfgucuGfcUfuuuccs usu		AAGGAAAAGCAGACGGCGA AUAU	
AD-1735589	gscsuuu(Gda)CfuGfGfGfuagugag csusa		VPusAfsgcuCfaCfUfacccAfgCfaaagcs asg		CUGCUUUGCUGGGUAGUGA GCUC	

Table 14. Unmodified Sense and Antisense Strand Sequences of PDE3B dsRNA Agents Comprising a GalNAc Derivative Targeting Ligand

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4
AD-1735591	UUCCUUCUUCAUCUUGAUCAA		2880-2900	UUGAUCAAGAUGAAGAAGGAAG U		2878-2900
AD-1735592	CACUCUAAAACUGAUGUUCA A		4621-4641	UUGAACAUCAGUUUUAGAGUGA A		4619-4641
AD-1735593	UCUUCUGUAUCACUGACUCAA		1752-1772	UUGAGUCAGUGAUACAGAAGAU G		1750-1772
AD-1735594	CAGAUCUUCUGACUGAUCCAA		1363-1383	UUGGAUCAGUCAGAAGAUCUGA C		1361-1383
AD-1735595	UGACACAUUUUUCUCCAUAA A		5958-5978	UUUAUGGAGAAAAAAUGUGUCAG U		5956-5978
AD-1735596	GGAAACUCAUUUUUACAUAA A		5617-5637	UUUAUGUAAAAAUGAGUUUCCA G		5615-5637
AD-1735597	AUCAGCAACUUAGAAAUUCU A		1966-1986	UAGAAUUUCUAAGUUGCUGAUA A		1964-1986
AD-1735598	CUUAUAUUUCUCUAGAGUAC A		5351-5371	UGUACUCUAGAGAAAUAUAAGG A		5349-5371
AD-1735599	AACUCCAAGAAUCUUUUAUC A		3229-3249	UGAUAAAAGAUUCUUGGAGUUU U		3227-3249
AD-1735600	CUUCAAACAUUCCUGCAUUAA		2680-2700	UUAAUGCAGGAAUGUUUGAAGA C		2678-2700
AD-1735601	UCGUUCUUCUCCUCAACUAGA		3206-3226	UCUAGUUGAGGAGAAGAACGAU C		3204-3226
AD-1735602	AAAGAUUAAUCCUCUCACACA		1460-1480	UGUGUGAGAGGAUUAAUCUUUG G		1458-1480
AD-1735603	ACUAACCUCAUCAAAGAUACA		4501-4521	UGUAUCUUUGAUGAGGUUAGUU U		4499-4521
AD-1735604	CACCACUUAUUACUAAUAAAA A		5283-5303	UUUUAUUAGUAAUAAGUGGUGG G		5281-5303
AD-1735605	UGGUACUAGAAAUAUUCUUU A		5915-5935	UAAAGAAUAUUUCUAGUACCAG C		5913-5935
AD-1735606	GCUGUCAUUUGUUCACUCUA		4608-4628	UUAGAGUGAACAAAUGACAGCU		4606-4628

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4
	A			A		
AD-1735607	ACUCAACAAUUUAUGAACUA A		2421-2441	UUAGUUCAUAAAUUGUUGAGUG G		2419-2441
AD-1735608	AGUAUGACUCAUUAAUAGAA A		2269-2289	UUUCUAUUAAUGAGUCAUACUC U		2267-2289
AD-1735609	CUGCUGAUUUUCUUAAUAAG A		1891-1911	UCUUAUUAAGAAAAUCAGCAGU A		1889-1911
AD-1735610	UAUCUUUAGAUCCACAUCUU A		4587-4607	UAAGAUGUGGAUCUAAAGAUAA C		4585-4607
AD-1735611	CGAGACAUUCCUUAUCACAAA		2466-2486	UUUGUGAUAAGGAAUGUCUCGA U		2464-2486
AD-1735612	UACUGAAUCAGAUUAAUUUC A		5850-5870	UGAAAUUAAUCUGAUUCAGUAA C		5848-5870
AD-1735613	CUUACUUAAAUCCUUCACUGA		3855-3875	UCAGUGAAGGAUUUAAGUAAGG G		3853-3875
AD-1735614	UCGAAAGAAUCAUUCAAACU A		2100-2120	UAGUUUGAAUGAUUCUUUCGAG A		2098-2120
AD-1735615	AAAUGACCUAUCACUACUUA A		4682-4702	UUAAGUAGUGAUAGGUCAUUUC U		4680-4702
AD-1735616	CAAGUCAUUUCCUCUCUACGA		1395-1415	UCGUAGAGAGGAAAUGACUUGU G		1393-1415
AD-1735617	AUGCAGUUUCUUACUUAUCU A		5079-5099	UAGAUAAGUAAGAAACUGCAUG C		5077-5099
AD-1735618	UCAAUGCAAUACACUGUUCA A		4124-4144	UUGAACAGUGUAUUGCAUUGAG C		4122-4144
AD-1735619	UCUAUGUACCUACUGACACAA		5945-5965	UUGUGUCAGUAGGUACAUAGAU A		5943-5965
AD-1735620	UGAAUUCCAGUCUUAUCUUA A		4312-4332	UUAAGAUAAGACUGGAAUUCAA A		4310-4332
AD-1735621	UUGCUGUAAUACCAAAACUA A		4485-4505	UUAGUUUUGGUAUUACAGCAAA U		4483-4505
AD-1735622	GGAUCACUCUUUCAAAUCA A		1061-1081	UUGAUUUGAAAGAAGUGAUCCA A		1059-1081

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4
AD-1735623	GAACUAGAAAACUAUUCUUA A		3795-3815	UUAAGAAUAGUUUUCUAGUUCC U		3793-3815
AD-1735624	ACAUUUCCAUACUGUCUGUU A		5484-5504	UAACAGACAGUAUGGAAAUGUG A		5482-5504
AD-1735625	UGAUCCUUCACAGUGUCAAU A		5158-5178	UAUUGACACUGUGAAGGAUCAA A		5156-5178
AD-1735626	GAUUUCUGAGAACAAGUAAA A		4729-4749	UUUUACUUGUUCUCAGAAAUCA G		4727-4749
AD-1735627	CCUACUUGUGAAAUACAUUU A		4906-4926	UAAAUGUAUUUCACAAGUAGGG U		4904-4926
AD-1735628	CAACUGGAAUUUUCCAAUUU A		2297-2317	UAAAUUGGAAAAUUCCAGUUGC U		2295-2317
AD-1735629	UCUAAUCCUGAUGAGAGUUA A		2649-2669	UUAACUCUCAUCAGGAUUAGAG C		2647-2669
AD-1735630	AGCCUCAUUAUCAAAAUUCU A		1288-1308	UAGAAUUUUGAUAAUGAGGCUU A		1286-1308
AD-1735631	AAUUUCUGAUGCUUUUUACU A		4220-4240	UAGUAAAAAGCAUCAGAAAUUG A		4218-4240
AD-1735632	UACCAUUAGAUGAAAUCUUA A		5788-5808	UUAAGAUUUCAUCUAAUGGUAC A		5786-5808
AD-1735633	CUGUGAAUUCUUCCAACCAUA		1816-1836	UAUGGUUGGAAGAAUUCACAGG A		1814-1836
AD-1735634	CUAAUACUCCAGAUUUUUAU A		1948-1968	UAUAAAAAUCUGGAGUAUUAGG U		1946-1968
AD-1735635	GGACACAUACAUUGAAUAAA A		4550-4570	UUUUAUUCAAUGUAUGUGUCCU U		4548-4570
AD-1735636	UUUGUCAUAAUGCUGCUUUG A		3887-3907	UCAAAGCAGCAUUAUGACAAAG U		3885-3907
AD-1735637	UUCAUCUUUCUGUUAAUUUC A		4637-4657	UGAAAUUAACAGAAAGAUGAAC A		4635-4657
AD-1735638	CAGUGAAACCAUUAAUUUUC A		5028-5048	UGAAAAUUAAUGGUUUCACUGU G		5026-5048
AD-1735639	UAACUGCAAGACUGAUUUCU		4716-4736	UAGAAAUCAGUCUUGCAGUUAG		4714-4736

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4
	A			G		
AD-1735640	AGAAUUCCUCCUUACCUCAAA		3547-3567	UUUGAGGUAAGGAGGAAUUCUC C		3545-3567
AD-1735641	UAUUACAGAUCUUACUUUGU A		5830-5850	UACAAAGUAAGAUCUGUAAUAU G		5828-5850
AD-1735642	UUAUCUGAAAGAUAUCAAUU A		5111-5131	UAAUUGAUAUCUUUCAGAUAAG C		5109-5131
AD-1735643	AGAUCUGUUCUGGAAAAUCA A		2811-2831	UUGAUUUUCCAGAACAGAUCUG U		2809-2831
AD-1735644	CCCAGAAUACAACUUCCUUCA		2867-2887	UGAAGGAAGUUGUAUUCUGGGC G		2865-2887
AD-1735645	GUUGAUCUUUCAGUGCUAAA A		1323-1343	UUUUAGCACUGAAAGAUCAACU C		1321-1343
AD-1735646	CUAAGCUUUAUUUAUUAGAC A		5191-5211	UGUCUAAUAAAUAAAGCUUAGU G		5189-5211
AD-1735647	AGCUUGGAAUCUAUAUCUUU A		2843-2863	UAAAGAUAUAGAUUCCAAGCUG A		2841-2863
AD-1735648	UUAUUAUUUCUGAAGCCUAA A		4699-4719	UUUAGGCUUCAGAAAUAAUAAG U		4697-4719
AD-1735649	CCUUUGUUGUAUUUAACAAA A		4187-4207	UUUUGUUAAAUACAACAAAGGU C		4185-4207
AD-1735650	GCUCUCUAACUAAUCGAUCAA		1852-1872	UUGAUCGAUUAGUUAGAGAGCC A		1850-1872
AD-1735651	AAAGACUACAUGACAGAAAU A		4666-4686	UAUUUCUGUCAUGUAGUCUUUA G		4664-4686
AD-1735652	CAGGAUUCGUAUUUUUAAAG A		4418-4438	UCUUUAAAAAUACGAAUCCUGA G		4416-4438
AD-1735653	CCUUGCUAAGUAAUUGACAU A		5659-5679	UAUGUCAAUUACUUAGCAAGGG U		5657-5679
AD-1735654	CCUAUGCACUUUCACAGGAAA		3778-3798	UUUCCUGUGAAAGUGCAUAGGA G		3776-3798
AD-1735655	AUGCUGAAAUAUGUUUCAAC A		2019-2039	UGUUGAAACAUAUUUCAGCAUU U		2017-2039

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4
AD-1735656	CCUUUUAAUUCAAAUCUACU A		1710-1730	UAGUAGAUUUGAAUUAAAAGGC C		1708-1730
AD-1735657	ACUGGACUUAUUGGAUUUAA A		5577-5597	UUUAAAUCCAAUAAGUCCAGUA U		5575-5597
AD-1735658	CAUCUGAAUCAGAUGGUACA A		2038-2058	UUGUACCAUCUGAUUCAGAUGU U		2036-2058
AD-1735659	AAUUCUGAUAGCAAUCUGUG A		1980-2000	UCACAGAUUGCUAUCAGAAUUU C		1978-2000
AD-1735660	UCAAGUCAAGGAUGCUAUCU A		1683-1703	UAGAUAGCAUCCUUGACUUGAA A		1681-1703
AD-1735661	UCACUGAAAACCACACAAGAUA A		3466-3486	UUAUCUUGUGGUUUUCAGUGAG G		3464-3486
AD-1735662	ACCUGUUGAACAGUCUUCAA A		1616-1636	UUUGAAGACUGUUCAACAGGUA G		1614-1636
AD-1735663	UCAAGUGACAUAUUUCAGUU A		3957-3977	UAACUGAAAUAUGUCACUUGAG U		3955-3977
AD-1735664	UCAGGAACUUCAGGAUUGCU A		1596-1616	UAGCAAUCCUGAAGUUCCUGAG C		1594-1616
AD-1735665	ACGGAGUAUUAGUAGCUUAA A		1412-1432	UUUAAGCUACUAAUACUCCGUA G		1410-1432
AD-1735666	AUUGUCAAUGAAUUUUAUGA A		3135-3155	UUCAUAAAAUUCAUUGACAAUG C		3133-3155
AD-1735667	GAACAGCAAACAAAUAUUGA A		2214-2234	UUCAAUAUUUGUUUGCUGUUCA C		2212-2234
AD-1735668	UGAACUAUUUUCGUGCAUUA A		2434-2454	UUAAUGCACGAAAAUAGUUCAU A		2432-2454
AD-1735669	ACUGGAAUACUUAUUUUUCA A		4751-4771	UUGAAAAAUAAGUAUUCCAGUU C		4749-4771
AD-1735670	UUAUCUUGCAGAGAUCUCUG A		1918-1938	UCAGAGAUCUCUGCAAGAUAAC G		1916-1938
AD-1735671	GAAGUGUUAGAAUUUUUUGAU A		5142-5162	UAUCAAAAAUUCUAACACUUCC A		5140-5162
AD-1735672	UCAAUUUAAGAUCUCUGGAA		5125-5145	UUUCCAGAGAUCUUAAAUUGAU		5123-5145

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4
	A			A		
AD-1735673	UGGACCAUAUUUACAAUGUU A		4856-4876	UAACAUUGUAAAUAUGGUCCAU U		4854-4876
AD-1735674	UAGUCAUUGAAGCAAUCCUU A		2926-2946	UAAGGAUUGCUUCAAUGACUAA A		2924-2946
AD-1735675	AGCUGUUUAGGUUUAACAAU A		4353-4373	UAUUGUUAAACCUAAACAGCUU U		4351-4373
AD-1735676	CAAGGCAAAUGAUGUAAAUA A		2993-3013	UUAUUUACAUCAUUUGCCUUGG C		2991-3013
AD-1735677	AUCCAAUUACUACUGGAAAC A		5603-5623	UGUUUCCAGUAGUAAUUGGAUU U		5601-5623
AD-1735678	ACUUACAAUAUAUAUAUCCU A		5328-5348	UAGGAUAUAUAUAUUGUAAGUG C		5326-5348
AD-1735679	AUGCAGUUUGGUAUCUGACA A		2512-2532	UUGUCAGAUACCAAACUGCAUG U		2510-2532
AD-1735680	CCUUAUUUCAAGACACUGGU A		2377-2397	UACCAGUGUCUUGAAAUAAGGU A		2375-2397
AD-1735681	GAAGGGAUUUAUUCUUUAGU A		4373-4393	UACUAAAGAAUAAAUCCCUUCA U		4371-4393
AD-1735682	AUCCUUGCUACGGAUCUUAA A		2940-2960	UUUAAGAUCCGUAGCAAGGAUU G		2938-2960
AD-1735683	ACUGACUAUCCCGAAGCAAAA		1727-1747	UUUUGCUUCGGGAUAGUCAGUA G		1725-1747
AD-1735684	UGUAUUUCUGCUAUUAUUUC A		5390-5410	UGAAAUAAUAGCAGAAAUACAC U		5388-5410
AD-1735685	UGUAACAAUAACUAGCCUAA A		5680-5700	UUUAGGCUAGUUAUUGUUACAU A		5678-5700
AD-1735686	GUUGUUUUUACUCUAGCUCA A		4400-4420	UUGAGCUAGAGUAAAAACAACA A		4398-4420
AD-1735687	CAGGCAGUUUUAUACAAUGA A		2790-2810	UUCAUUGUAUAAAACUGCCUGA G		2788-2810
AD-1735688	AGGAUUCUCAGUCAGGUUAU A		2352-2372	UAUAACCUGACUGAGAAUCCUU C		2350-2372

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4
AD-1735689	AUUUUCCAUCAUGUUUUAAGUA		5371-5391	UACUUAAAACAUGAUGGAAAAUGU		5369-5391
AD-1735690	UGCCACUUUUUGUUACCAUUGA		5238-5258	UCAAUGGUAACAAAAAGUGGCAGC		5236-5258
AD-1735691	ACUUGCUAGUGUGUGGAUAUA		4882-4902	UAUAUCCACACACUAGCAAGUUU		4880-4902
AD-1735692	AAUCUUACUUGAGAAAUUGCA		5801-5821	UGCAAUUUCUCAAGUAAGAUUUC		5799-5821
AD-1735693	AGUUCGAGACUUUGCAUUUGAA		3101-3121	UUCAAAUGCAAGUCUCGAACUUU		3099-3121
AD-1735694	CCAUAGAAUUUCCUGAUACUA		1873-1893	UAGUAUCAGGAAAUUCUAUGGGU		1871-1893
AD-1735695	AGGUAAUUCCUUUAGAAUAUA		5050-5070	UAUAUUCUAAAGGAAUUACCUUG		5048-5070
AD-1735696	CUUAUGGAAACUCAACAAGAA		2118-2138	UUCUUGUUGAGUUUCCAUAAGUU		2116-2138
AD-1735697	AAGCAGCAUUUUAAAUUACGA		5554-5574	UCGUAAUUUAAAAUGCUGCUUUU		5552-5574
AD-1735698	UGACUCUCAACUGACCAUUCA		3699-3719	UGAAUGGUCAGUUGAGAGUCAGC		3697-3719
AD-1735699	AGGUUUAUCCAUGAAGGACUA		4161-4181	UAGUCCUUCAUGGAUAAACCUAG		4159-4181
AD-1735700	ACCAAGAAUUUUGGCAUUUCA		1666-1686	UUGAAAUGCCAAAUUCUUGGUGA		1664-1686
AD-1735701	UAUCUAGAAUAUUUUGGCUUA		5094-5114	UUAAGCCAAAUAUUCUAGAUAAA		5092-5114
AD-1735702	CUCCUGCAGAAUACAUACAAA		5412-5432	UUUGUAUGUAUUCUGCAGGAGA		5410-5432
AD-1735703	UCACACCAUUUUCCUGGAUUUA		1474-1494	UAAAUCCAGGAAAUGGUGUGAGA		1472-1494
AD-1735704	AUGUGGAAUUCAAGCGCUUUA		2899-2919	UAAAGCGCUUGAAUUCCACAUGA		2897-2919
AD-1735705	AUUGUGUAUUAUCUACUAUG		4240-4260	UCAUAGUAGAUAAUACACAAUAA		4238-4260

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4
	A			G		
AD-1735706	AAUGGAGUAAUGAAAAUGAUA		3025-3045	UAUCAUUUUCAUUACUCCAUUCU		3023-3045
AD-1735707	ACUGGUUUAUUGGAAAUAUUA		2391-2411	UAAUAUUUCCAAUAAACCAGUGU		2389-2411
AD-1735708	CAAGUGUAUGUGUAUAAAGUA		5429-5449	UACUUUAUACACAUACACUUGUU		5427-5449
AD-1735709	UACAAGCAUGCAUAUUGAGAA		5457-5477	UUCUCAAUAUGCAUGCUUGUAC		5455-5477
AD-1735710	UGUGUCUUUUAUGUCUUUGAA		4036-4056	UUCAAAGACAUAAAAGACACAC		4034-4056
AD-1735711	AUUUUCUCGCAGAAUUCAAUA		2971-2991	UAUUGAAUUCUGCGAGAAAAUC		2969-2991
AD-1735712	UAGCGACAGUUUGAGUAAAAA		3609-3629	UUUUUACUCAAACUGUCGCUAUU		3607-3629
AD-1735713	CUGGUGUAUGAAUACUUUGUA		3872-3892	UACAAAGUAUUCAUACACCAGUG		3870-3892
AD-1735714	GUGAUAAGUGGCUAACAGAAA		2182-2202	UUUCUGUUAGCCACUUAUCACCU		2180-2202
AD-1735715	GUAGGCUAAUAUUUUCUAUUA		4962-4982	UAAUAGAAAAUAUUAGCCUACCA		4960-4982
AD-1735716	CCUCUUCAUCCUCGACUGUCA		1089-1109	UGACAGUCGAGGAUGAAGAGGGC		1087-1109
AD-1735717	AAUUGCCAUAAGCCAUAUUUA		5815-5835	UUAAAUAUGGCUUAUGGCAAUUU		5813-5835
AD-1735718	GCGAAUAUUUUGUCAGCUAAA		3437-3457	UUUAGCUGACAAAAUAUUCGCCG		3435-3457
AD-1735719	AUCCAGUGUUGCCUUUCUGAA		4093-4113	UUCAGAAAGGCAACACUGGAUUC		4091-4113
AD-1735720	AAAGUCUAUGCCUGUCUAAAA		4068-4088	UUUUAGACAGGCAUAGACUUUUC		4066-4088
AD-1735721	GGACAUCAGAAGUUUGAAUUA		4298-4318	UAAUUCAAACUUCUGAUGUCCAU		4296-4318

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4
AD-1735722	GGCGAAUUGCUUAUAUUUCUA		2617-2637	UAGAAAUAUAAGCAAUUCGCCCA		2615-2637
AD-1735723	CACACUAUGUGUAAACCAGUA		5261-5281	UACUGGUUUACACAUAGUGUGUG		5259-5281
AD-1735724	CAGGUGAAGAAGAAAACAUUA		2077-2097	UAAUGUUUUCUUCUUCACCUGAU		2075-2097
AD-1735725	GUGAGCUCUUAUUUUUCACUA		3914-3934	UAGUGAAAAAUAAGAGCUCACUA		3912-3934
AD-1735726	AAAGCUGAUGGGAAUAAAACU		3519-3539	UAGUUUAUUCCCAUCAGCUUUAC		3517-3539
AD-1735727	GUGUCGUUAGGAGAAACUGCA		1164-1184	UGCAGUUUCUCCUAACGACACGC		1162-1184
AD-1735728	GGGACUUAAAAACAAUGGUAUA		1267-1287	UAUACCAUUGUUUUAAGUCCCAA		1265-1287
AD-1735729	CUGAUGGUAGAAUUAACCAUA		2596-2616	UAUGGUUAAUUCUACCAUCAGAA		2594-2616
AD-1735730	ACUAUGUGUGUUUUAUUUCUA		4254-4274	UAGAAAUAAAACACACAUAGUAG		4252-4274
AD-1735731	CUGAUAAUUUAUAUUUGCACA		5310-5330	UGUGCAAAUAUAAAUUAUCAGUC		5308-5330
AD-1735732	GUCCUUAAAUUAUUUAACCCA		5641-5661	UGGGUUAAAUAAUUUAAGGACUA		5639-5661
AD-1735733	CGCAAUAUGGUGUCAGAUCUA		1350-1370	UAGAUCUGACACCAUAUUGCGAG		1348-1370
AD-1735734	UUCGAAGAGGCUGCUCUAAUC		2636-2656	UGAUUAGAGGCAGCUCUUCGAAG		2634-2656
AD-1735735	UUUCUGCUGAGAGUAUUCAGA		4269-4289	UCUGAAUACUCUCAGCAGAAAUA		4267-4289
AD-1735736	UUGAACAGGAAGUAUCACUGA		2230-2250	UCAGUGAUACUUCCUGUUCAAUA		2228-2250
AD-1735737	UGCCUUGUAUUUCCAGAGAAA		1228-1248	UUUCUCUGGAAAUACAAGGCAAC		1226-1248
AD-1735738	GUUACUAUGGCAGUUGCAAAA		1189-1209	UUUUGCAACUGCCAUAGUAACUC		1187-1209

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4
	A			G		
AD-1735739	AUGGCUGAAUUUUAAAGCUG A		4338-4358	UCAGCUUUAAAAUUCAGCCAUG G		4336-4358
AD-1735740	GUCCAUUCAUGGAUCGUUCU A		3193-3213	UAGAACGAUCCAUGAAUGGACU G		3191-3213
AD-1735741	UGUGUAACUCCUAUGAUGCU A		3268-3288	UAGCAUCAUAGGAGUUACACAG G		3266-3288
AD-1735742	UGGCAGUUUCCCACUCCUAUA		3763-3783	UAUAGGAGUGGGAAACUGCCAG C		3761-3783
AD-1735743	CCUCAAGCAGAUGAGAUUCA A		3561-3581	UUGAAUCUCAUCUGCUUGAGGU A		3559-3581
AD-1735744	AUGUUGUUUUCUCAAAAGCA A		5539-5559	UUGCUUUUGAGAAAACAACAUA A		5537-5559
AD-1735745	GAGGGAUUUUCUGCUCAAUGC A		4111-4131	UGCAUUGAGCAGAAAUCCCUCA G		4109-4131
AD-1735746	GCCUUCUUCUUCCUCACCUGA		654-674	UCAGGUGAGGAAGAAGAAGGCA C		652-674
AD-1735747	UUGAGAUUGAAUCACAUUUC A		5471-5491	UGAAAUGUGAUUCAAUCUCAAU A		5469-5491
AD-1735748	CUGUUCAGUGCUAUUCUCCCA		4137-4157	UGGGAGAAUAGCACUGAACAGU G		4135-4157
AD-1735749	CCUGGCUUACAGCAGAUCCAA		2544-2564	UUGGAUCUGCUGUAAGCCAGGA A		2542-2564
AD-1735750	GACAGCAGAAAAUUAUUUCA A		2157-2177	UUGAAAUAAUUUUCUGCUGUCU U		2155-2177
AD-1735751	UUGGGUUUCUUUAGUUUAUG A		5522-5542	UCAUAAACUAAAGAAACCCAAU A		5520-5542
AD-1735752	CACCAUGUAGGUCUCAGAAG A		1770-1790	UCUUCUGAGACCUACAUGGUGA G		1768-1790
AD-1735753	GUUGUGGAACAGGAAAUGAA A		2569-2589	UUUCAUUUCCUGUUCCACAACC A		2567-2589
AD-1735754	GGAGAACAUAUCAUAUUUUG A		4988-5008	UCAAAAUAUGAUAUGUUCUCCA A		4986-5008

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4
AD-1735755	CAGCCAAAAAUGAUGGCAAAA A		4940-4960	UUUUUGCCAUCAUUUUGGCUGC U		4938-4960
AD-1735756	CCAAUUUUUUGAACUUGUAGA A		2310-2330	UUCUACAAGUUCAAAAAUUGGA A		2308-2330
AD-1735757	AUAGGAAUAGUUUGCCAACU A		1558-1578	UAGUUGGCAAACUAUUCCUAUU U		1556-1578
AD-1735758	UUUGAAUGUUUUGGAGAAAA A		4051-4071	UUUUUCUCCAAAACAUUCAAAG A		4049-4071
AD-1735759	GUCAAUAUUUAAUGAAUCAC A		5172-5192	UGUGAUUCAUUAAAUAUUGACA C		5170-5192
AD-1735760	UGAGAAUAUAUUAAAUGCAC A		5764-5784	UGUGCAUUUAAUAUUCUCAC A		5762-5784
AD-1735761	UAACAAGGGACUAAAUAGGA A		1544-1564	UUCCUAUUUAGUCCCUUGUUAA G		1542-1564
AD-1735762	GGCUUCUUCUUCCACCUCUGA		408-428	UCAGAGGUGGAAGAAGAAGCCG C		406-428
AD-1735763	UUGGAACAUGUGGUUAUCUU A		4573-4593	UAAGAUAACCACAUGUUCCAAU U		4571-4593
AD-1735764	CAGAGAACAGAUGAUUCUUU A		1241-1261	UAAAGAAUCAUCUGUUCUCUGG A		1239-1261
AD-1735765	CUGUUAUUUUAUUGGGUUUU A		5499-5519	UAAAACCCAAUAAAAUAACAGA C		5497-5519
AD-1735766	AUGAAGAAGCAAAUCUUGGU A		3163-3183	UACCAAGAUUUGCUUCUUCAUC U		3161-3183
AD-1735767	UUUGGAAUCAUGCAAUUUUG A		5004-5024	UCAAAAUUGCAUGAUUCCAAAA U		5002-5024
AD-1735768	CAAUGUUUUGUAAACUUGCU A		4869-4889	UAGCAAGUUUACAAAACAUUGU A		4867-4889
AD-1735769	GGAUCGUAAUAAUGGCAAAA A		1640-1660	UUUUUGCCAUUAUUACGAUCCC A		1638-1660
AD-1735770	GUGCUUUCUCAGGUUCCUGU A		1435-1455	UACAGGAACCUGAGAAAGCACC C		1433-1455
AD-1735771	AUGAUACUGAAAGUGGUGAU		3331-3351	UAUCACCACUUUCAGUAUCAUU		3329-3351

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4
	A			A		
AD-1735772	UCACUGGACCUGAUUUUAGUA		2244-2264	UACUAAAAUCAGGUCCAGUGAUA		2242-2264
AD-1735773	GAACUUUUUGCUUUUAUGAAA		3991-4011	UUUCAUAAAAGCAAAAAGUUCCU		3989-4011
AD-1735774	GAACACAGCACAGAUUUGUUA		4451-4471	UAACAAAUCUGUGCUGUGUUCAU		4449-4471
AD-1735775	AUAUGGAAGGAAAUCGUAGAA		3483-3503	UUCUACGAUUUCCUUCCAUAUCU		3481-3503
AD-1735776	GCUAUCUAAAUGGGCCUUUUA		1696-1716	UAAAAGGCCCAUUUAGAUAGCAU		1694-1716
AD-1735777	CAAAACCACCAAGAAGGAAAA		3409-3429	UUUUCCUUCUUGGUGGUUUUGG		3407-3429
AD-1735778	CCACAGAUGUGCUACAUGCAA		2497-2517	UUGCAUGUAGCACAUCUGUGGC		2495-2517
AD-1735779	AAAGUCAUACAUGUACAAGCA		5444-5464	UGCUUGUACAUGUAUGACUUUA		5442-5464
AD-1735780	UAGAAGCAGAAGAGGAUAAUA		3313-3333	UAUUAUCCUCUUCUGCUUCUAAC		3311-3333
AD-1735781	CGUGUGUUCGCACAGCUUGAA		611-631	UUCAAGCUGUGCGAACACACGCU		609-631
AD-1735782	GCUGGUGUUUUGUCCAGUCUA		1791-1811	UAGACUGGACAAAACACCAGCUC		1789-1811
AD-1735783	AUGGAAAACAAUCUAAAAUCCA		3390-3410	UGGAUUUAGAUUGUUUUCCAUUU		3388-3410
AD-1735784	CAUUAGAAAAUGGCUAUCGAA		2449-2469	UUCGAUAGCCAUUUUCUAAUGCA		2447-2469
AD-1735785	AUGGACAGAAGGCAUUGUCAA		3122-3142	UUGACAAUGCCUUCUGUCCAUUU		3120-3142
AD-1735786	CAGAUUGCUGCAGUGGAAAAA		2056-2076	UUUUUCCACUGCAGCAAUCUGU		2054-2076
AD-1735787	AGGUGGAAAUGGAGUUGAUCA		1310-1330	UGAUCAACUCCAUUUCCACCUC		1308-1330

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4
AD-1735788	CUGGGCAAUGCACCUAAUACA		1935-1955	UGUAUUAGGUGCAUUGCCCAGA G		1933-1955
AD-1735789	AUUUCCCUCUGCCUAAAGACA		4652-4672	UGUCUUUAGGCAGAGGGAAAUU A		4650-4672
AD-1735790	CGCUUCUGCAACGUGGAGCUA		429-449	UAGCUCCACGUUGCAGAAGCGG C		427-449
AD-1735791	AGAUUCAUAUUGUAUUUCCC A		4014-4034	UGGGAAAUACAAUAUGAAUCUA U		4012-4034
AD-1735792	AGGACAAAUGCAUUUCUAGU A		2754-2774	UACUAGAAAUGCAUUUGUCCUC C		2752-2774
AD-1735793	UUAGACGUGUUGAGUGAGUG A		5205-5225	UCACUCACUCAACACGUCUAAU A		5203-5225
AD-1735794	CUGUGGACAUCAAAUGCUGA A		2006-2026	UUCAGCAUUUGAUGUCCACAGC U		2004-2026
AD-1735795	AGGCCUUAAUACUGUGAGAG A		3729-3749	UCUCUCACAGUAUUAAGGCCUG U		3727-3749
AD-1735796	AGAAAUCAUUGCCUAGUGUU A		3672-3692	UAACACUAGGCAAUGAUUUCUG C		3670-3692
AD-1735797	UGAGUGCUGAGUUCCUUGCU A		5219-5239	UAGCAAGGAACUCAGCACUCAC U		5217-5239
AD-1735798	GCCAUGCAUGAUUAUGAUCA A		2727-2747	UUGAUCAUAAUCAUGCAUGGCA G		2725-2747
AD-1735799	UGCUGCUGGUUUGCUACCAG A		3284-3304	UCUGGUAGCAAACCAGCAGCAU C		3282-3304
AD-1735800	CAGAUGAAGAGGAAUAGCGA A		3595-3615	UUCGCUAUUCCUCUUCAUCUGC C		3593-3615
AD-1735801	AUCCAGGUGCAUCAAUUUCU A		4207-4227	UAGAAAUUGAUGCACCUGGAUU U		4205-4227
AD-1735802	AAUAAGCCAAGCGUUAUCUU A		1905-1925	UAAGAUAACGCUUGGCUUAUUA A		1903-1925
AD-1735803	GAGAGGAUCCUUGCUCUGCU A		3744-3764	UAGCAGAGCAAGGAUCCUCUCA C		3742-3764
AD-1735804	AUGAUGAAGACGGUGAAGAA		3349-3369	UUUCUUCACCGUCUUCAUCAUC		3347-3369

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4
	A			A		
AD-1735805	UCGUAAGUGUAAGAAAGAAU A		5743-5763	UAUUCUUUCUUACACUUACGAA U		5741-5763
AD-1735806	AUCUGUGUAACAGCUGUGGA A		1993-2013	UUCCACAGCUGUUACACAGAUU G		1991-2013
AD-1735807	AUUUAAAAAUUCCCACUCAACA		2408-2428	UGUUGAGUGGGAAUUUUAAAUA U		2406-2428
AD-1735808	GACCAGUGUCUACUGGCUCUA		1837-1857	UAGAGCCAGUAGACACUGGUCC A		1835-1857
AD-1735809	CGCUUUCGUUUUUUAGUCAU A		2913-2933	UAUGACUAAAAAACGAAAGCGC U		2911-2933
AD-1735810	UCCGUGUUGACCCAUGUUGCA		3829-3849	UGCAACAUGGGUCAACACGGAU G		3827-3849
AD-1735811	AUACAGAAGAUGAAGAAAUG A		3373-3393	UCAUUUCUUCAUCUUCUGUAUC U		3371-3393
AD-1735812	UCUCCCGAGCUGAAACUUAAA		5719-5739	UUUAAGUUUCAGCUCGGGAGAG A		5717-5739
AD-1735813	UGCAUCAAACUGGCAGAUAU A		3066-3086	UAUAUCUGCCAGUUUGAUGCAC A		3064-3086
AD-1735814	UUGCAAAAUAUUCAGGAGAC A		1202-1222	UGUCUCCUGAAUAUUUUGCAAC U		1200-1222
AD-1735815	ACAAUCGUAUACAUGCCACAA		2482-2502	UUGUGGCAUGUAUACGAUUGUG A		2480-2502
AD-1735816	AAUAGAAAAGAUGAGCAACU A		2282-2302	UAGUUGCUCAUCUUUUCUAUUA A		2280-2302
AD-1735817	UAUCUUAUGUUCCAUGGCUG A		4325-4345	UCAGCCAUGGAACAUAAGAUAA G		4323-4345
AD-1735818	CUACGUGAAGAGCUGCGUGA A		362-382	UUCACGCAGCUCUUCACGUAGC C		360-382
AD-1735819	GAAUUGAUGGCUCUAUACGU A		2700-2720	UACGUAUAGAGCCAUCAAUUCU A		2698-2720
AD-1735820	UUCAGGUAAUUGAAGAGGCA A		3577-3597	UUGCCUCUUCAAUUACCUGAAU C		3575-3597

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4
AD-1735821	AAGGACUGAGUGACCUUUGUA		4174-4194	UACAAAGGUCACUCAGUCCUUCA		4172-4194
AD-1735822	CGAGAGUCUGAGGAACGGCUA		344-364	UAGCCGUUCCUCAGACUCUCGGG		342-364
AD-1735823	AUUCUUUGGGAUUGGGACUUA		1254-1274	UAAGUCCCAAUCCCAAAGAAUCA		1252-1274
AD-1735824	UACCAGGUCAGUGGUUAGAAA		3298-3318	UUUCUAACCACUGACCUGGUAGC		3296-3318
AD-1735825	AUUCAGGUUUGCCAUGGACAA		4283-4303	UUGUCCAUGGCAAACCUGAAUAC		4281-4303
AD-1735826	GCAGCUAAACUGGUCCUGGAA		34-54	UUCCAGGACCAGUUUAGCUGCCG		32-54
AD-1735827	AGUAAUGGCAUAGAAUGGAGA		3012-3032	UCUCCAUUCUAUGCCAUUACUAU		3010-3032
AD-1735828	AAUUGCAAGAAAAUGGACCAA		4843-4863	UUGGUCCAUUUUCUUGCAAUUAU		4841-4863
AD-1735829	CGGCACUGCGUUCUGGUGCUA		921-941	UAGCACCAGAACGCAGUGCCGGA		919-941
AD-1735830	AGUCAUAUUGAAGAAGCCCAA		3633-3653	UUGGGCUUCUUCAAUAUGACUUU		3631-3653
AD-1735831	UCAUCAUGCUGCGUCAGCUUA		2828-2848	UAAGCUGACGCAGCAUGAUGAU		2826-2848
AD-1735832	AAAUGAUCGCCUCUUGGUAU		3038-3058	UAUACCAAGAGGCGAUCAUUUUC		3036-3058
AD-1735833	AUUUGAAGAUAUAAAGAGCA		4922-4942	UUGCUCUUUAUAUCUUCAAAUGU		4920-4942
AD-1735834	GGUCUCCUUCACCAGCUCUCGA		965-985	UCGAGGCUGGUGAAGGAGACCCA		963-985
AD-1735835	GAAACAGAGAAGAAAGACAGA		2142-2162	UCUGUCUUUCUUCUCUGUUUCCU		2140-2162
AD-1735836	UUCUAGUGGCUACAAAUGCCA		2767-2787	UGGCAUUUGUAGCCACUAGAAAU		2765-2787
AD-1735837	GGAGAGAAAUCAGGAAGGAUU		2337-2357	UAUCCUUCCUGAUUUCUCUCCCC		2335-2357

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4
	A			A		
AD-1735838	AUAUAGUGAGCCCUAAAGGAA		4533-4553	UUCCUUUAGGGCUCACUAUAUU		4531-4553
AD-1735839	GCUGCCUUUGUCCUCGCCCUA		528-548	UAGGGCGAGGACAAAGGCAGCC		526-548
AD-1735840	GGCAAAAGACCUCACCAAGAA		1653-1673	UUCUUGGUGAGGUCUUUUGCCA		1651-1673
AD-1735841	UUCAGCAUCGCCUGUGCCUUA		639-659	UAAGGCACAGGCGAUGCUGAAG		637-659
AD-1735842	GCUAAAUGAGGCUCGCAAUA		1337-1357	UUAUUGCGAGCCUCAUUUAGCA		1335-1357
AD-1735843	CAGCUUCGUCUGGUGGGUCU		950-970	UAGACCCACCAGACGAAGCUGG		948-970
AD-1735844	AUAUGGUAUUGGCAUGCAGU		5066-5086	UACUGCAUGCCAAUACCAUAUU		5064-5086
AD-1735845	AAACUGCAGGUGGAGAAUUC		3534-3554	UGAAUUCUCCACCUGCAGUUUA		3532-3554
AD-1735846	UAUGGCUGCCUGUCUUCAAA		2667-2687	UUUUGAAGACAGGCAGCCAUAA		2665-2687
AD-1735847	CUGUUCUGAAAUAGAGGACC		1499-1519	UGGUCCUCUAUUUCAGAACAGG		1497-1519
AD-1735848	UCUAUUUUUAAAGCCGCUGG		5898-5918	UCCAGCGGCUUUAAAAAUAGAA		5896-5918
AD-1735849	GCUGAGGAGAAGCUCAGGAA		1583-1603	UUUCCUGAGCUUCUCCUCAGCU		1581-1603
AD-1735850	CAAGCCUUCCACCACAAGUCA		1381-1401	UGACUUGUGGUGGAAGGCUUGG		1379-1401
AD-1735851	UUCAGUUACCAAAGUGGCCA		3970-3990	UUGGCCACUUUGGUAACUGAAA		3968-3990
AD-1735852	CACCUGCUUCCUCACCCGAA		668-688	UUCCGGGUGAGGAAGCAGGUGA		666-688
AD-1735853	UUUUAUCACCCACAUAGUGG A		3242-3262	UCCACUAUGUGGGUGAUAAAAG A		3240-3262

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000922.4
AD-1735854	AGGAGACCGUCGUUGCCUUGA		1215-1235	UCAAGGCAACGACGGUCUCCUGA		1213-1235
AD-1735855	AUGGCCCAGCAAAAGUUCGAA		3088-3108	UUCGAACUUUUGCUGGGCCAUUU		3086-3108
AD-1735856	AGACGCCAAAGCCAUGCGGUA		290-310	UACCGCAUGGCUUUGGCGUCUCG		288-310
AD-1735857	CAGCUAAUGCACCACCUCACA		3450-3470	UGUGAGGUGGUGCAUUAGCUGAC		3448-3470
AD-1735858	GGAAAAGCAGACGGCGAAUAA		3424-3444	UUAUUCGCCGUCUGCUUUUCCUU		3422-3444
AD-1735859	GCUUUGCUGGGUAGUGAGCUA		3901-3921	UAGCUCACUACCCAGCAAAGCAG		3899-3921
AD-1735860	AAAUGAAACAGAUUCUGAUGA		2582-2602	UCAUCAGAAUCUGUUUCAUUUCC		2580-2602

Table 15. Modified Sense and Antisense Strand Sequences of PDE3B dsRNA Agents Comprising a GalNAc Derivative Targeting Ligand

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-1735591	ususccuuCfuUfCfAfucuugaucsasa		VPusUfsgauCfaAfGfaugaAfgAfaggaasgsu		ACUUCCUUCUUCAUCUUGAUCAU	
AD-1735592	csascucuAfaAfAfCfugauguucsasa		VPusUfsgaaCfaUfCfaguuUfuAfgagugsasa		UUCACUCUAAAACUGAUGUUCAU	
AD-1735593	uscsuucuGfuAfUfCfacugacucsasa		VPusUfsgagUfcAfGfugauAfcAfgaagasusg		CAUCUUCUGUAUCACUGACUCAC	
AD-1735594	csasgaucUfuCfUfGfacugauccsasa		VPusUfsggaUfcAfGfucagAfaGfaucugsasc		GUCAGAUCUUCUGACUGAUCCAA	
AD-1735595	usgsacacAfuUfUfUfucuccauasasa		VPusUfsuauGfgAfGfaaaaAfuGfugucasgsu		ACUGACACAUUUUUCUCCAUAAA	
AD-1735596	gsgsaaacUfcAfUfUfuuuacauasasa		VPusUfsuauGfuAfAfaaauGfaGfuuuccsasg		CUGGAAACUCAUUUUUACAUAAU	
AD-	asuscagcAfaCfUfUfagaaauu		VPusAfsgaaUfuUfCfuaagUfuGfcuga		UUAUCAGCAACUUAGAAAU	

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:
1735597	csusa		usasa		UCUG	
AD-1735598	csusuauaUfuUfCfUfcuagagu ascsa		VPusGfsuacUfcUfAfgagaAfaUfauaaa gsgsa		UCCUUAUAUUUCUCUAGAG UACA	
AD-1735599	asascuccAfaGfAfAfucuuuua uscsa		VPusGfsauaAfaAfGfauucUfuGfgag uususu		AAAACUCCAAGAAUCUUUU AUCA	
AD-1735600	csusucaaAfcAfUfUfccugcau usasa		VPusUfsaauGfcAfGfgaauGfuUfugaa gsasc		GUCUUCAAACAUUCCUGCA UUAG	
AD-1735601	uscsguucUfuCfUfCfcucaacu asgsa		VPusCfsuagUfuGfAfggagAfaGfaacg asusc		GAUCGUUCUUCUCCUCAAC UAGC	
AD-1735602	asasagauUfaAfUfCfcucucac ascsa		VPusGfsuguGfaGfAfggauUfaAfucu uusgsg		CCAAAGAUUAAUCCUCUCA CACC	
AD-1735603	ascsuaacCfuCfAfUfcaaagau ascsa		VPusGfsuauCfuUfUfgaugAfgGfuua gususu		AAACUAACCUCAUCAAAGA UACA	
AD-1735604	csasccacUfuAfUfUfUfacuaaua asasa		VPusUfsuuaUfuAfGfuaauAfaGfugg ugsgsg		CCCACCACUUAUUACUAAU AAAA	
AD-1735605	usgsguacUfaGfAfAfafauauucu ususa		VPusAfsaagAfaUfAfuuuuUfaGfuacc asgsc		GCUGGUACUAGAAAUAUUC UUUU	
AD-1735606	gscsugucAfuUfUfUfGfuucacuc usasa		VPusUfsagaGfuGfAfacaaAfuGfacag csusa		UAGCUGUCAUUUGUUCACU CUAA	
AD-1735607	ascsucaaCfaAfUfUfUfuaugaac usasa		VPusUfsaguUfcAfUfaaauUfgUfuga gusgsg		CCACUCAACAAUUUAUGAA CUAU	
AD-1735608	asgsuaugAfcUfCfAfUfuuaauag asasa		VPusUfsucuAfuUfUfAfaugaGfuCfauac uscsu		AGAGUAUGACUCAUUAAUA GAAA	
AD-1735609	csusgcugAfuUfUfUfUfcuuaaua asgsa		VPusCfsuuaUfuAfAfgaaaAfuCfagca gsusa		UACUGCUGAUUUUUCUUAAU AAGC	
AD-1735610	usasucuuUfaGfAfUfUfccacauc ususa		VPusAfsagaUfgUfUfGfgaucUfaAfagau asasc		GUUAUCUUUAGAUCCACAU CUUA	
AD-1735611	csgsagacAfuUfUfCfCfuuaucac asasa		VPusUfsuguGfaUfAfaggaAfuGfucu cgsasu		AUCGAGACAUUCCUUAUCA CAAU	
AD-1735612	usascugaAfuCfAfGfGfauuaauu uscsa		VPusGfsaaaUfuAfAfucugAfuUfcag uasasc		GUUACUGAAUCAGAUUAAU UUCU	
AD-1735613	csusuacuUfaAfAfUfUfccuucac usgsa		VPusCfsaguGfaAfGfgauuUfaAfguaa gsgsg		CCCUUACUUAAAUCCUUCA CUGG	
AD-1735614	uscsgaaaGfaAfUfCfCfauucaaa csusa		VPusAfsguuUfgAfAfugauUfcUfuuc gasgsa		UCUCGAAAGAAUCAUUCAA ACUU	

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-1735615	asasaugaCfcUfAfUfcacuacu usasa		VPusUfsaagUfaGfUfgauaGfgUfcauu uscsu		AGAAAUGACCUAUCACUAC UUAU	
AD-1735616	csasagucAfuUfUfCfcucucua csgsa		VPusCfsguaGfaGfAfggaaAfuGfacuu gsusg		CACAAGUCAUUUCCUCUCU ACGG	
AD-1735617	asusgcagUfuUfCfUfuacuuau csusa		VPusAfsgauAfaGfUfaagaAfaCfugca usgsc		GCAUGCAGUUUCUUACUUA UCUA	
AD-1735618	uscsaaugCfaAfUfAfcacuguu csasa		VPusUfsgaaCfaGfUfguauUfgCfauug asgsc		GCUCAAUGCAAUACACUGU UCAG	
AD-1735619	uscsuaugUfaCfCfUfacugaca csasa		VPusUfsgugUfcAfGfuaggUfaCfaua gasusa		UAUCUAUGUACCUACUGAC ACAU	
AD-1735620	usgsaauuCfcAfGfUfcuuaucu usasa		VPusUfsaagAfuAfAfgacuGfgAfauu casasa		UUUGAAUUCCAGUCUUAUC UUAU	
AD-1735621	ususgcugUfaAfUfAfccaaaac usasa		VPusUfsaguUfuUfGfguauUfaCfagca asasu		AUUUGCUGUAAUACCAAAA CUAA	
AD-1735622	gsgsaucaCfuUfCfUfuucaaau csasa		VPusUfsgauUfuGfAfaagaAfgUfgau ccsasa		UUGGAUCACUUCUUUCAAA UCAG	
AD-1735623	gsasacuaGfaAfAfAfcuauucu usasa		VPusUfsaagAfaUfAfguuuUfcUfagu ucscsu		AGGAACUAGAAAACUAUUC UUAA	
AD-1735624	ascsauuuCfcAfUfAfcugucug ususa		VPusAfsacaGfaCfAfguauGfgAfaaug usgsa		UCACAUUUCCAUACUGUCU GUUA	
AD-1735625	usgsauccUfuCfAfCfaguguca asusa		VPusAfsuugAfcAfCfugugAfaGfgau casasa		UUUGAUCCUUCACAGUGUC AAUA	
AD-1735626	gsasuuucUfgAfGfAfacaagua asasa		VPusUfsuuaCfuUfGfuucuCfaGfaaau csasg		CUGAUUUCUGAGAACAAGU AAAG	
AD-1735627	cscsuacuUfgUfGfAfaauacau ususa		VPusAfsaauGfuAfUfuucaCfaAfguag gsgsu		ACCCUACUUGUGAAAUACA UUUG	
AD-1735628	csasacugGfaAfUfUfuuccaau ususa		VPusAfsaauUfgGfAfaaauUfcCfaguu gscsu		AGCAACUGGAAUUUUCCAA UUUU	
AD-1735629	uscsuaauCfcUfGfAfugagagu usasa		VPusUfsaacUfcUfCfaucaGfgAfuuag asgsc		GCUCUAAUCCUGAUGAGAG UUAU	
AD-1735630	asgsccucAfuUfAfUfcaaaauu csusa		VPusAfsgaaUfuUfUfgauaAfuGfagg cususa		UAAGCCUCAUUAUCAAAAU UCUG	
AD-1735631	asasuuucUfgAfUfGfcuuuuua csusa		VPusAfsguaAfaAfAfgcauCfaGfaaau usgsa		UCAAUUUCUGAUGCUUUUU ACUA	
AD-	usasccauUfaGfAfUfgaaaucu		VPusUfsaagAfuUfUfcaucUfaAfugg		UGUACCAUUAGAUGAAAUC	

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:
1735632	usasa		uascsa		UUAC	
AD-1735633	csusguga AfuUfCfUfuccaacc asusa		VPusAfsuggUfuGfGfaagaAfuUfcaca gsgsa		UCCUGUGAAUUCUUCCAAC CAUG	
AD-1735634	csusaauaCfuCfCfCfAfgauuuuu asusa		VPusAfsuaaAfaAfUfcuggAfgUfauu agsgsu		ACCUAAUACUCCAGAUUUU UAUC	
AD-1735635	gsgsacacAfuAfCfCfAfuugaaua asasa		VPusUfsuuaUfuCfAfauguAfuGfugu ccsusu		AAGGACACAUACAUUGAAU AAAU	
AD-1735636	ususugucAfuAfAfAfUfgcugcu uusgsa		VPusCfsaaaGfcAfGfcauuAfuGfacaa asgsu		ACUUUGUCAUAAUGCUGCU UUGC	
AD-1735637	ususcauc UfuUfCfUfguuaauu uscsa		VPusGfsaaaUfuAfAfcagaAfaGfauga ascsa		UGUUCAUCUUUCUGUUAAU UUCC	
AD-1735638	csasguga AfaCfCfAfuuaauuu uscsa		VPusGfsaaaAfuUfAfauggUfuUfcacu gsusg		CACAGUGAAACCAUUAAUU UUCC	
AD-1735639	usasacug CfaAfGfAfcugauuu csusa		VPusAfsgaaAfuCfAfgucuUfgCfagu uasgsg		CCUAACUGCAAGACUGAUU UCUG	
AD-1735640	asgsaauu CfcUfCfCfcuuaccuc asasa		VPusUfsugaGfgUfAfaggaGfgAfauu cuscsc		GGAGAAUUCCUCCCUUACCU CAAG	
AD-1735641	usasuuac AfgAfUfCfuuacuuu gsusa		VPusAfscaaAfgUfAfagauCfuGfuaau asusg		CAUAUUACAGAUCUUACUU UGUU	
AD-1735642	ususaucu GfaAfAfGfauaucaa ususa		VPusAfsauuGfaUfAfucuuUfcAfgau aasgsc		GCUUAUCUGAAAGAUAUCA AUUU	
AD-1735643	asgsaucu GfuUfCfUfggaaaau csasa		VPusUfsgauUfuUfCfcagaAfcAfgauc usgsu		ACAGAUCUGUUCUGGAAAA UCAU	
AD-1735644	csc scagaAfuAfCfAfacuuccu uscsa		VPusGfsaagGfaAfGfuuguAfuUfcug ggscsg		CGCCCAGAAUACAACUUCC UUCU	
AD-1735645	gsusugau CfuUfUfCfagugcua asasa		VPusUfsuuaGfcAfCfugaaAfgAfucaa csusc		GAGUUGAUCUUUCAGUGCU AAAU	
AD-1735646	csusaagc UfuUfAfUfuuauuag ascsa		VPusGfsucuAfaUfAfaauaAfaGfcuua gsusg		CACUAAGCUUUAUUUAUUA GACG	
AD-1735647	asgscuug GfaAfUfCfuauaucu usgsa		VPusAfsaagAfuAfUfagauUfcCfaagc uuuc		UCAGCUUGGAAUCUAUAUC UUUC	
AD-1735648	ususauua UfuUfCfUfgaagccu asasa		VPusUfsuagGfcUfUfcagaAfaUfaaua asgsu		ACUUAUUAUUUCUGAAGCC UAAC	
AD-1735649	cscsuuug UfuGfUfAfuuuaaca asasa		VPusUfsuugUfuAfAfauacAfaCfaaag gsusc		GACCUUUGUUGUAUUUAAC AAAA	

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-1735650	gscsucucUfaAfCfUfaaucgau csasa		VPusUfsgauCfgAfUfuaguUfaGfaga gcscsa		UGGCUCUCUAACUAAUCGA UCAC	
AD-1735651	asasagacUfaCfAfUfgacagaa asusa		VPusAfsuuuCfuGfUfcaugUfaGfucu uusasg		CUAAAGACUACAUGACAGA AAUG	
AD-1735652	csasggauUfcGfUfAfuuuuuaa asgsa		VPusCfsuuuAfaAfAfauacGfaAfuccu gsasg		CUCAGGAUUCGUAUUUUUA AAGA	
AD-1735653	cscsuugcUfaAfGfUfaauugac asusa		VPusAfsuguCfaAfUfuacuUfaGfcaag gsgsu		ACCCUUGCUAAGUAAUUGA CAUA	
AD-1735654	cscsuaugCfaCfUfUfucacagg asasa		VPusUfsuccUfgUfGfaaagUfgCfauag gsasg		CUCCUAUGCACUUUCACAG GAAC	
AD-1735655	asusgcugAfaAfUfAfuguuuca ascsa		VPusGfsuugAfaAfCfauauUfuCfagca ususu		AAAUGCUGAAAUAUGUUUC AACA	
AD-1735656	cscsuuuuAfaUfUfCfaaaucua csusa		VPusAfsguaGfaUfUfugaaUfuAfaaag gscsc		GGCCUUUUAAUUCAAAUCU ACUG	
AD-1735657	ascsuggaCfuUfAfUfuggauuu asasa		VPusUfsuaaAfuCfCfaauaAfgUfccag usasu		AUACUGGACUUAUUGGAUU UAAU	
AD-1735658	csasucugAfaUfCfAfgauggua csasa		VPusUfsguaCfcAfUfcugaUfuCfagau gsusu		AACAUCUGAAUCAGAUGGU ACAG	
AD-1735659	asasuucuGfaUfAfGfcaaucug usgsa		VPusCfsacaGfaUfUfgcuaUfcAfgaau ususc		GAAAUUCUGAUAGCAAUCU GUGU	
AD-1735660	uscsaaguCfaAfGfGfgaugcuau csusa		VPusAfsgauAfgCfAfuccuUfgAfcuu gasasa		UUUCAAGUCAAGGAUGCUA UCUA	
AD-1735661	uscsacugAfaAfAfCfcacaaga usasa		VPusUfsaucUfuGfUfgguuUfuCfagu gasgsg		CCUCACUGAAAACCACAAG AUAU	
AD-1735662	ascscuguUfgAfAfCfagucuuc asasa		VPusUfsugaAfgAfCfuguuCfaAfcag gusasg		CUACCUGUUGAACAGUCUU CAAG	
AD-1735663	uscsaaguGfaCfAfUfauuucag ususa		VPusAfsacuGfaAfAfuaugUfcAfcuu gasgsu		ACUCAAGUGACAUAUUUCA GUUA	
AD-1735664	uscsaggaAfcUfUfCfaggauug csusa		VPusAfsgcaAfuCfCfugaaGfuUfccug asgsc		GCUCAGGAACUUCAGGAUU GCUA	
AD-1735665	ascsggagUfaUfUfAfguagcuu asasa		VPusUfsuaaGfcUfAfcuaaUfaCfuccg usasg		CUACGGAGUAUUAGUAGCU UAAU	
AD-1735666	asusugucAfaUfGfAfauuuuau gsasa		VPusUfscauAfaAfAfuucaUfuGfacaa usgsc		GCAUUGUCAAUGAAUUUUA UGAG	
AD-	gsasacagCfaAfAfCfaaauauu		VPusUfscaaUfaUfUfuguuUfgCfugu		GUGAACAGCAAACAAAUAU	

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:
1735667	gsasa		ucsasc		UGAA	
AD-1735668	usgsaacuAfuUfUfUfcgugcau usasa		VPusUfsaauGfcAfCfgaaaAfuAfguuc asusa		UAUGAACUAUUUUUCGUGCA UUAG	
AD-1735669	ascsuggaAfuAfCfUfuauuuuu csasa		VPusUfsgaaAfaAfUfaaguAfuUfccag ususc		GAACUGGAAUACUUAUUUU UCAU	
AD-1735670	ususauccuUfgCfAfGfagaucuc usgsa		VPusCfsagaGfaUfCfucugCfaAfgaua ascsg		CGUUAUCUUGCAGAGAUCU CUGG	
AD-1735671	gsasagugUfuAfGfGfAfauuuuu gasusa		VPusAfsucaAfaAfAfuucuAfaCfacuu cscsa		UGGAAGUGUUAGAAUUUUU GAUC	
AD-1735672	uscsaauuUfaAfGfAfucucugg asasa		VPusUfsuccAfgAfGfaucuUfaAfauu gasusa		UAUCAAUUUAAGAUCUCUG GAAG	
AD-1735673	usgsgaccAfuAfUfUfuacaaug ususa		VPusAfsacaUfuGfUfaaauAfuGfgucc asusu		AAUGGACCAUAUUUACAAU GUUU	
AD-1735674	usasgucaUfuGfAfAfAfgcaaucc uasasa		VPusAfsaggAfuUfGfcuucAfaUfgac uasasa		UUUAGUCAUUGAAGCAAUC CUUG	
AD-1735675	asgscuguUfuAfGfGfGfuuuaaca asusa		VPusAfsuugUfuAfAfaccuAfaAfcagc ususu		AAAGCUGUUUAGGUUUAAC AAUG	
AD-1735676	csasaggcAfaAfUfUfGfauguaaa usasa		VPusUfsauuUfaCfAfucauUfuGfccuu gsgsc		GCCAAGGCAAAUGAUGUAA AUAG	
AD-1735677	asusccaaUfuAfCfUfacuggaa ascsa		VPusGfsuuuCfcAfGfuaguAfaUfugg aususu		AAAUCCAAUUACUACUGGA AACU	
AD-1735678	ascsuuacAfaUfAfUfauauauc csusa		VPusAfsggaUfaUfAfuauaUfuGfuaa gusgsc		GCACUUACAAUAUAUAUAU CCUG	
AD-1735679	asusgcagUfuUfGfGfGfuaucuga csasa		VPusUfsgucAfgAfUfaccaAfaCfugca usgsu		ACAUGCAGUUUGGUAUCUG ACAA	
AD-1735680	cscsuuauUfuCfAfAfAfgacacug gsusa		VPusAfsccaGfuGfUfcuugAfaAfuaag gsusa		UACCUUAUUUCAAGACACU GGUU	
AD-1735681	gsasagggAfuUfUfUfAfuucuuu agsusa		VPusAfscuaAfaGfAfauaaAfuCfccuu csasu		AUGAAGGGAUUUAUUCUUU AGUC	
AD-1735682	asusccuuGfcUfAfCfGfgaucuu asasa		VPusUfsuaaGfaUfCfcguaGfcAfagga ususg		CAAUCCUUGCUACGGAUCU UAAA	
AD-1735683	ascsugacUfaUfCfCfCfgaagca asasa		VPusUfsuugCfuUfCfgggaUfaGfuca gusasg		CUACUGACUAUCCCGAAGC AAAG	
AD-1735684	usgsuauuUfcUfGfCfuauuauu uscsa		VPusGfsaaaUfaAfUfagcaGfaAfauac ascsu		AGUGUAUUUCUGCUAUUAU UUCC	

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-1735685	usgsuaacAfaUfAfAfcuagccu asasa		VPusUfsuagGfcUfAfguuaUfuGfuua casusa		UAUGUAACAAUAACUAGCC UAAA	
AD-1735686	gsusuguuUfuUfAfCfucuagc ucsasa		VPusUfsgagCfuAfGfaguaAfaAfacaa csasa		UUGUUGUUUUUACUCUAGC UCAG	
AD-1735687	csasggcaGfuUfUfUfUfauacaau gsasa		VPusUfscauUfgUfAfuaaaAfcUfgccu gsasg		CUCAGGCAGUUUUAUACAA UGAC	
AD-1735688	asgsgauuCfuCfAfGfucagguu asusa		VPusAfsuaaCfcUfGfacugAfgAfaucc ususc		GAAGGAUUCUCAGUCAGGU UAUG	
AD-1735689	asusuuucCfaUfCfAfuguuuaa gsusa		VPusAfscuuAfaAfCfaugaUfgGfaaaa usgsu		ACAUUUUCCAUCAUGUUUA AGUG	
AD-1735690	usgsccacUfuUfUfGfuuaccau usgsa		VPusCfsauuGfgUfAfacaaAfaGfuggc asgsc		GCUGCCACUUUUGUUACCA UUGU	
AD-1735691	ascsuugcUfaGfUfGfuguggau asusa		VPusAfsuauCfcAfCfacacUfaGfcaag ususu		AAACUUGCUAGUGUGUGGA UAUG	
AD-1735692	asasucuuAfcUfUfGfgagaaauu gscsa		VPusGfscaaUfuUfCfucaaGfuAfagau ususc		GAAAUCUUACUUGAGAAAU UGCC	
AD-1735693	asgsuucgAfgAfCfUfugcauuu gsasa		VPusUfscaaAfuGfCfaaguCfuCfgaac ususu		AAAGUUCGAGACUUGCAUU UGAA	
AD-1735694	cscsauagAfaUfUfUfccugaua csusa		VPusAfsguaUfcAfGfgaaaUfuCfuaug gsgsu		ACCCAUAGAAUUUCCUGAU ACUG	
AD-1735695	asgsguaaUfuCfCfUfuuagaau asusa		VPusAfsuauUfcUfAfaaggAfaUfuacc ususg		CAAGGUAAUUCCUUUAGAA UAUG	
AD-1735696	csusuaugGfaAfAfCfucaacaa gsusa		VPusUfscuuGfuUfGfaguuUfcCfauaa gsusu		AACUUAUGGAAACUCAACA AGAA	
AD-1735697	asasgcagCfaUfUfUfuaaauua csgsa		VPusCfsguaAfuUfUfaaaaUfgCfugcu ususu		AAAAGCAGCAUUUUAAAUU ACGA	
AD-1735698	usgsacucUfcAfAfCfugaccau uscsa		VPusGfsaauGfgUfCfaguuGfaGfaguc asgsc		GCUGACUCUCAACUGACCA UUCC	
AD-1735699	asgsguuuAfuCfCfAfugaagga csusa		VPusAfsgucCfuUfCfauggAfuAfaacc usasg		CUAGGUUUAUCCAUGAAGG ACUG	
AD-1735700	ascscaagAfaUfUfUfggcauuu csasa		VPusUfsgaaAfuGfCfcaaaUfuCfuugg usgsa		UCACCAAGAAUUUGGCAUU UCAA	
AD-1735701	usasucuaGfaAfUfAfuuuggcu usasa		VPusUfsaagCfcAfAfauauUfcUfagau asasg		CUUAUCUAGAAUAUUUGGC UUAU	
AD-	csusccugCfaGfAfAfuacauac		VPusUfsuguAfuGfUfauucUfgCfagg		CUCUCCUGCAGAAUACAUA	

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:
1735702	asasa		agsasg		CAAG	
AD-1735703	uscsacacCfaUfUfUfUfccuggau ususa		VPusAfsaauCfcAfGfgaaaUfgGfugug asgsa		UCUCACACCAUUUCCUGGA UUUU	
AD-1735704	asusguggAfaUfUfCfaagcgcu ususa		VPusAfsaagCfgCfUfugaaUfuCfcaca usgsa		UCAUGUGGAAUUCAAGCGC UUUC	
AD-1735705	asusugugUfaUfUfUfAfucuacua usgsa		VPusCfsauaGfuAfGfauaaUfaCfacaa usasg		CUAUUGUGUAUUAUCUACU AUGU	
AD-1735706	asasuggaGfuAfAfUfUfgaaaaug asusa		VPusAfsucaUfuUfUfcauuAfcUfccau uscsu		AGAAUGGAGUAAUGAAAAU GAUC	
AD-1735707	ascsugguUfuAfUfUfUfggaaaua ususa		VPusAfsauaUfuUfCfcaauAfaAfccag usgsu		ACACUGGUUUAUUGGAAAU AUUU	
AD-1735708	csasagugUfaUfGfUfguauaaa gsusa		VPusAfscuuUfaUfAfcacaUfaCfacuu gsusa		UACAAGUGUAUGUGUAUAA AGUC	
AD-1735709	usascaagCfaUfGfCfCfauauuga gsasa		VPusUfscucAfaUfAfugcaUfgCfuug uascsa		UGUACAAGCAUGCAUAUUG AGAU	
AD-1735710	usgsgucUfuUfUfUfAfugucuu ugsasa		VPusUfscaaAfgAfCfauaaAfaGfacac ascsu		AGUGUGUCUUUUAUGUCUU UGAA	
AD-1735711	asusuuucUfcGfCfCfAfgaauuca asusa		VPusAfsuugAfaUfUfcugcGfaGfaaaa uscsa		UGAUUUUCUCGCAGAAUUC AAUG	
AD-1735712	usasgcgaCfaGfUfUfUfugaguaa asasa		VPusUfsuuuAfcUfCfaaacUfgUfcgcu asusu		AAUAGCGACAGUUUGAGUA AAAG	
AD-1735713	csusggugUfaUfGfAfauacuuu gsusg		VPusAfscaaAfgUfAfuucaUfaCfacca gsusg		CACUGGUGUAUGAAUACUU UGUC	
AD-1735714	gsusgauaAfgUfGfGfcuaacag asasa		VPusUfsucuGfuUfAfgccaCfuUfauca cscsu		AGGUGAUAAGUGGCUAACA GAAG	
AD-1735715	gsusaggcUfaAfUfAfuuuucua ususa		VPusAfsauaGfaAfAfauauUfaGfccua cscsa		UGGUAGGCUAAUAUUUUCU AUUA	
AD-1735716	cscsucuuCfaUfCfCfcucgacug uscsa		VPusGfsacaGfuCfGfaggaUfgAfagag gscsg		CGCCUCUUCAUCCUCGACUG UCC	
AD-1735717	asasuugcCfaUfAfAfgccauau usasa		VPusUfsaauAfuGfGfcuuaUfgGfcaau ususc		GAAAUUGCCAUAAGCCAUA UUAC	
AD-1735718	gscsgaauAfuUfUfUfgucagcu asasa		VPusUfsuagCfuGfAfcaaaAfuAfuucg cscsg		CGGCGAAUAUUUUGUCAGC UAAU	
AD-1735719	asusccagUfgUfUfGfccuuucu gsasa		VPusUfscagAfaAfGfgcaaCfaCfugga ususc		GAAUCCAGUGUUGCCUUUC UGAG	

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-1735720	asasagucUfaUfGfCfcugucua asasa		VPusUfsuuaGfaCfAfggcaUfaGfacuu ususc		GAAAAGUCUAUGCCUGUCU AAAA	
AD-1735721	gsgsacauCfaGfAfAfAfguuugaa ususa		VPusAfsauuCfaAfAfcuucUfgAfugu ccsasu		AUGGACAUCAGAAGUUUGA AUUC	
AD-1735722	gsgscgaaUfuGfCfUfuauauuu csusa		VPusAfsgaaAfuAfUfaagcAfaUfucgc cscsa		UGGGCGAAUUGCUUAUAUU UCUU	
AD-1735723	csascacuAfuGfUfGfuaaacca gsusa		VPusAfscugGfuUfUfacacAfuAfgug ugsusg		CACACACUAUGUGUAAACC AGUC	
AD-1735724	csasggugAfaGfAfAfgaaaaca ususa		VPusAfsaugUfuUfUfcuucUfuCfaccu gsasu		AUCAGGUGAAGAAGAAAAC AUUU	
AD-1735725	gsusgagcUfcUfUfAfuuuuuca csusa		VPusAfsgugAfaAfAfauaaGfaGfcuca csusa		UAGUGAGCUCUUAUUUUUC ACUG	
AD-1735726	asasagcuGfaUfGfGfgaauaaa csusa		VPusAfsguuUfaUfUfcccaUfcAfgcuu usasc		GUAAAGCUGAUGGGAAUAA ACUG	
AD-1735727	gsusgucgUfuAfGfGfagaaacu gscsa		VPusGfscagUfuUfCfuccuAfaCfgaca csgsc		GCGUGUCGUUAGGAGAAAC UGCA	
AD-1735728	gsgsgacuUfaAfAfAfcaauggu asusa		VPusAfsuacCfaUfUfguuuUfaAfgucc csasa		UUGGGACUUAAAACAAUGG UAUA	
AD-1735729	csusgaugGfuAfGfAfauuaacc asusa		VPusAfsuggUfuAfAfuucuAfcCfauc agsasa		UUCUGAUGGUAGAAUUAAC CAUG	
AD-1735730	ascsuaugUfgUfGfUfuuuauu ucsusa		VPusAfsgaaAfuAfAfaacaCfaCfauag usasg		CUACUAUGUGUGUUUUAUU UCUG	
AD-1735731	csusgauaAfuUfUfAfuauuugc ascsa		VPusGfsugcAfaAfUfauaaAfuUfauca gsusc		GACUGAUAAUUUAUAUUUG CACU	
AD-1735732	gsusccuuAfaAfUfUfauuuaac cscsa		VPusGfsggUfaAfAfuaauUfuAfagg acsusa		UAGUCCUUAAAUUAUUUAA CCCU	
AD-1735733	csgscaauAfuGfGfUfugucagau csusa		VPusAfsgauCfuGfAfcaccAfuAfuugc gsasg		CUCGCAAUAUGGUGUCAGA UCUU	
AD-1735734	ususcgaaGfaGfCfUfgcucuaa uscsa		VPusGfsauuAfgAfGfcagcUfcUfucga asgsa		UCUUCGAAGAGCUGCUCUA AUCC	
AD-1735735	ususucugCfuGfAfGfaguauuc asgsa		VPusCfsugaAfuAfCfucucAfgCfagaa asusa		UAUUUCUGCUGAGAGUAUU CAGG	
AD-1735736	ususgaacAfgGfAfAfguaucac usgsa		VPusCfsaguGfaUfAfcuucCfuGfuuca asusa		UAUUGAACAGGAAGUAUCA CUGG	
AD-	usgsccuuGfuAfUfUfuccagag		VPusUfsucuCfuGfGfaaauAfcAfaggc		GUUGCCUUGUAUUUCCAGA	

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:
1735737	asasa		asasc		GAAC	
AD-1735738	gsusuacuAfuGfGfCfaguugca asasa		VPusUfsuugCfaAfCfugccAfuAfguaa csusg		CAGUUACUAUGGCAGUUGC AAAA	
AD-1735739	asusggcuGfaAfUfUfuuaaagc usgsa		VPusCfsagcUfuUfAfaaauUfcAfgcca usgsg		CCAUGGCUGAAUUUUAAAG CUGU	
AD-1735740	gsusccauUfcAfUfGfgaucguu csusa		VPusAfsgaaCfgAfUfccauGfaAfugga csusg		CAGUCCAUUCAUGGAUCGU UCUU	
AD-1735741	usgsguaaAfcUfCfCfuaugaug csusa		VPusAfsgcaUfcAfUfaggaGfuUfacac asgsg		CCUGUGUAACUCCUAUGAU GCUG	
AD-1735742	usgsgcagUfuUfCfCfcacuccu asusa		VPusAfsuagGfaGfUfgggaAfaCfugcc asgsc		GCUGGCAGUUUCCCACUCC UAUG	
AD-1735743	cscsucaaGfcAfGfAfugagauu csasa		VPusUfsgaaUfcUfCfaucuGfcUfugag gsusa		UACCUCAAGCAGAUGAGAU UCAG	
AD-1735744	asusguugUfuUfUfCfucaaaag csasa		VPusUfsgcuUfuUfGfagaaAfaCfaaca usasa		UUAUGUUGUUUUCUCAAAA GCAG	
AD-1735745	gsasgggaUfuUfCfUfgcucaau gscsa		VPusGfscauUfgAfGfcagaAfaUfcccu csasg		CUGAGGGAUUUCUGCUCAA UGCA	
AD-1735746	gscscuucUfuCfUfUfccucacc usgsa		VPusCfsaggUfgAfGfgaagAfaGfaagg csasc		GUGCCUUCUUCUUCCUCACC UGC	
AD-1735747	ususgagaUfuGfAfAfucacauu uscsa		VPusGfsaaaUfgUfGfauucAfaUfcuca asusa		UAUUGAGAUUGAAUCACAU UUCC	
AD-1735748	csusguucAfgUfGfCfuauucuc cscsa		VPusGfsggaGfaAfUfagcaCfuGfaaca gsusg		CACUGUUCAGUGCUAUUCU CCCA	
AD-1735749	cscsuggcUfuAfCfCfAfgcagauc csasa		VPusUfsggaUfcUfGfcuguAfaGfccag gsasa		UUCCUGGCUUACAGCAGAU CCAC	
AD-1735750	gsascagcAfgAfAfAfauuauuu csasa		VPusUfsgaaAfuAfAfuuuuCfuGfcug ucsusu		AAGACAGCAGAAAAUUAUU UCAG	
AD-1735751	ususggguUfuCfUfUfuaguuu ausgsa		VPusCfsauaAfaCfUfuaaaGfaAfccca asusa		UAUUGGGUUUCUUUAGUUU AUGU	
AD-1735752	csasccauGfuAfGfGfucucaga asgsa		VPusCfsuucUfgAfGfaccuAfcAfugg ugsasg		CUCACCAUGUAGGUCUCAG AAGA	
AD-1735753	gsusugugGfaAfCfAfggaaaug asasa		VPusUfsucaUfuUfCfcuguUfcCfacaa cscsa		UGGUUGUGGAACAGGAAAU GAAA	
AD-1735754	gsgsagaaCfaUfAfUfcauauuu usgsa		VPusCfsaaaAfuAfUfgauaUfgUfucuc csasa		UUGGAGAACAUAUCAUAUU UUGG	

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-1735755	csasgccaAfaAfUfGfauggcaa asasa		VPusUfsuuuGfcCfAfucauUfuUfggc ugscsu		AGCAGCCAAAAUGAUGGCA AAAU	
AD-1735756	cscsaauuUfuUfGfAfacuugua gsasa		VPusUfscuaCfaAfGfuucaAfaAfauug gsasa		UUCCAAUUUUUGAACUUGU AGAA	
AD-1735757	asusaggaAfuAfGfUfuugccaa csusa		VPusAfsguuGfgCfAfaacuAfuUfccua ususu		AAAUAGGAAUAGUUUGCCA ACUC	
AD-1735758	ususugaaUfgUfUfUfuggagaa asasa		VPusUfsuuuCfuCfCfaaaaCfaUfucaa asgsa		UCUUUGAAUGUUUUGGAGA AAAG	
AD-1735759	gsuscaauAfuUfUfAfaugaauc ascsa		VPusGfsugaUfuCfAfuuaaAfuAfuug acsasc		GUGUCAAUAUUUAAUGAAU CACU	
AD-1735760	usgsagaaUfaUfAfUfUfuaaaugc ascsa		VPusGfsugcAfuUfUfaauaUfaUfucuc ascsa		UGUGAGAAUAUAUUAAAUG CACA	
AD-1735761	usasacaaGfgGfAfCfuaaauag gsasa		VPusUfsccuAfuUfUfagucCfcUfugu uasasg		CUUAACAAGGGACUAAAUA GGAA	
AD-1735762	gsgscuucUfuCfUfUfccaccuc usgsa		VPusCfsagaGfgUfGfgaagAfaGfaagc csgsc		GCGGCUUCUUCUUCCACCUC UGC	
AD-1735763	ususggaaCfaUfGfUfgguuauc ususa		VPusAfsagaUfaAfCfcacaUfgUfucca asusu		AAUUGGAACAUGUGGUUAU CUUU	
AD-1735764	csasgagaAfcAfGfAfugauucu ususa		VPusAfsaagAfaUfCfaucuGfuUfcucu gsgsa		UCCAGAGAACAGAUGAUUC UUUG	
AD-1735765	csusguuaUfuUfUfAfuugggu uususa		VPusAfsaaaCfcCfAfauaaAfaUfaaca gsasc		GUCUGUUAUUUUAUUGGGU UUUA	
AD-1735766	asusgaagAfaGfCfAfaaucuug gsusa		VPusAfsccaAfgAfUfuugcUfuCfuuca uscsu		AGAUGAAGAAGCAAAUCUU GGUC	
AD-1735767	ususuggaAfuCfAfUfUfgcaauuu usgsa		VPusCfsaaaAfuUfUfGfcaugAfuUfccaa asasu		AUUUUGGAAUCAUGCAAUU UUGC	
AD-1735768	csasauguUfuUfGfUfaaacuug csusa		VPusAfsgcaAfgUfUfuacaAfaAfcauu gsusa		UACAAUGUUUUGUAAACUU GCUA	
AD-1735769	gsgsaucgUfaAfUfAfauggcaa asasa		VPusUfsuuuGfcCfAfuuauUfaCfgauc cscsa		UGGGAUCGUAAUAAUGGCA AAAG	
AD-1735770	gsusgcuuUfcUfCfAfgguuccu gsusa		VPusAfscagGfaAfCfcugaGfaAfagca cscsc		GGGUGCUUUCUCAGGUUCC UGUA	
AD-1735771	asusgauaCfuGfAfAfaguggug asusa		VPusAfsucaCfcAfCfuuucAfgUfauca ususa		UAAUGAUACUGAAAGUGGU GAUG	
AD-	uscsacugGfaCfCfUfgauuuua		VPusAfscuaAfaAfUfcaggUfcCfagug		UAUCACUGGACCUGAUUUU	

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:
1735772	gsusa		asusa		AGUA	
AD-1735773	gsasacuuUfuUfGfCfuuuuaug asasa		VPusUfsucaUfaAfAfagcaAfaAfaguu cscsu		AGGAACUUUUUGCUUUUAU GAAA	
AD-1735774	gsasacacAfgCfAfCfagauuug ususa		VPusAfsacaAfaUfCfugugCfuGfugu ucsasu		AUGAACACAGCACAGAUUU GUUA	
AD-1735775	asusauggAfaGfGfAfaaucgua gsasa		VPusUfscuaCfgAfUfuuccUfuCfcaua uscsu		AGAUAUGGAAGGAAAUCGU AGAG	
AD-1735776	gscsuaucUfaAfAfUfgggccuu usasa		VPusAfsaaaGfgCfCfcauuUfaGfauag csasu		AUGCUAUCUAAAUGGGCCU UUUA	
AD-1735777	csasaaacCfaCfCfAfagaaggaa sasa		VPusUfsuucCfuUfCfuuggUfgGfuuu ugsgsa		UCCAAAACCACCAAGAAGG AAAA	
AD-1735778	cscsacagAfuGfUfGfcuacaug csasa		VPusUfsgcaUfgUfAfgcacAfuCfugu ggscsa		UGCCACAGAUGUGCUACAU GCAG	
AD-1735779	asasagucAfuAfCfAfuguacaa gscsa		VPusGfscuuGfuAfCfauguAfuGfacu uusasu		AUAAAGUCAUACAUGUACA AGCA	
AD-1735780	usasgaagCfaGfAfAfgaggaua asusa		VPusAfsuuaUfcCfUfcuucUfgCfuucu asasc		GUUAGAAGCAGAAGAGGAU AAUG	
AD-1735781	csgsugugUfuCfGfCfacagcuu gsasa		VPusUfscaaGfcUfGfugcgAfaCfacac gscsu		AGCGUGUGUUCGCACAGCU UGAG	
AD-1735782	gscsugguGfuUfUfUfguccag ucsusa		VPusAfsgacUfgGfAfcaaaAfcAfccag csusc		GAGCUGGUGUUUUGUCCAG UCUG	
AD-1735783	asusggaaAfaCfAfAfucuaaau cscsa		VPusGfsgauUfuAfGfauugUfuUfucc aususu		AAAUGGAAAACAAUCUAAA UCCA	
AD-1735784	csasuuagAfaAfAfUfggcuauc gsasa		VPusUfscgaUfaGfCfcauuUfuCfuaau gscsa		UGCAUUAGAAAAUGGCUAU CGAG	
AD-1735785	asusggacAfgAfAfGfgcauugu csasa		VPusUfsgacAfaUfGfccuuCfuGfucca ususu		AAAUGGACAGAAGGCAUUG UCAA	
AD-1735786	csasgauuGfcUfGfCfaguggaa asasa		VPusUfsuuuCfcAfCfugcaGfcAfaucu gsusa		UACAGAUUGCUGCAGUGGA AAAU	
AD-1735787	asgsguggAfaAfUfGfgaguug auscsa		VPusGfsaucAfaCfUfccauUfuCfcacc uscsc		GGAGGUGGAAAUGGAGUUG AUCU	
AD-1735788	csusgggcAfaUfGfCfaccuaau ascsa		VPusGfsuauUfaGfGfugcaUfuGfccca gsasg		CUCUGGGCAAUGCACCUAA UACU	
AD-1735789	asusuuccCfuCfUfGfccuaaag ascsa		VPusGfsucuUfuAfGfgcagAfgGfgaa aususa		UAAUUUCCCUCUGCCUAAA GACU	

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-1735790	csgscuucUfgCfAfAfcguggag csusa		VPusAfsgcuCfcAfCfguugCfaGfaagc gsgsc		GCCGCUUCUGCAACGUGGA GCUG	
AD-1735791	asgsauucAfuAfUfUfguauuuc cscsa		VPusGfsggaAfaUfAfcauuAfuGfaauc usasu		AUAGAUUCAUAUUGUAUUU CCCA	
AD-1735792	asgsgacaAfaUfGfCfauuucua gsusa		VPusAfscuaGfaAfAfugcaUfuUfgucc uscsc		GGAGGACAAAUGCAUUUCU AGUG	
AD-1735793	ususagacGfuGfUfUfgagugag usgsa		VPusCfsacuCfaCfUfcaacAfcGfucua asusa		UAUUAGACGUGUUGAGUGA GUGC	
AD-1735794	csusguggAfcAfUfCfaaaugcu gsasa		VPusUfscagCfaUfUfugauGfuCfcaca gscsu		AGCUGUGGACAUCAAAUGC UGAA	
AD-1735795	asgsgccuUfaAfUfAfcugugag asgsa		VPusCfsucuCfaCfAfguauUfaAfggcc usgsu		ACAGGCCUUAAUACUGUGA GAGG	
AD-1735796	asgsaaauCfaUfUfGfccuagug ususa		VPusAfsacaCfuAfGfgcaaUfgAfuuuc usgsc		GCAGAAAUCAUUGCCUAGU GUUC	
AD-1735797	usgsagugCfuGfAfGfuuccuuu gcsusa		VPusAfsgcaAfgGfAfacucAfgCfacuc ascsu		AGUGAGUGCUGAGUUCCUU GCUG	
AD-1735798	gscscaugCfaUfGfAfuuaugau csasa		VPusUfsgauCfaUfAfaucaUfgCfaugg csasg		CUGCCAUGCAUGAUUAUGA UCAC	
AD-1735799	usgscugcUfgGfUfUfugcuacc asgsa		VPusCfsuggUfaGfCfaaacCfaGfcagc asusc		GAUGCUGCUGGUUUGCUAC CAGG	
AD-1735800	csasgaugAfaGfAfGfgaauagc gsasa		VPusUfscgcUfaUfUfccucUfuCfaucu gscsc		GGCAGAUGAAGAGGAAUAG CGAC	
AD-1735801	asusccagGfuGfCfAfucaauuu csusa		VPusAfsgaaAfuUfGfaugcAfcCfugga ususu		AAAUCCAGGUGCAUCAAUU UCUG	
AD-1735802	asasuaagCfcAfAfGfcguuauc ususa		VPusAfsagaUfaAfCfgcuuGfgCfuuau usasa		UUAAUAAGCCAAGCGUUAU CUUG	
AD-1735803	gsasgaggAfuCfCfUfugcucug csusa		VPusAfsgcaGfaGfCfaaggAfuCfcucu csasc		GUGAGAGGAUCCUUGCUCU GCUG	
AD-1735804	asusgaugAfaGfAfCfggugaag asasa		VPusUfsucuUfcAfCfcgucUfuCfauca uscsa		UGAUGAUGAAGACGGUGAA GAAU	
AD-1735805	uscsguaaGfuGfUfAfagaaaga asusa		VPusAfsuucUfuUfCfuuacAfcUfuacg asasu		AUUCGUAAGUGUAAGAAAG AAUG	
AD-1735806	asuscuguGfuAfAfCfagcugug gsasa		VPusUfsccaCfaGfCfuguuAfcAfcaga ususg		CAAUCUGUGUAACAGCUGU GGAC	
AD-	asusuuaaAfaUfUfCfccacuca		VPusGfsuugAfgUfGfggaaUfuUfuaa		AUAUUUAAAAUUCCCACUC	

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:
1735807	ascsa		ausasu		AACA	
AD-1735808	gsasccagUfgUfCfUfacuggcu csusa		VPusAfsgagCfcAfGfuagaCfaCfuggu cscsa		UGGACCAGUGUCUACUGGC UCUC	
AD-1735809	csgscuuuCfgUfUfUfuuuaguc asusa		VPusAfsugaCfuAfAfaaaaCfgAfaagc gscsu		AGCGCUUUCGUUUUUUAGU CAUU	
AD-1735810	uscscgugUfuGfAfCfccauguu gscsa		VPusGfscaaCfaUfGfggucAfaCfacgg asusg		CAUCCGUGUUGACCCAUGU UGCA	
AD-1735811	asusacagAfaGfAfUfgaagaaa usgsa		VPusCfsauuUfcUfUfcaucUfuCfugua uscsu		AGAUACAGAAGAUGAAGAA AUGG	
AD-1735812	uscsucccGfaGfCfUfgaaacuu asasa		VPusUfsuaaGfuUfUfcagcUfcGfggag asgsa		UCUCUCCCGAGCUGAAACU UAAA	
AD-1735813	usgscaucAfaAfCfUfggcagau asusa		VPusAfsuauCfuGfCfcaguUfuGfaugc ascsa		UGUGCAUCAAACUGGCAGA UAUA	
AD-1735814	ususgcaaAfaUfAfUfucaggag ascsu		VPusGfsucuCfcUfGfaauaUfuUfugca ascsu		AGUUGCAAAAUAUUCAGGA GACC	
AD-1735815	ascsaaucGfuAfUfAfcaugcca csasa		VPusUfsgugGfcAfUfguauAfcGfauu gusgsa		UCACAAUCGUAUACAUGCC ACAG	
AD-1735816	asasuagaAfaAfGfAfugagcaa csusa		VPusAfsguuGfcUfCfaucuUfuUfcua uusasa		UUAAUAGAAAAGAUGAGCA ACUG	
AD-1735817	usasucuuAfuGfUfUfccauggc usgsa		VPusCfsagcCfaUfGfgaacAfuAfagau asasg		CUUAUCUUAUGUUCCAUGG CUGA	
AD-1735818	csusacguGfaAfGfAfgcugcgu gsasa		VPusUfscacGfcAfGfcucuUfcAfcgua gscsc		GGCUACGUGAAGAGCUGCG UGAG	
AD-1735819	gsasauugAfuGfGfCfcuauuac gsusa		VPusAfscguAfuAfGfagccAfuCfaauu csusa		UAGAAUUGAUGGCUCUAUA CGUG	
AD-1735820	ususcaggUfaAfUfUfUfgaagagg csasa		VPusUfsgccUfcUfUfcaauUfaCfcuga asusc		GAUUCAGGUAAUUGAAGAG GCAG	
AD-1735821	asasggacUfgAfGfUfUfgaccuuu gsusa		VPusAfscaaAfgGfUfUfcacuCfaGfuccu uscsa		UGAAGGACUGAGUGACCUU UGUU	
AD-1735822	csgsagagUfcUfGfAfggaacgg csusa		VPusAfsgccGfuUfCfcucaGfaCfucuc gsgsg		CCCGAGAGUCUGAGGAACG GCUA	
AD-1735823	asusucuuUfgGfGfAfuuggga cususa		VPusAfsaguCfcCfAfauccCfaAfagaa uscsa		UGAUUCUUUGGGAUUGGGA CUUA	
AD-1735824	usasccagGfuCfAfGfugguuag asasa		VPusUfsucuAfaCfCfacugAfcCfuggu asgsc		GCUACCAGGUCAGUGGUUA GAAG	

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-1735825	asusucagGfuUfUfGfccaugga csasa		VPusUfsgucCfaUfGfgcaaAfcCfugaa usasc		GUAUUCAGGUUUGCCAUGG ACAU	
AD-1735826	gscsagcuAfaAfCfUfgguccug gsasa		VPusUfsccaGfgAfCfcaguUfuAfgcug cscsg		CGGCAGCUAAACUGGUCCU GGAG	
AD-1735827	asgsuaauGfgCfAfUfagaaugg asgsa		VPusCfsuccAfuUfCfuaugCfcAfuuac usasu		AUAGUAAUGGCAUAGAAUG GAGU	
AD-1735828	asasuugcAfaGfAfAfaauggac csasa		VPusUfsgguCfcAfUfuuucUfuGfcaa uusasu		AUAAUUGCAAGAAAAUGGA CCAU	
AD-1735829	csgsgcacUfgCfGfUfucuggug csusa		VPusAfsgcaCfcAfGfaacgCfaGfugcc gsgsa		UCCGGCACUGCGUUCUGGU GCUG	
AD-1735830	asgsucauAfuUfGfAfagaagcc csasa		VPusUfsgggCfuUfCfuucaAfuAfuga cususu		AAAGUCAUAUUGAAGAAGC CCAG	
AD-1735831	uscsaucaUfgCfUfGfcgucagc ususa		VPusAfsagcUfgAfCfgcagCfaUfgaug asusu		AAUCAUCAUGCUGCGUCAG CUUG	
AD-1735832	asasaugaUfcGfCfCfucuuggu asusa		VPusAfsuacCfaAfGfaggcGfaUfcauu ususc		GAAAAUGAUCGCCUCUUGG UAUG	
AD-1735833	asususugaAfgAfUfAfuaaagag csasa		VPusUfsgcuCfuUfUfauauCfuUfcaaa usgsu		ACAUUUGAAGAUAUAAAGA GCAG	
AD-1735834	gsgsucucCfuUfCfAfccagccu csgsa		VPusCfsggaGfcUfGfgugaAfgGfagac cscsa		UGGGUCUCCUUCACCAGCC UCGG	
AD-1735835	gsasaacaGfaGfAfAfgaaagac asgsa		VPusCfsuguCfuUfUfcuucUfcUfguu ucscsu		AGGAAACAGAGAAAGAAAGA CAGC	
AD-1735836	ususcuagUfgGfCfUfacaaaug cscsa		VPusGfsgcaUfuUfGfuagcCfaCfuaga asasu		AUUUCUAGUGGCUACAAAU GCCC	
AD-1735837	gsgsagagAfaAfUfCfaggaagg asusa		VPusAfsuccUfuCfCfUfgauUfuCfucuc cscsa		UGGGAGAGAAAUCAGGAAG GAUU	
AD-1735838	asusauagUfgAfGfCfccuaaag gsasa		VPusUfsccuUfuAfGfggcuCfaCfuaua ususu		AAAUAUAGUGAGCCCUAAA GGAC	
AD-1735839	gscsugccUfuUfGfUfUfccucgcc csusa		VPusAfsgggCfgAfGfgacaAfaGfgcag cscsa		UGGCUGCCUUUGUCCUCGC CCUG	
AD-1735840	gsgscaaaAfgAfCfCfucaccaa gsasa		VPusUfscuuGfgUfGfagguCfuUfuug ccsasu		AUGGCAAAAGACCUCACCA AGAA	
AD-1735841	ususcagcAfuCfGfCfcugugcc ususa		VPusAfsaggCfaCfAfggcgAfuGfcuga asgsa		UCUUCAGCAUCGCCUGUGC CUUC	
AD-	gscsuaaaUfgAfGfGfcucgcaa		VPusUfsauuGfcGfAfgccuCfaUfuuag		GUGCUAAAUGAGGCUCGCA	

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:
1735842	usasa		csasc		AUAU	
AD-1735843	csasgcuuCfgUfCfUfggugggucsusa		VPusAfsgacCfcAfCfcagaCfgAfagcugsgsc		GCCAGCUUCGUCUGGUGGGUCUC	
AD-1735844	asusauggUfaUfUfGfgcaugcagsusa		VPusAfscugCfaUfGfccaaUfaCfcauaususc		GAAUAUGGUAUUGGCAUGCAGUU	
AD-1735845	asasacugCfaGfGfUfUfggagaauuscsa		VPusGfsaauUfcUfCfcaccUfgCfaguuusasu		AUAAACUGCAGGUGGAGAAUUCC	
AD-1735846	usasuggcUfgCfCfUfgucuucaasasa		VPusUfsuugAfaGfAfcaggCfaGfccauasasc		GUUAUGGCUGCCUGUCUUCAAAC	
AD-1735847	csusguucUfgAfAfAfuagaggacscsa		VPusGfsgucCfuCfUfauuuCfaGfaacagsgsg		CCCUGUUCUGAAAUAGAGGACCC	
AD-1735848	uscsuauuUfuUfAfAfagccgcugsgsa		VPusCfscagCfgGfCfuuuaAfaAfauagasasa		UUUCUAUUUUUAAAGCCGCUGGU	
AD-1735849	gscsugagGfaGfAfAfgcucaggasasa		VPusUfsuccUfgAfGfcuucUfcCfucagcsusg		CAGCUGAGGAGAAGCUCAGGAAC	
AD-1735850	csasagccUfuCfCfCfAfccacaaguscsa		VPusGfsacuUfgUfGfguggAfaGfgcuugsgsa		UCCAAGCCUUCCCACCACAAGUCA	
AD-1735851	ususcaguUfaCfCfCfAfaaguggccsasa		VPusUfsggcCfaCfUfuuggUfaAfcugaasasu		AUUUCAGUUACCAAAGUGGCCAG	
AD-1735852	csasccugCfuUfCfCfCfucacccggsasa		VPusUfsccgGfgUfGfaggaAfgCfaggugsasg		CUCACCUGCUUCCUCACCCGGAC	
AD-1735853	ususuuauCfaCfCfCfCfacauagugsgsa		VPusCfscacUfaUfGfugggUfgAfuaaaasgsa		UCUUUUAUCACCCACAUAGUGGG	
AD-1735854	asgsgagaCfcGfUfCfCfguugccuusgsa		VPusCfsaagGfcAfAfcgacGfgUfcucculsgsa		UCAGGAGACCGUCGUUGCCUUGU	
AD-1735855	asusggccCfaGfCfCfAfaaaguucgsasa		VPusUfscgaAfcUfUfuugcUfgGfgccaususu		AAAUGGCCCAGCAAAAGUUCGAG	
AD-1735856	asgsacgcCfaAfAfGfccaugcggsusa		VPusAfsccgCfaUfGfgcuuUfgGfcgucuscsg		CGAGACGCCAAAGCCAUGCGGUC	
AD-1735857	csasgcuaAfuGfCfCfAfccacccucascsa		VPusGfsugaGfgUfGfgugcAfuUfagcugsasc		GUCAGCUAAUGCACCACCUCACU	
AD-1735858	gsgsaaaaGfcAfGfAfcggcgaausasa		VPusUfsauuCfgCfCfgucuGfcUfuuuccsusu		AAGGAAAAGCAGACGGCGAAUAU	
AD-1735859	gscsuuugCfuGfGfGfuaguggcsusa		VPusAfsgcuCfaCfUfacccAfgCfaaagcsasg		CUGCUUUGCUGGGUAGUGAGCUC	

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-1735860	asasaugaAfaCfAfGfauucuga usgsa		VPusCfsaucAfgAfAfucugUfuUfcau uuscsc		GGAAAUGAAACAGAUUCUG AUGG	

Table 16. Unmodified Sense and Antisense Strand Sequences of INHBC dsRNA Agents Comprising a GalNAc Derivative Targeting Ligand

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005538.4	Antisense Sequence 5' to 3	SEQ ID NO:	Range in NM_005538.4
AD-1730493	UCUUCCAGGGCCUCUGGCA GU		6-26	ACUGCCAGAGGCCCUGGAAG AAG		4-26
AD-1730512	CAGGACAGAGUUGAGACCA CU		27-47	AGUGGUCUCAACUCUGUCCU GGC		25-47
AD-1730529	CACAGCUGUUGAGACCCUG AU		44-64	AUCAGGGUCUCAACAGCUGU GGU		42-64
AD-1730554	GAGUCUGUAUUGCUCAAGA AU		69-89	AUUCUUGAGCAAUACAGACU CAG		67-89
AD-1730570	UGACCUCCUCAUUGCUUCU GU		105-125	ACAGAAGCAAUGAGGAGGUC AUU		103-125
AD-1730588	UGGCCUUUCUCCUCCUGGC UU		123-143	AAGCCAGGAGGAGAAAGGCC AGA		121-143
AD-1730606	CUCCAACCACAGUGGCCAC UU		141-161	AAGUGGCCACUGUGGUUGGA GCC		139-161
AD-1730636	GCGGUCAGUGUCCAGCAUG UU		171-191	AACAUGCUGGACACUGACCG CCA		169-191
AD-1730643	ACCUUGGAACUGGAGAGCC AU		200-220	AUGGCUCUCCAGUUCCAAGG UGG		198-220
AD-1730667	GAGCUGCUUCUUGAUCUGG CU		224-244	AGCCAGAUCAAGAAGCAGCU CCC		222-244
AD-1730691	AGAAGCAUCUUGGACAAGC UU		248-268	AAGCUUGUCCAAGAUGCUUC UCU		246-268
AD-1730726	CCAACACUGAACCGCCCUG UU		284-304	AACAGGGCGGUUCAGUGUUG GGC		282-304
AD-1730749	CAGAGCUGCUUUGAGGACU		307-327	ACAGUCCUCAAAGCAGCUCU		305-327

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005538.4	Antisense Sequence 5' to 3	SEQ ID NO:	Range in NM_005538.4
	GU			GGA		
AD-1730765	ACUGCACUGCAGCACCUCC AU		323-343	AUGGAGGUGCUGCAGUGCAG UCC		321-343
AD-1730769	GCACUUCUAGAGGACAACA GU		359-379	ACUGUUGUCCUCUAGAAGUG CCC		357-379
AD-1730790	GAACAGGAAUGUGAAAUCA UU		380-400	AAUGAUUUCACAUUCCUGUU CCC		378-400
AD-1730807	CAUCAGCUUUGCUGAGACA GU		397-417	ACUGUCUCAGCAAAGCUGAU GAU		395-417
AD-1730825	AGGCCUCUCCCACCAUCAACC U		415-435	AGGUUGAUGGUGGAGAGGCC UGU		413-435
AD-1730841	AACCAGACUCGUCUUGAUU UU		431-451	AAAAUCAAGACGAGUCUGGU UGA		429-451
AD-1730857	AUUUUCACUUCUCCUCUGA UU		447-467	AAUCAGAGGAGAAGUGAAA AUCA		445-467
AD-1730873	UGAUAGAACUGCUGGUGAC AU		463-483	AUGUCACCAGCAGUUCUAUC AGA		461-483
AD-1730910	AGUCUCAUGUUCUUUGUGC AU		500-520	AUGCACAAAGAACAUGAGAC UGG		498-520
AD-1730926	UGCAGCUCCCUUCCAAUAC CU		516-536	AGGUAUUGGAAGGGAGCUGC ACA		514-536
AD-1730942	UACCACUUGGACCUUGAAA GU		532-552	ACUUUCAAGGUCCAAGUGGU AUU		530-552
AD-1730958	AAAGUGAGAGUCCUUGUGC UU		548-568	AAGCACAAGGACUCUCACUU UCA		546-568
AD-1730982	CCACAUAAUACCAACCUCA CU		572-592	AGUGAGGUUGGUAUUAUGU GGAC		570-592
AD-1731003	UUGGCUACUCAGUACCUGC UU		593-613	AAGCAGGUACUGAGUAGCCA AGG		591-613
AD-1731019	UGCUGGAGGUGGAUGCCAG UU		609-629	AACUGGCAUCCACCUCCAGC AGG		607-629
AD-1731035	CAGUGGCUGGCAUCAACUC CU		625-645	AGGAGUUGAUGCCAGCCACU GGC		623-645

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005538.4	Antisense Sequence 5' to 3	SEQ ID NO:	Range in NM_005538.4
AD-1731042	CCUGAAGCUCAAGCUGCCU GU		653-673	ACAGGCAGCUUGAGCUUCAG GCC		651-673
AD-1731064	GAGCUGGUACUUGAAGGCC AU		695-715	AUGGCCUUCAAGUACCAGCU CCA		693-715
AD-1731088	GCCCAGAGCUCAGUCAUCC UU		719-739	AAGGAUGACUGAGCUCUGGG CUA		717-739
AD-1731117	UGCCCAUAGGCCUUUUGUG GU		748-768	ACCACAAAAGGCCUAUGGGC AGC		746-768
AD-1731134	UGGCAGCCCCGGGUGAGAGU UU		765-785	AAACUCUCACCCGGGCUGCC ACA		763-785
AD-1731137	GCAAACACCAGAUUCACCG AU		789-809	AUCGGUGAAUCUGGUGUUUG CCC		787-809
AD-1731156	ACGAGGCAUCGACUGCCAA GU		808-828	ACUUGGCAGUCGAUGCCUCG UCG		806-828
AD-1731173	AAGGAGGGUCCAGGAUGUG CU		825-845	AGCACAUCCUGGACCCUCCU UGG		823-845
AD-1731189	GUGCUGUCGACAAGAGUUU UU		841-861	AAAAACUCUUGUCGACAGCA CAU		839-861
AD-1731205	UUUUUUGUGGACUUCCGUG AU		857-877	AUCACGGAAGUCCACAAAAA ACU		855-877
AD-1731234	GCACGACUGGAUCAUCCAG CU		886-906	AGCUGGAUGAUCCAGUCGUG CCA		884-906
AD-1731264	CGCCAUGAACUUCUGCAUA GU		916-936	ACUAUGCAGAAGUUCAUGGC GUA		914-936
AD-1731289	UGCCCACUACACAUAGCAG GU		941-961	ACCUGCUAUGUGUAGUGGGC ACU		939-961
AD-1731307	GGCAUGCCUGGUAUUGCUG CU		959-979	AGCAGCAAUACCAGGCAUGC CUG		957-979
AD-1731323	CUGCCUCCUUUCACACUGC AU		975-995	AUGCAGUGUGAAAGGAGGCA GCA		973-995
AD-1731340	GCAGUGCUCAAUCUUCUCA AU		992-1012	AUUGAGAAGAUUGAGCACUG CAG		990-1012
AD-1731358	AAGGCCAACACAGCUGCAG		1010-1030	ACCUGCAGCUGUGUUGGCCU		1008-1030

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005538.4	Antisense Sequence 5' to 3	SEQ ID NO:	Range in NM_005538.4
	GU			UGA		
AD-1731371	GCUCAUGCUGUGUACCCAC GU		1044-1064	ACGUGGGUACACAGCAUGAG CCC		1042-1064
AD-1731380	GUCUCUGCUCUAUUAUGAC AU		1078-1098	AUGUCAUAAUAGAGCAGAGA CAG		1076-1098
AD-1731398	GACAGGGACAGCAACAUUG UU		1094-1114	AACAAUGUUGCUGUCCCUGU CAU		1092-1114
AD-1731415	UGUCAAGACUGACAUACCU GU		1111-1131	ACAGGUAUGUCAGUCUUGAC AAU		1109-1131
AD-1731431	CCUGACAUGGUAGUAGAGG CU		1127-1147	AGCCUCUACUACCAUGUCAG GUA		1125-1147
AD-1731457	AGUUAGUCUAUGUGUGGUA UU		1157-1177	AAUACCACACAUAGACUAAC UGC		1155-1177
AD-1731484	CCAAGGUUGCAUGGGAAAA CU		1184-1204	AGUUUUCCCAUGCAACCUUG GGC		1182-1204
AD-1731492	ACAGAAGUGCACUUCCUUG AU		1212-1232	AUCAAGGAAGUGCACUUCUG UAG		1210-1232
AD-1731511	AGAGGAGGGAAUGACCUCA UU		1231-1251	AAUGAGGUCAUUCCCUCCUC UCA		1229-1251
AD-1731527	UCAUUCUCUGUCCAGAAUG UU		1247-1267	AACAUUCUGGACAGAGAAUG AGG		1245-1267
AD-1731545	GUGGACUCCCUCUUCCUGA GU		1265-1285	ACUCAGGAAGAGGGAGUCCA CAU		1263-1285
AD-1731562	GAGCAUCUUAUGGAAAUUA CU		1282-1302	AGUAAUUUCCAUAAGAUGCU CAG		1280-1302
AD-1731564	CACCUUUGACUUGAAGAAA CU		1304-1324	AGUUUCUUCAAGUCAAAGGU GGG		1302-1324
AD-1731584	CUUCAUCUAAAGCAAGUCA CU		1324-1344	AGUGACUUGCUUUAGAUGAA GGU		1322-1344
AD-1731600	UCACUGUGCCAUCUUCCUG AU		1340-1360	AUCAGGAAGAUGGCACAGUG ACU		1338-1360
AD-1731618	GACCACUACCCUCUUUCCU AU		1358-1378	AUAGGAAAGAGGGUAGUGG UCAG		1356-1378

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005538.4	Antisense Sequence 5' to 3	SEQ ID NO:	Range in NM_005538.4
AD-1731646	UCCAUCCCGCUAGUCCAUCCU		1386-1406	AGGAUGGACUAGCGGGAUGGACU		1384-1406
AD-1731671	ACCCAUCUCCCAACCAUGAGCU		1431-1451	AGCUCAUGGUUGGGAGAUGGGUCU		1429-1451
AD-1731687	GAGCAAUGCCAUCUGGUUCCU		1447-1467	AGGAACCAGAUGGCAUUGCUCAU		1445-1467
AD-1731704	UCCCAGGCAAAGACACCCUUU		1464-1484	AAAGGGUGUCUUUGCCUGGGAAC		1462-1484
AD-1731720	CCUUAGCUCACCUUUAAUAGU		1480-1500	ACUAUUAAAGGUGAGCUAAGGGU		1478-1500
AD-1731728	ACCCACUAUGCCUUCCUGUCU		1508-1528	AGACAGGAAGGCAUAGUGGGUUA		1506-1528
AD-1731745	GUCCUUUCUACUCAAUGGUCU		1525-1545	AGACCAUUGAGUAGAAAGGACAG		1523-1545
AD-1731750	UCCAAGAUGAGUUGACACAAU		1550-1570	AUUGUGUCAACUCAUCUUGGAGU		1548-1570
AD-1731753	CAAUUUUUGUGGAUCUCCAGU		1580-1600	ACUGGAGAUCCCACAAAAAUUGGG		1578-1600
AD-1731782	UCUUUGGAUUCACCAAAGUUU		1609-1629	AAACUUUGGUGAAUCCAAAGAAG		1607-1629
AD-1731813	UGCCCAAAAUAGAGGCUUACU		1640-1660	AGUAAGCCUCUAUUUUGGGCAGC		1638-1660
AD-1731819	CUGUCCUUCUUAGUUGUCCAU		1685-1705	AUGGACAACUAAGAAGGACAGGG		1683-1705
AD-1731842	GAACUACUAAAGCUCUCUUUU		1708-1728	AAAAGAGAGCUUUAGUAGUUCAC		1706-1728
AD-1731858	CUUUGCAUACCUUCAUCCAUU		1724-1744	AAUGGAUGAAGGUAUGCAAAGAG		1722-1744
AD-1731874	CCAUUUUUUGUCCUUCUCUGU		1740-1760	ACAGAGAAGGACAAAAAAAUGGAU		1738-1760
AD-1731890	GCCUUUCUCUAUGCCCUUAAU		1759-1779	AUUAAGGGCAUAGAGAAAGGCAG		1757-1779
AD-1731906	UUAAGGGCUGACUUGCCUG		1775-1795	AUCAGGCAAGUCAGCCCUUA		1773-1795

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005538.4	Antisense Sequence 5' to 3	SEQ ID NO:	Range in NM_005538.4
	AU			AGG		
AD-1731923	UGAGCUCUAUCACCUGAGC UU		1792-1812	AAGCUCAGGUGAUAGAGCUC AGG		1790-1812
AD-1731932	UCUGGCUUCCUGCUGAGGU CU		1821-1841	AGACCUCAGCAGGAAGCCAG AGG		1819-1841
AD-1731958	UUUCUUAUCCCUGUUCCCU CU		1847-1867	AGAGGGAACAGGGAUAAGA AAUG		1845-1867
AD-1731978	UCUGUCUAGGUGUCAUGGU UU		1867-1887	AAACCAUGACACCUAGACAG AGA		1865-1887
AD-1731997	UCUGUGUAACUGUGGCUAU UU		1886-1906	AAAUAGCCACAGUUACACAG AAC		1884-1906
AD-1732013	UAUUCUGUGUCCCUACACU AU		1902-1922	AUAGUGUAGGGACACAGAAU AGC		1900-1922
AD-1732031	GCCUACAUUCUGAUAUAAC UU		1953-1973	AAGUUAUAUCAGAAUGUAG GCAG		1951-1973
AD-1732048	CCUAAAGGCUUUCUAUCUU GU		1991-2011	ACAAGAUAGAAAGCCUUUAG GAC		1989-2011
AD-1732062	CUCAACAUCUCAUACUGGU UU		2025-2045	AAACCAGUAUGAGAUGUUGA GGC		2023-2045
AD-1732078	GGUUCCCUUAACUCUGCCU AU		2041-2061	AUAGGCAGAGUUAAGGGAAC CAG		2039-2061
AD-1732094	CCUAUACCUCUGUAAAUAA UU		2057-2077	AAUUAUUUACAGAGGUAUA GGCA		2055-2077
AD-1732110	UAAUUCCUUCACUAAGUUC UU		2073-2093	AAGAACUUAGUGAAGGAAU UAUU		2071-2093
AD-1732157	AAAGUCCUCUAUCUCCUAC AU		2120-2140	AUGUAGGAGAUAGAGGACU UUUC		2118-2140
AD-1732173	UACAAGGGCCCUAACUGGC AU		2136-2156	AUGCCAGUUAGGGCCCUUGU AGG		2134-2156
AD-1732176	CAGAUGACACAGAGCCUGC CU		2159-2179	AGGCAGGCUCUGUGUCAUCU GGG		2157-2179
AD-1732195	CUGCUUAUGCUGUAGUCUG CU		2178-2198	AGCAGACUACAGCAUAAGCA GGC		2176-2198

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005538.4	Antisense Sequence 5' to 3	SEQ ID NO:	Range in NM_005538.4
AD-1732217	ACUCUGCUGUCUCUUCACAUU		2200-2220	AAUGUGAAGAGACAGCAGAGUAG		2198-2220
AD-1732235	AUGGUCUCCUCAGAACUGAAU		2218-2238	AUUCAGUUCUGAGGAGACCAUGU		2216-2238
AD-1732253	AACUAUUGUAUCCAUCUCACU		2236-2256	AGUGAGAUGGAUACAAUAGUUCA		2234-2256
AD-1732269	UCACACUUUAUGCCUCUUCUU		2252-2272	AAGAAGAGGCAUAAAGUGUGAGA		2250-2272
AD-1732291	AUCCUUCCAGAACCAUCUUUU		2294-2314	AAAAGAUGGUUCUGGAAGGAUGG		2292-2314
AD-1732308	UUUGAGGUCUCAUGGCUAAUU		2311-2331	AAUUAGCCAUGAGACCUCAAAGA		2309-2331
AD-1732335	UAGGCUUUACCUGUUCCCUCU		2338-2358	AGAGGGAACAGGUAAAGCCUAGG		2336-2358
AD-1732353	UCUGUAAUCCCUCCAAAAGAU		2356-2376	AUCUUUUGGAGGGAUUACAGAGG		2354-2376
AD-1732372	AUGAGACAGAUCUAUGCUUGU		2375-2395	ACAAGCAUAGAUCUGUCUCAUCU		2373-2395
AD-1732389	UUGGUCAUCCAGUAAACUGAU		2392-2412	AUCAGUUUACUGGAUGACCAAGC		2390-2412
AD-1732415	GUGGGCACGCAAGUGUGGGAU		2418-2438	AUCCCACACUUGCGUGCCCACAG		2416-2438
AD-1732440	AGGCAUGCUCAGAGCUGGCUU		2443-2463	AAGCCAGCUCUGAGCAUGCCUCU		2441-2463
AD-1732469	UCUGACUUGCCUUCCUUUCAU		2472-2492	AUGAAAGGAAGGCAAGUCAGAGG		2470-2492
AD-1732479	UGCUCCACCCAGGAGUCCUGU		2503-2523	ACAGGACUCCUGGGUGGAGCACU		2501-2523
AD-1732500	CUGGAAGCUGGAAUGGGCAAU		2524-2544	AUUGCCCAUUCCAGCUUCCAGGC		2522-2544
AD-1732520	GGGCUGCUGGAGUGGGACAGU		2544-2564	ACUGUCCCACUCCAGCAGCCCUU		2542-2564
AD-1732533	CAGGGAGAAGAGGAAGGCC		2561-2581	AAGGCCUUCCUCUUCUCCCU		2559-2581

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005538.4	Antisense Sequence 5' to 3	SEQ ID NO:	Range in NM_005538.4
	UU			GUC		
AD-1732549	GCCUGGAUGAGGAGAGGGU GU		2577-2597	ACACCCUCUCCUCAUCCAGG CCU		2575-2597
AD-1732565	GUGGCAUUUGCUCUGAGAC UU		2594-2614	AAGUCUCAGAGCAAAUGCCA CCC		2592-2614
AD-1732584	UGGGUCCUUUUUAGACCUU UU		2613-2633	AAAAGGUCUAAAAAGGACCC AGU		2611-2633
AD-1732604	CUCCCUUUGGCUGGACAGU CU		2654-2674	AGACUGUCCAGCCAAAGGGA GGA		2652-2674
AD-1732625	UGAACCAUGAGGUCGAUAA UU		2675-2695	AAUUAUCGACCUCAUGGUUC AGG		2673-2695
AD-1732644	UGUCUGCAGCCCAAGGCCG AU		2694-2714	AUCGGCCUUGGGCUGCAGAC AUU		2692-2714
AD-1732661	CGAGUUUGCGCAAAACCCA UU		2711-2731	AAUGGGUUUUGCGCAAACUC GGC		2709-2731
AD-1732677	CCAUGUGUUCUUUGGUAAA CU		2727-2747	AGUUUACCAAAGAACACAUG GGU		2725-2747
AD-1732696	CGUGAUGUCUGUGUUUGCU CU		2746-2766	AGAGCAAACACAGACAUCAC GUU		2744-2766
AD-1732708	CUCCUAUGAGGGUAAGAGG UU		2779-2799	AACCUCUUACCCUCAUAGGA GGG		2777-2799
AD-1732728	CCCUGAAAUAGGAACCCUA GU		2799-2819	ACUAGGGUUCCUAUUUCAGG GAC		2797-2819
AD-1732744	CUAGAGGAGAAAAGUCUGAA AU		2815-2835	AUUUCAGACUUUCUCCUCUA GGG		2813-2835
AD-1732757	GACUGUAAAUCUGAGCUUG AU		2849-2869	AUCAAGCUCAGAUUUACAGU CCC		2847-2869
AD-1732786	GAGCAACCCAUGGAAGUUA UU		2878-2898	AAUAACUUCCAUGGGUUGCU CAG		2876-2898
AD-1732807	CCACCUUUGACUUGAGGAG AU		2899-2919	AUCUCCUCAAGUCAAAGGUG GGA		2897-2919
AD-1732827	CCUUCAUCUAAGGAGAAUC UU		2919-2939	AAGAUUCUCCUUAGAUGAAG GUC		2917-2939

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005538.4	Antisense Sequence 5' to 3	SEQ ID NO:	Range in NM_005538.4
AD-1732849	GGAGGCCUUCUGGUGUCUCCU		2941-2961	AGGAGACACCAGAAGGCCUCCUU		2939-2961
AD-1732865	UCCCAAUUACAGCUUAGUCUU		2995-3015	AAGACUAAGCUGUAAUUGGGAAG		2993-3015
AD-1732881	GUCUCCAGGGCUAGGACUGGU		3011-3031	ACCAGUCCUAGCCCUGGAGACUA		3009-3031
AD-1732885	AAGCAAAGUGAGUCAUUCACU		3035-3055	AGUGAAUGACUCACUUUGCUUUA		3033-3055
AD-1732890	GUGGUGAACAAUUUAUUAAUU		3079-3099	AAUUAAUAAAUUGUUCACCACCC		3077-3099
AD-1732908	UAGGACUUUAAUGCAAUAUUU		3104-3124	AAAUAUUGCAUUAAAGUCCUAUC		3102-3124
AD-1732940	GAACAAAAUAGCCUACUUUUU		3160-3180	AAAAAGUAGGCUAUUUUGUUCAU		3158-3180

Table 17. Modified Sense and Antisense Strand Sequences of INHBC dsRNA Agents Comprising a GalNAc Derivative Targeting Ligand

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Sense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1730493	uscsuuccAfgGfGfCfcucuggcaguL96		asCfsugcCfaGfAfggccCfuGfgaagasasg		CUUCUUCCAGGGCCUCUGGCAGC	
AD-1730512	csasggacAfgAfGfUfugagaccacuL96		asGfsuggUfcUfCfaacuCfuGfuccugsgsc		GCCAGGACAGAGUUGAGACCACA	
AD-1730529	csascagcUfgUfUfGfagacccugauL96		asUfscagGfgUfCfucaaCfaGfcugugsgsu		ACCACAGCUGUUGAGACCCUGAG	
AD-1730554	gsasgucuGfuAfUfUfgcucaagaauL96		asUfsucuUfgAfGfcaauAfcAfgacucsasg		CUGAGUCUGUAUUGCUCAAGAAG	
AD-1730570	usgsaccuCfcUfCfAfuugcuucuguL96		asCfsagaAfgCfAfaugaGfgAfggucasusu		AAUGACCUCCUCAUUGCUUCUGG	
AD-1730588	usgsgccuUfuCfUfCfcuccuggcuuL96		asAfsgccAfgGfAfggagAfaAfggccasgsa		UCUGGCCUUUCUCCUCCUGGCUC	
AD-	csusccaaCfcAfCfAfguggccacu		asAfsgugGfcCfAfcuguGfgUfugga		GGCUCCAACCACAGUGGCC	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Sense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
1730606	uL96		gscsc		ACUC	
AD-1730636	gscsggucAfgUfGfUfccagcaug uuL96		asAfscauGfcUfGfgacaCfuGfaccgc scsa		UGGCGGUCAGUGUCCAGCA UGUG	
AD-1730643	ascscuugGfaAfCfUfggagagcca uL96		asUfsggcUfcUfCfcaguUfcCfaaggu sgsg		CCACCUUGGAACUGGAGAG CCAG	
AD-1730667	gsasgcugCfuUfCfUfugaucugg cuL96		asGfsccaGfaUfCfaagaAfgCfagcuc scsc		GGGAGCUGCUUCUUGAUCU GGCC	
AD-1730691	asgsaagcAfuCfUfUfggacaagcu uL96		asAfsgcuUfgUfCfcaagAfuGfcuuc uscsu		AGAGAAGCAUCUUGGACAA GCUG	
AD-1730726	cscsaacaCfuGfAfAfcgcccugu uL96		asAfscagGfgCfGfguucAfgUfguug gsgsc		GCCCAACACUGAACCGCCCU GUG	
AD-1730749	csasgagcUfgCfUfUfugaggacu guL96		asCfsaguCfcUfCfaaagCfaGfcucug sgsa		UCCAGAGCUGCUUUGAGGA CUGC	
AD-1730765	ascsugcaCfuGfCfCfAfgcaccucca uL96		asUfsggaGfgUfGfcugcAfgUfgcag uscsc		GGACUGCACUGCAGCACCU CCAC	
AD-1730769	gscsacuuCfuAfGfAfggacaacag uL96		asCfsuguUfgUfCfcucuAfgAfagug cscsc		GGGCACUUCUAGAGGACAA CAGG	
AD-1730790	gsasacagGfaAfUfGfugaaaucau uL96		asAfsugaUfuUfCfacauUfcCfuguuc scsc		GGGAACAGGAAUGUGAAAU CAUC	
AD-1730807	csasucagCfuUfUfGfcugagacag uL96		asCfsuguCfuCfAfgcaaAfgCfugaug sasu		AUCAUCAGCUUUGCUGAGA CAGG	
AD-1730825	asgsgccuCfuCfCfAfccaucaacc uL96		asGfsguuGfaUfGfguggAfgAfggcc usgsu		ACAGGCCUCUCCACCAUCAA CCA	
AD-1730841	asasccagAfcUfCfGfucuugauuu uL96		asAfsaauCfaAfGfacgaGfuCfugguu sgsa		UCAACCAGACUCGUCUUGA UUUU	
AD-1730857	asusuuucAfcUfUfCfuccucuga uuL96		asAfsucaGfaGfGfagaaGfuGfaaaau scsa		UGAUUUUCACUUCUCCUCU GAUA	
AD-1730873	usgsauagAfaCfUfGfcuggugac auL96		asUfsgucAfcCfAfgcagUfuCfuauca sgsa		UCUGAUAGAACUGGCUGGUG ACAG	
AD-1730910	asgsucucAfuGfUfUfcuuugugc auL96		asUfsgcaCfaAfAfgaacAfuGfagacu sgsg		CCAGUCUCAUGUUCUUUGU GCAG	
AD-1730926	usgscagcUfcCfCfUfuccaauacc uL96		asGfsguaUfuGfGfaaggGfaGfcugc ascsa		UGUGCAGCUCCCUUCCAAU ACCA	
AD-1730942	usasccacUfuGfGfAfccuugaaag uL96		asCfsuuuCfaAfGfguccAfaGfuggu asusu		AAUACCACUUGGACCUUGA AAGU	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Sense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1730958	asasagugAfgAfGfUfccuugugc uuL96		asAfsgcaCfaAfGfgacuCfuCfacuuu scsa		UGAAAGUGAGAGGUCCUUGU GCUG	
AD-1730982	cscsacauAfaUfAfCfcaaccucac uL96		asGfsugaGfgUfUfgguaUfuAfugug gsasc		GUCCACAUAAUACCAACCU CACC	
AD-1731003	ususggcuAfcUfCfAfguaccugc uuL96		asAfsgcaGfgUfAfcugaGfuAfgccaa sgsg		CCUUGGCUACUCAGUACCU GCUG	
AD-1731019	usgscuggAfgGfUfCfgaugccag uuL96		asAfscugGfcAfUfccacCfuCfcagca sgsg		CCUGCUGGAGGUGGAUGCC AGUG	
AD-1731035	csasguggCfuGfGfCfaucaacucc uL96		asGfsgagUfuGfAfugccAfgCfcacu gsgsc		GCCAGUGGCUGGCAUCAAC UCCC	
AD-1731042	cscsugaaGfcUfCfAfagcugccug uL96		asCfsaggCfaGfCfuugaGfcUfucagg scsc		GGCCUGAAGCUCAAGCUGC CUGC	
AD-1731064	gsasgcugGfuAfCfUfugaaggcc auL96		asUfsggcCfuUfCfaaguAfcCfagcuc scsa		UGGAGCUGGUACUUGAAGG CCAG	
AD-1731088	gscsccagAfgCfUfCfagucauccu uL96		asAfsggaUfgAfCfugagCfuCfuggg csusa		UAGCCCAGAGCUCAGUCAU CCUG	
AD-1731117	usgscccaUfaGfGfCfcuuuugug guL96		asCfscacAfaAfAfggccUfaUfgggca sgsc		GCUGCCCAUAGGCCUUUUG UGGC	
AD-1731134	usgsgcagCfcCfGfGfgugagagu uuL96		asAfsacuCfuCfAfcccgGfgCfugcca scsa		UGUGGCAGCCCGGGUGAGA GUUG	
AD-1731137	gscsaaacAfcCfAfGfauucaccga uL96		asUfscggUfgAfAfucugGfuGfuuug cscsc		GGGCAAACACCAGAUUCAC CGAC	
AD-1731156	ascsgaggCfaUfCfGfacugccaag uL96		asCfsuugGfcAfGfucgaUfgCfcucg uscsg		CGACGAGGCAUCGACUGCC AAGG	
AD-1731173	asasggagGfgUfCfCffaggaugug cuL96		asGfscacAfuCfCfuggaCfcCfuccuu sgsg		CCAAGGAGGGUCCAGGAUG UGCU	
AD-1731189	gsusgcugUfcGfAfCfaagaguuu uuL96		asAfsaaaCfuCfUfugucGfaCfagcac sasu		AUGUGCUGUCGACAAGAGU UUUU	
AD-1731205	ususuuuuGfuGfGfAfcuuccgug auL96		asUfscacGfgAfAfguccAfcAfaaaaa scsu		AGUUUUUUGUGGACUUCCG UGAG	
AD-1731234	gscsacgaCfuGfGfAfucauccagc uL96		asGfscugGfaUfGfauccAfgUfcgug cscsa		UGGCACGACUGGAUCAUCC AGCC	
AD-1731264	csgsccauGfaAfCfUfucugcauag uL96		asCfsuauGfcAfGfaaguUfcAfuggc gsusa		UACGCCAUGAACUUCUGCA UAGG	
AD-	usgscccaCfuAfCfAfcauagcagg		asCfscugCfuAfUfguguAfgUfgggc		AGUGCCCACUACACAUAGC	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Sense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
1731289	uL96		ascsu		AGGC	
AD-1731307	gsgscaugCfcUfGfGfuauugcug cuL96		asGfscagCfaAfUfaccaGfgCfaugcc susg		CAGGCAUGCCUGGUAUUGC UGCC	
AD-1731323	csusgccuCfcUfUfUfcacacugca uL96		asUfsgcaGfuGfUfgaaaGfgAfggca gscsa		UGCUGCCUCCUUUCACACU GCAG	
AD-1731340	gscsagugCfuCfAfAfucuucucaa uL96		asUfsugaGfaAfGfauugAfgCfacug csasg		CUGCAGUGCUCAAUCUUCU CAAG	
AD-1731358	asasggccAfaCfAfCfagcugcagg uL96		asCfscugCfaGfCfugugUfuGfgccu usgsa		UCAAGGCCAACACAGCUGC AGGC	
AD-1731371	gscsucauGfcUfGfUfguacccacg uL96		asCfsguGfgUfAfcacaGfcAfugagc scsc		GGGCUCAUGCUGUGUACCC ACGG	
AD-1731380	gsuscucuGfcUfCfUfauuaugaca uL96		asUfsgucAfuAfAfuagaGfcAfgaga csasg		CUGUCUCUGCUCUAUUAUG ACAG	
AD-1731398	gsascaggGfaCfAfGfcaacauugu uL96		asAfscaaUfgUfUfgcugUfcCfcuguc sasu		AUGACAGGGACAGCAACAU UGUC	
AD-1731415	usgsucaaGfaCfUfGfacauaccug uL96		asCfsaggUfaUfGfucagUfcUfugaca sasu		AUUGUCAAGACUGACAUAC CUGA	
AD-1731431	cscsugacAfuGfGfUfaguagagg cuL96		asGfsccuCfuAfCfuaccAfuGfucagg susa		UACCUGACAUGGUAGUAGA GGCC	
AD-1731457	asgsuuagUfcUfAfUfguguggua uuL96		asAfsuacCfaCfAfcauaGfaCfuaacu sgsc		GCAGUUAGUCUAUGUGUGG UAUG	
AD-1731484	cscsaaggUfuGfCfAfugggaaaac uL96		asGfsuuuUfcCfCfaugcAfaCfcuugg sgsc		GCCCAAGGUUGCAUGGGAA AACA	
AD-1731492	ascsagaaGfuGfCfCfAfcuuccuuga uL96		asUfscaaGfgAfAfgugcAfcUfucug usasg		CUACAGAAGUGCACUUCCU UGAG	
AD-1731511	asgsaggaGfgGfAfAfugaccuca uuL96		asAfsugaGfgUfCfauucCfcUfccucu scsa		UGAGAGGAGGGAAUGACCU CAUU	
AD-1731527	uscsauucUfcUfGfUfccagaaugu uL96		asAfscauUfcUfUfGfgacaGfaGfaauga sgsg		CCUCAUUCUCUGUCCAGAA UGUG	
AD-1731545	gsusggacUfcCfCfUfcuuccugag uL96		asCfsucaGfgAfAfgaggGfaGfuccac sasu		AUGUGGACUCCCUCUUCCU GAGC	
AD-1731562	gsasgcauCfuUfAfUfggaaauuac uL96		asGfsuaaUfuUfCfcauaAfgAfugcuc sasg		CUGAGCAUCUUAUGGAAAU UACC	
AD-1731564	csasccuuUfgAfCfUfugaagaaac uL96		asGfsuuuCfuUfCfaaguCfaAfaggu gsgsg		CCCACCUUUGACUUGAAGA AACC	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Sense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1731584	csusucauCfuAfAfAfgcaagucacuL96		asGfsugaCfuUfGfcuuuAfgAfugaagsgsu		ACCUUCAUCUAAAGCAAGUCACU	
AD-1731600	uscsacugUfgCfCfCfAfucuuccugauL96		asUfscagGfaAfGfauggCfaCfagugascsu		AGUCACUGUGCCAUCUUCCUGAC	
AD-1731618	gsasccacUfaCfCfCfCfucuuuccuauL96		asUfsaggAfaAfGfagggUfaGfuggucsasg		CUGACCACUACCCUCUUUCCUAG	
AD-1731646	uscscaucCfcGfCfUfUfaguccaucuL96		asGfsgauGfgAfCfuagcGfgGfaugguascsu		AGUCCAUCCCGCUAGUCCAUCCC	
AD-1731671	ascsccauCfuCfCfAfaccaugagcuL96		asGfscucAfuGfGfuuggAfgAfuggguscsu		AGACCCAUCUCCAACCAUGAGCA	
AD-1731687	gsasgcaaUfgCfCfAfucugguuccuL96		asGfsgaaCfcAfGfauggCfaUfugcucsasu		AUGAGCAAUGCCAUCUGGUUCCC	
AD-1731704	uscsccagGfcAfAfAfgacacccuuuL96		asAfsaggGfuGfUfcuuuGfcCfugggasasc		GUUCCCAGGCAAAGACACCCUUA	
AD-1731720	cscsuuagCfuCfAfCfcuuuaaauagL96		asCfsuauUfaAfAfggugAfgCfuaaggsgsu		ACCCUUAGCUCACCUUUAAUAGA	
AD-1731728	ascsccacUfaUfGfCfcuuccugucuL96		asGfsacaGfgAfAfggcaUfaGfuggguusa		UAACCCACUAUGCCUUCCUGUCC	
AD-1731745	gsusccuuUfcUfAfCfucaauggucuL96		asGfsaccAfuUfGfaguaGfaAfaggacsasg		CUGUCCUUUCUACUCAAUGGUCC	
AD-1731750	uscscaagAfuGfAfGfuugacacaauL96		asUfsuguGfuCfAfacucAfuCfuugasgsu		ACUCCAAGAUGAGUUGACACAAC	
AD-1731753	csasauuuUfuGfUfGfgaucccaguL96		asCfsuggAfgAfUfccacAfaAfaauugsgsg		CCCAAUUUUUGUGGAUCUCCAGA	
AD-1731782	uscsuuugGfaUfUfCfaccaaaguuuL96		asAfsacuUfuGfGfugaaUfcCfaaagasasg		CUUCUUUGGAUUCACCAAAGUUU	
AD-1731813	usgsgcccAfaAfUfAfgaggcuuacuL96		asGfsuaaGfcCfUfcuauUfuUfgggcasgsc		GCUGCCCAAAAUAGAGGCUUACC	
AD-1731819	csusguccUfuCfUfUfaguugucccuL96		asUfsggaCfaAfCfuaagAfaGfgacagsgsg		CCCUGUCCUUCUUAGUUGUCCAG	
AD-1731842	gsasacuaCfuAfAfAfgcucucuuuuL96		asAfsaagAfgAfGfcuuuAfgUfaguucsasc		GUGAACUACUAAAGCUCUCUUUG	
AD-1731858	csusuugcAfuAfCfCfUfucauccauuL96		asAfsuggAfuGfAfagguAfuGfcaaagsasg		CUCUUUGCAUACCUUCAUCCAUU	
AD-	cscsauuuUfuUfGfUfccuucucuuL96		asCfsagaGfaAfGfgacaAfaAfaauggsusa		AUCCAUUUUUUGUCCUUCUUU	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Sense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
1731874	guL96		sasu		CUGC	
AD-1731890	gscscuuuCfuCfUfAfugcccuuaauL96		asUfsuaaGfgGfCfauagAfgAfaaggcsasg		CUGCCUUUCUCUAUGCCCUUAAG	
AD-1731906	ususaaggGfcUfGfAfcuugccugauL96		asUfscagGfcAfAfgucaGfcCfcuuaasgsg		CCUUAAGGGCUGACUUGCCUGAG	
AD-1731923	usgsagcuCfuAfUfCfaccugagcuuL96		asAfsgcuCfaGfGfugauAfgAfgcucasgsg		CCUGAGCUCUAUCACCUGAGCUC	
AD-1731932	uscsuggcUfuCfCfUfgcugaggucuL96		asGfsaccUfcAfGfcaggAfaGfccagasgsg		CCUCUGGCUUCCUGCUGAGGUCA	
AD-1731958	ususucuuAfuCfCfCfuguucccucuL96		asGfsaggGfaAfCfagggAfuAfagaaasusg		CAUUUCUUAUCCCUGUUCCCUCU	
AD-1731978	uscsugucUfaGfGfUfgucauggguuL96		asAfsaccAfuGfAfcaccUfaGfacagasgsa		UCUCUGUCUAGGUGUCAUGGUUC	
AD-1731997	uscsugugUfaAfCfUfguggcuauuuL96		asAfsauaGfcCfAfcaguUfaCfacagasasc		GUUCUGUGUAACUGUGGCUAUUC	
AD-1732013	usasuucuGfuGfUfCfccuacacuauL96		asUfsaguGfuAfGfggacAfcAfgaauasgsc		GCUAUUCUGUGUCCCUACACUAC	
AD-1732031	gscscuacAfuUfCfUfgauauaacuuL96		asAfsguuAfuAfUfcagaAfuGfuaggcsasg		CUGCCUACAUUCUGAUAUAACUG	
AD-1732048	cscsuaaaGfgCfUfUfucuauucuugL96		asCfsaagAfuAfGfaaagCfcUfuuaggsasc		GUCCUAAAGGCUUUCUAUCUUGC	
AD-1732062	csuscaacAfuCfUfCfauacugguuuL96		asAfsaccAfgUfAfugagAfuGfuugagsgsc		GCCUCAACAUCUCAUACUGGUUC	
AD-1732078	gsgsuuccCfuUfAfAfcucugccuauL96		asUfsaggCfaGfAfguuaAfgGfgaaccsasg		CUGGUUCCCUUAACUCUGCCUAU	
AD-1732094	cscsuauaCfcUfCfUfguaaauaauuL96		asAfsuuaUfuUfAfcagaGfgUfauaggscsa		UGCCUAUACCUCUGUAAAUAAUU	
AD-1732110	usasauucCfuUfCfAfcuaaguucuuL96		asAfsgaaCfuUfAfgugaAfgGfaauuasusu		AAUAAUUCCUUCACUAAGUUCUC	
AD-1732157	asasagucCfuCfUfAfucuccuacauL96		asUfsguaGfgAfGfauagAfgGfacuuususc		GAAAAGUCCUCUAUCUCCUACAA	
AD-1732173	usascaagGfgCfCfCfuaacuggcauL96		asUfsgccAfgUfUfuagggCfcCfuugusgsg		CCUACAAGGGCCCUAACUGGCAC	
AD-1732176	csasgaugAfcAfCfAfgagccugccuL96		asGfsgcaGfgCfUfcuguGfuCfaucugsgsg		CCCAGAUGACACAGAGGCCUGCCU	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Sense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1732195	csusgcuuAfuGfCfUfguagucug cuL96		asGfscagAfcUfAfcagcAfuAfagcag sgsc		GCCUGCUUAUGCUGUAGUC UGCC	
AD-1732217	ascsucugCfuGfUfCfcuuucacau uL96		asAfsuguGfaAfGfagacAfgCfagag usasg		CUACUCUGCUGUCUCUUCA CAUG	
AD-1732235	asusggucUfcCfUfCfagaacugaa uL96		asUfsucaGfuUfCfugagGfaGfaccau sgsu		ACAUGGUCUCCUCAGAACU GAAC	
AD-1732253	asascuauUfgUfAfUfccaucucac uL96		asGfsugaGfaUfGfgauaCfaAfuagu uscsa		UGAACUAUUGUAUCCAUCU CACA	
AD-1732269	uscsacacUfuUfAfUfgccucuucu uL96		asAfsgaaGfaGfGfcauaAfaGfuguga sgsa		UCUCACACUUUAUGCCUCU UCUU	
AD-1732291	asusccuuCfcAfGfAfaccaucuuu uL96		asAfsaagAfuGfGfuucuGfgAfagga usgsg		CCAUCCUUCCAGAACCAUCU UUG	
AD-1732308	ususugagGfuCfUfCfauggcuaa uuL96		asAfsuuaGfcCfAfugagAfcCfucaaa sgsa		UCUUUGAGGUCUCAUGGCU AAUA	
AD-1732335	usasggcuUfuAfCfCfuguucccu cuL96		asGfsaggGfaAfCfagguAfaAfgccua sgsg		CCUAGGCUUUACCUGUUCC CUCU	
AD-1732353	uscsuguaAfuCfCfCfuccaaaaga uL96		asUfscuuUfuGfGfagggAfuUfacag asgsg		CCUCUGUAAUCCCUCCAAA AGAU	
AD-1732372	asusgagaCfaGfAfUfcuaugcuu guL96		asCfsaagCfaUfAfgaucUfgUfcucau scsu		AGAUGAGACAGAUCUAUGC UUGG	
AD-1732389	ususggucAfuCfCfAfguaaacug auL96		asUfscagUfuUfAfcuggAfuGfaccaa sgsc		GCUUGGUCAUCCAGUAAAC UGAC	
AD-1732415	gsusgggcAfcGfCfAfaguguggg auL96		asUfscccAfcAfCfuugcGfuGfcccac sasg		CUGUGGGCACGCAAGUGUG GGAG	
AD-1732440	asgsgcauGfcUfCfAfgagcuggc uuL96		asAfsgccAfgCfUfcugaGfcAfugccu scsu		AGAGGCAUGCUCAGAGCUG GCUG	
AD-1732469	uscsugacUfuGfCfCfuuccuuuca uL96		asUfsgaaAfgGfAfaggcAfaGfucaga sgsg		CCUCUGACUUGCCUUCCUU UCAC	
AD-1732479	usgscuccAfcCfCfAfggaguccug uL96		asCfsaggAfcUfCfcuggGfuGfgagca scsu		AGUGCUCCACCCAGGAGUC CUGC	
AD-1732500	csusggaaGfcUfGfGfaaugggcaa uL96		asUfsugcCfcAfUfuccaGfcUfuccag sgsc		GCCUGGAAGCUGGAAUGGG CAAG	
AD-1732520	gsgsgcugCfuGfGfAfgugggaca guL96		asCfsuguCfcCfCfAfcuccAfgCfagccc susu		AAGGGCUGCUGGAGUGGGA CAGG	
AD-	csasgggaGfaAfGfAfggaaggcc		asAfsggcCfuUfCfcucuUfcUfccccug		GACAGGGAGAAGAGGAAGG	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Sense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
1732533	uuL96		susc		CCUG	
AD-1732549	gscscuggAfuGfAfGfgagagggu guL96		asCfsaccCfuCfUfccucAfuCfcaggc scsu		AGGCCUGGAUGAGGAGAGG GUGG	
AD-1732565	gsusggcaUfuUfGfCfucugagac uuL96		asAfsgucUfcAfGfagcaAfaUfgccac scsc		GGGUGGCAUUUGCUCUGAG ACUG	
AD-1732584	usgsggucCfuUfUfUfuagaccuu uuL96		asAfsaagGfuCfUfaaaaAfgGfaccca sgsu		ACUGGGUCCUUUUUAGACC UUUG	
AD-1732604	csusccccuUfuGfGfCfuggacaguc uL96		asGfsacuGfuCfCfagccAfaAfgggag sgsa		UCCUCCCUUUGGCUGGACA GUCC	
AD-1732625	usgsaaccAfuGfAfGfgucgauaa uuL96		asAfsuuaUfcGfAfccucAfuGfguuc asgsg		CCUGAACCAUGAGGUCGAU AAUG	
AD-1732644	usgsucugCfaGfCfCfcaaggccga uL96		asUfscggCfcUfUfgggcUfgCfagaca susu		AAUGUCUGCAGCCCAAGGC CGAG	
AD-1732661	csgsaguuUfgCfGfCfaaaacccau uL96		asAfsuggGfuUfUfugcgCfaAfacuc gsgsc		GCCGAGUUUUGCGCAAAACC CAUG	
AD-1732677	cscsauguGfuUfCfUfuugguaaa cuL96		asGfsuuuAfcCfAfaagaAfcAfcaugg sgsu		ACCCAUGUGUUCUUUGGUA AACG	
AD-1732696	csgsugauGfuCfUfGfuguuugcu cuL96		asGfsagcAfaAfCfacagAfcAfucacg susu		AACGUGAUGUCUGUGUUUG CUCA	
AD-1732708	csusccuaUfgAfGfGfGfguaagagg uuL96		asAfsccuCfuUfAfcccuCfaUfaggag sgsg		CCCUCCUAUGAGGGUAAGA GGUC	
AD-1732728	cscscugaAfaUfAfGfgaacccuag uL96		asCfsuagGfgUfUfccuaUfuUfcagg gsasc		GUCCCUGAAAUAGGAACCC UAGA	
AD-1732744	csusagagGfaGfAfAfagucugaaa uL96		asUfsuucAfgAfCfuuucUfcCfucua gsgsg		CCCUAGAGGAGAAAGUCUG AAAA	
AD-1732757	gsascuguAfaAfUfCfugagcuug auL96		asUfscaaGfcUfCfagauUfuAfcaguc scsc		GGGACUGUAAAUCUGAGCU UGAG	
AD-1732786	gsasgcaaCfcCfAfUfggaaguuau uL96		asAfsuaaCfuUfCfcaugGfgUfugcuc sasg		CUGAGCAACCCAUGGAAGU UAUC	
AD-1732807	cscsaccuUfuGfAfCfuugaggaga uL96		asUfscucCfuCfCfAfagucAfaAfggug gsgsa		UCCCACCUUUGACUUGAGG AGAC	
AD-1732827	cscsuucaUfcUfAfAfggagaaucu uL96		asAfsgauUfcUfCfcuuaGfaUfgaagg susc		GACCUUCAUCUAAGGAGAA UCUA	
AD-1732849	gsgsaggcCfuUfCfUfggugcuc cuL96		asGfsgagAfcAfCfcagaAfgGfccucc susu		AAGGAGGCCUUCUGGUGUC UCCC	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Sense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1732865	uscsccaaUfuAfCfAfgcuuagucuuL96		asAfsgacUfaAfGfcuguAfaUfuggg asasg		CUUCCCAAUUACAGCUUAG UCUC	
AD-1732881	gsuscuccAfgGfGfCfuaggacugguL96		asCfscagUfcCfUfagccCfuGfgagac susa		UAGUCUCCAGGGCUAGGAC UGGG	
AD-1732885	asasgcaaAfgUfGfAfgucauuucacuL96		asGfsugaAfuGfAfcucaCfuUfugcu ususa		UAAAGCAAAGUGAGUCAUU CACC	
AD-1732890	gsusggugAfaCfAfAfuuuauuaauuL96		asAfsuuaAfuAfAfauugUfuCfaccac scsc		GGGUGGUGAACAAUUUAUU AAUC	
AD-1732908	usasggacUfuUfAfAfugcaauauuuL96		asAfsauaUfuGfCfauuaAfaGfuccua susc		GAUAGGACUUUAAUGCAAU AUUA	
AD-1732940	gsasacaaAfaUfAfGfccuacuuuuuL96		asAfsaaaGfuAfGfgcuaUfuUfuguu csasu		AUGAACAAAAUAGCCUACU UUUA	

Table 18. Single dose screen for dsRNA agents targeting INHBE in Hep3b cells

Duplex Name	INHBE/gapdh		INHBE/gapdh	
	10 nM		1 nM	
	Average % message remaining	SD	Average % message remaining	SD
AD-1657845.1	111.502	7.324	91.264	6.933
AD-1657834.1	73.740	4.726	60.700	3.044
AD-1657822.1	44.254	6.361	31.710	2.225
AD-1657811.1	57.311	6.952	42.989	3.234
AD-1657793.1	57.109	9.054	57.657	1.772
AD-1657776.1	31.680	4.646	29.169	6.609
AD-1657760.1	20.839	4.152	19.336	1.898
AD-1657744.1	34.473	7.839	30.596	0.788
AD-1657741.1	74.347	14.701	74.106	5.550
AD-1657727.1	72.423	11.797	80.936	2.697
AD-1657716.1	22.638	3.700	23.912	6.962
AD-1657704.1	28.552	6.159	28.798	6.146
AD-1657687.1	54.039	9.112	54.137	1.783
AD-1657674.1	47.061	4.830	43.380	3.109
AD-1657653.1	31.466	2.523	32.508	1.736
AD-1657641.1	24.346	3.640	25.044	1.349
AD-1657615.1	48.959	8.120	56.602	4.347
AD-1657600.1	68.423	6.167	71.585	7.687
AD-1657586.1	54.978	13.599	52.685	2.375
AD-1657575.1	55.241	7.227	57.979	7.288
AD-1657564.1	45.901	2.503	54.016	1.990
AD-1657552.1	82.298	13.007	76.189	6.130
AD-1657540.1	22.575	2.322	21.798	2.756
AD-1657529.1	33.762	2.785	32.357	0.747
AD-1657520.1	40.770	2.904	40.577	2.140
AD-1657503.1	81.097	10.061	95.267	5.483
AD-1657463.1	104.817	3.003	102.395	7.680
AD-1657475.1	32.866	3.805	36.728	3.060
AD-1657457.1	55.309	7.525	62.481	4.757
AD-1657446.1	64.718	5.426	70.633	2.386
AD-1657431.1	82.429	3.640	94.677	7.863
AD-1657410.1	85.127	11.511	95.982	4.312
AD-1657395.1	34.606	4.035	44.299	3.633
AD-1657385.1	25.376	4.571	30.272	1.859
AD-1657374.1	34.005	3.832	40.414	6.995
AD-1657359.1	36.416	4.539	42.496	1.445
AD-1657347.1	49.056	7.109	53.442	1.120
AD-1657335.1	38.944	8.573	57.606	15.402
AD-1657324.1	67.982	8.933	60.199	1.498
AD-1657322.1	70.552	6.423	98.389	1.565
AD-1657299.1	51.716	10.063	51.866	3.171
AD-1657286.1	58.362	4.990	59.650	3.084
AD-1657274.1	49.867	7.374	55.066	2.475
AD-1657261.1	67.171	10.247	75.283	5.022

Duplex Name	INHBE/gapdh		INHBE/gapdh	
	10 nM		1 nM	
	Average % message remaining	SD	Average % message remaining	SD
AD-1657245.1	107.148	10.325	107.609	3.856
AD-1657234.1	49.466	10.471	55.763	3.564
AD-1657211.1	66.217	9.659	89.842	2.170
AD-1657202.1	24.284	0.920	30.464	1.354
AD-1657185.1	52.769	4.360	57.078	1.715
AD-1657164.1	98.337	9.509	102.454	1.987
AD-1657147.1	33.650	4.858	37.393	2.032
AD-1657133.1	47.322	3.533	59.465	4.976
AD-1657119.1	33.540	5.318	27.596	0.347
AD-1657113.1	19.963	4.057	20.771	1.598
AD-1657099.1	34.125	3.942	37.359	1.925
AD-1657085.1	37.089	9.439	33.790	1.346
AD-1657069.1	40.171	5.158	39.186	5.693
AD-1657058.1	22.085	1.950	23.312	5.043
AD-1657045.1	37.085	2.715	32.953	2.922
AD-1657037.1	27.931	2.008	28.287	1.070
AD-1657022.1	43.503	4.641	49.124	2.709
AD-1657013.1	25.911	5.728	31.816	2.016
AD-1656996.1	66.202	1.771	84.949	2.887
AD-1656969.1	22.138	0.831	20.535	1.620
AD-1656958.1	15.865	1.070	16.371	1.040
AD-1656954.1	40.878	9.408	53.844	4.173
AD-1656942.1	30.879	6.184	43.036	3.002
AD-1656926.1	83.175	10.550	103.354	10.184
AD-1656915.1	43.426	5.790	45.498	3.633
AD-1656900.1	57.647	7.574	71.612	1.628
AD-1656888.1	20.414	2.786	20.645	0.527
AD-1656876.1	41.507	8.799	64.531	3.928
AD-1656873.1	95.455	1.755	110.427	4.031
AD-1656862.1	28.261	3.728	25.877	4.127
AD-1656849.1	42.736	6.226	53.757	4.118
AD-1656832.1	22.284	4.193	24.704	1.507
AD-1656820.1	36.282	2.484	49.723	2.973
AD-1656808.1	33.056	6.984	23.344	1.171
AD-1656792.1	32.327	4.602	63.303	4.848
AD-1656775.1	78.089	6.399	74.958	10.131
AD-1656762.1	34.695	5.445	45.070	2.460
AD-1656754.1	68.025	10.751	95.733	6.112
AD-1656740.1	109.099	15.708	110.169	5.851
AD-1656728.1	58.629	6.016	78.387	19.524
AD-1656716.1	58.703	8.377	76.566	8.896
AD-1656701.1	101.804	8.079	101.812	6.138
AD-1656690.1	72.753	13.083	85.011	9.161
AD-1656679.1	26.622	3.632	44.404	2.181
AD-1656667.1	84.688	16.798	93.321	4.608

Duplex Name	INHBE/gapdh		INHBE/gapdh	
	10 nM		1 nM	
	Average % message remaining	SD	Average % message remaining	SD
AD-1656647.1	52.261	9.437	79.158	1.290
AD-1656634.1	68.804	4.037	72.522	8.828
AD-1656622.1	64.773	3.958	61.094	3.211
AD-1656602.1	90.930	8.206	97.503	6.469
AD-1656591.1	67.929	6.205	50.621	2.250
AD-1656587.1	130.517	14.507	112.466	5.072
AD-1656570.1	54.831	8.259	67.275	4.341
AD-1656559.1	99.324	16.587	94.525	10.986
AD-1656547.1	47.881	6.431	47.546	13.507
AD-1656535.1	45.730	4.759	47.345	3.749
AD-1656504.1	18.728	1.669	28.522	5.548
AD-1656492.1	56.190	5.381	90.874	4.381
AD-1656480.1	123.739	13.306	109.755	2.612
AD-1656468.1	109.278	12.715	110.494	6.230
AD-1656449.1	59.340	4.424	63.755	3.688
AD-1656437.1	37.011	10.928	37.870	1.699
AD-1656417.1	71.490	5.406	76.482	4.881
AD-1656406.1	24.283	4.442	22.173	1.760
AD-1656392.1	32.989	8.824	25.987	9.238
AD-1656383.1	136.848	18.447	130.314	12.433
AD-1656372.1	108.305	5.297	103.207	3.375
AD-1656360.1	67.214	8.162	87.294	8.571
AD-1656333.1	28.433	5.041	26.718	2.141
AD-1656319.1	56.184	4.092	52.184	3.756
AD-1656307.1	102.315	8.887	96.572	4.261
AD-1656292.1	26.799	5.415	30.140	4.062
AD-1656280.1	42.240	7.706	36.464	2.246
AD-1656265.1	72.020	14.577	80.758	6.589
AD-1656260.1	102.537	13.790	115.141	23.155
AD-1656254.1	114.062	4.103	126.823	2.379
AD-1656233.1	99.276	14.267	93.223	3.260
AD-1656220.1	52.087	6.444	47.137	2.748
AD-1656196.1	69.556	7.457	78.281	3.008
AD-1656185.1	59.059	6.916	59.771	1.753
AD-1656164.1	52.037	5.249	49.894	1.671
AD-1656146.1	61.416	9.782	69.569	10.125
AD-1656139.1	81.533	5.159	79.120	3.969
AD-1656125.1	106.018	7.449	120.205	7.924
AD-1656108.1	92.474	5.568	120.457	12.135
AD-1656097.1	86.405	6.346	95.682	6.379
AD-1656086.1	97.906	14.028	98.562	6.521
AD-1656074.1	78.172	13.741	91.731	5.480
AD-1656054.1	85.044	8.142	90.847	4.543
AD-1656043.1	50.700	6.709	47.910	3.196
AD-1656026.1	109.741	12.514	93.624	7.670

Duplex Name	INHBE/gapdh 10 nM		INHBE/gapdh 1 nM	
	Average % message remaining	SD	Average % message remaining	SD
AD-1656008.1	86.662	8.226	98.543	23.583

Example 4. Design, Synthesis and *In Vitro* Screening of Additional dsRNA Duplexes

Additional siRNAs were designed, synthesized, and prepared using methods known in the art and described above in Example 2.

A detailed list of the additional unmodified INHBE sense and antisense strand nucleotide sequences is shown in Table 19. A detailed list of the modified INHBE sense and antisense strand nucleotide sequences is shown in Table 20.

Single dose screens of the additional agents were performed by free uptake and transfection.

For free uptake, experiments were performed by adding 2.5 µl of siRNA duplexes in PBS per well into a 96 well plate. Complete growth media (47.5 µl) containing about 1.5 x 10^4 primary human hepatocytes (PHH) or primary cynomolgus hepatocytes (PCH) were then added to the siRNA. Cells were incubated for 48 hours prior to RNA purification and RT-qPCR. Single dose experiments were performed at 250 nM, 100 nM, 10 nM and 1 nM final duplex concentration.

For transfections, cells (*i.e.,* Hep3b cells, primary human hepatocytes, or primary cynomolgus hepatocytes) were grown to near confluence at 37°C in an atmosphere of 5% CO2 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 7.5 µl of Opti-MEM plus 0.1 µl of Lipofectamine RNAiMax per well (Invitrogen, Carlsbad CA. cat # 13778-150) to 2.5 µl of each siRNA duplex to an individual well in a 384-well plate. The mixture was then incubated at room temperature for 15 minutes. Forty µl of complete growth media without antibiotic containing ~1.5 x10^4 cells were then added to the siRNA mixture. Cells were incubated for 24 hours prior to RNA purification. Single dose experiments were performed at 10, 1 and 0.1 nM final duplex concentration.

Total RNA isolation was performed using DYNABEADS. Briefly, cells were lysed in 10 µl of Lysis/Binding Buffer containing 3 µL of beads per well and 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 3 µl) once in Buffer A, once in Buffer B, and twice in Buffer E, with aspiration steps in between. Following a final aspiration, complete 12 µl RT mixture was added to each well, as described below.

For cDNA synthesis, a master mix of 1.5µl 10X Buffer, 0.6 µl 10X dNTPs, 1.5 µl Random primers, 0.75 µl Reverse Transcriptase, 0.75 µl RNase inhibitor and 9.9 µl of H2O per reaction were added per well. Plates were sealed, agitated for 10 minutes on an electrostatic shaker, and then incubated at 37 degrees C for 2 hours. Following this, the plates were agitated at 80 degrees C for 8 minutes.

RT-qPCR was performed as described above and relative fold change was calculated as described above.

The results of the transfection assays of the dsRNA agents listed in Tables 19 and 20 in Hep3b cells are shown in Table 21A.

The results of the free uptake experiments and the transfection assays of the dsRNA agents listed in Tables 19 and 20 in primary human hepatocytes (PHH) are shown in Table 21B.

The results of the free uptake experiments and the transfection assays of the dsRNA agents listed in Tables 19 and 20 in primary cynomolgus hepatocytes (PCH) are shown in Table 21C.

Table 19. Unmodified Sense and Antisense Strand Sequences of INHBE dsRNA Agents

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO.	Range in NM_031479.5	Antisense Strand Sequence 5' to 3'	SEQ ID NO.	Range in NM_031479.5
AD-1706265.1	GCCAGACAUGAGCUGUGAGGU		5-25	ACCUCACAGCUCAUGUCUGGCUA		3-25
AD-1706266.1	CCAGACAUGAGCUGUGAGGGU		6-26	ACCCTCACAGCTCAUGUCUGGCU		4-26
AD-1706268.1	AGACAUGAGCUGUGAGGGUCU		8-28	AGACCCTCACAGCUCAUGUCUGG		6-28
AD-1706269.1	GACAUGAGCUGUGAGGGUCAU		9-29	ATGACCCUCACAGCUCAUGUCUG		7-29
AD-1706270.1	ACAUGAGCUGUGAGGGUCAAU		10-30	ATUGACCCUCACAGCUCAUGUCU		8-30
AD-1706271.1	CAUGAGCUGUGAGGGUCAAGU		11-31	ACUUGACCCUCACAGCUCAUGUC		9-31
AD-1706272.1	AUGAGCUGUGAGGGUCAAGCU		12-32	AGCUTGACCCUCACAGCUCAUGU		10-32
AD-1706273.1	UGAGCUGUGAGGGUCAAGCAU		13-33	ATGCTUGACCCTCACAGCUCAUG		11-33
AD-1706274.1	GAGCUGUGAGGGUCAAGCACU		14-34	AGUGCUTGACCCUCACAGCUCAU		12-34
AD-1706275.1	AGCUGUGAGGGUCAAGCACAU		15-35	ATGUGCTUGACCCUCACAGCUCA		13-35
AD-1706276.1	GCUGUGAGGGUCAAGCACAGU		16-36	ACUGTGCUUGACCCUCACAGCUC		14-36
AD-1706277.1	CUGUGAGGGUCAAGCACAGCU		17-37	AGCUGUGCUUGACCCUCACAGCU		15-37
AD-1706278.1	UGUGAGGGUCAAGCACAGCUU		18-38	AAGCTGTGCUUGACCCUCACAGC		16-38
AD-1706279.1	GUGAGGGUCAAGCACAGCUAU		19-39	ATAGCUGUGCUTGACCCUCACAG		17-39
AD-1706280.1	UGAGGGUCAAGCACAGCUAUU		20-40	AAUAGCTGUGCTUGACCCUCACA		18-40
AD-1706281.1	GAGGGUCAAGCACAGCUAUCU		21-41	AGAUAGCUGUGCUUGACCCUCAC		19-41
AD-1706282.1	AGGGUCAAGCACAGCUAUCCU		22-42	AGGATAGCUGUGCUUGACCCUCA		20-42
AD-1706283.1	GGGUCAAGCACAGCUAUCCAU		23-43	ATGGAUAGCUGTGCUUGACCCUC		21-43
AD-1706287.1	CAAGCACAGCUAUCCAUCAGU		27-47	ACUGAUGGAUAGCUGUGCUUGAC		25-47
AD-1706288.1	AAGCACAGCUAUCCAUCAGAU		28-48	ATCUGATGGAUAGCUGUGCUUGA		26-48
AD-1706290.1	GCACAGCUAUCCAUCAGAUGU		30-50	ACAUCUGAUGGAUAGCUGUGCUU		28-50
AD-1706291.1	CACAGCUAUCCAUCAGAUGAU		31-51	ATCATCTGAUGGAUAGCUGUGCU		29-51
AD-1706292.1	ACAGCUAUCCAUCAGAUGAUU		32-52	AAUCAUCUGAUGGAUAGCUGUGC		30-52
AD-1706293.1	CAGCUAUCCAUCAGAUGAUCU		33-53	AGAUCATCUGATGGAUAGCUGUG		31-53
AD-1706294.1	AGCUAUCCAUCAGAUGAUCUU		34-54	AAGATCAUCUGAUGGAUAGCUGU		32-54
AD-1706295.1	GCUAUCCAUCAGAUGAUCUAU		35-55	ATAGAUCAUCUGAUGGAUAGCUG		33-55

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO.	Range in NM_031479.5	Antisense Strand Sequence 5' to 3'	SEQ ID NO.	Range in NM_031479.5
AD-1706296.1	CUAUCCAUCAGAUGAUCUACU		36-56	AGUAGATCAUCTGAUGGAUAGCU		34-56
AD-1706297.1	UAUCCAUCAGAUGAUCUACUU		37-57	AAGUAGAUCAUCUGAUGGAUAGC		35-57
AD-1706298.1	AUCCAUCAGAUGAUCUACUUU		38-58	AAAGTAGAUCATCUGAUGGAUAG		36-58
AD-1706299.1	UCCAUCAGAUGAUCUACUUUU		39-59	AAAAGUAGAUCAUCUGAUGGAUA		37-59
AD-1706300.1	CCAUCAGAUGAUCUACUUUCU		40-60	AGAAAGTAGAUCAUCUGAUGGAU		38-60
AD-1706301.1	CAUCAGAUGAUCUACUUUCAU		41-61	ATGAAAGUAGATCAUCUGAUGGA		39-61
AD-1706302.1	AUCAGAUGAUCUACUUUCAGU		42-62	ACUGAAAGUAGAUCAUCUGAUGG		40-62
AD-1706303.1	UCAGAUGAUCUACUUUCAGCU		43-63	AGCUGAAAGUAGAUCAUCUGAUG		41-63
AD-1706304.1	CAGAUGAUCUACUUUCAGCCU		44-64	AGGCTGAAAGUAGAUCAUCUGAU		42-64
AD-1706305.1	AGAUGAUCUACUUUCAGCCUU		45-65	AAGGCUGAAAGTAGAUCAUCUGA		43-65
AD-1706306.1	GAUGAUCUACUUUCAGCCUUU		46-66	AAAGGCTGAAAGUAGAUCAUCUG		44-66
AD-1706307.1	AUGAUCUACUUUCAGCCUUCU		47-67	AGAAGGCUGAAAGUAGAUCAUCU		45-67
AD-1706308.1	UGAUCUACUUUCAGCCUUCCU		48-68	AGGAAGGCUGAAAGUAGAUCAUC		46-68
AD-1706309.1	GAUCUACUUUCAGCCUUCCUU		49-69	AAGGAAGGCUGAAAGUAGAUCAU		47-69
AD-1706310.1	AUCUACUUUCAGCCUUCCUGU		50-70	ACAGGAAGGCUGAAAGUAGAUCA		48-70
AD-1706311.1	UCUACUUUCAGCCUUCCUGAU		51-71	ATCAGGAAGGCTGAAAGUAGAUC		49-71
AD-1706312.1	CUACUUUCAGCCUUCCUGAGU		52-72	ACUCAGGAAGGCUGAAAGUAGAU		50-72
AD-1706313.1	UACUUUCAGCCUUCCUGAGUU		53-73	AACUCAGGAAGGCUGAAAGUAGA		51-73
AD-1706314.1	ACUUUCAGCCUUCCUGAGUCU		54-74	AGACTCAGGAAGGCUGAAAGUAG		52-74
AD-1706318.1	UCAGCCUUCCUGAGUCCCAGU		58-78	ACUGGGACUCAGGAAGGCUGAAA		56-78
AD-1706337.1	GACAAUAGAAGACAGGUGGCU		77-97	AGCCACCUGUCTUCUAUUGUCUG		75-97
AD-1706338.1	ACAAUAGAAGACAGGUGGCUU		78-98	AAGCCACCUGUCUUCUAUUGUCU		76-98
AD-1706380.1	GUGGCAGUGGUGUCUGCUGUU		120-140	AACAGCAGACACCACUGCCACAC		118-140
AD-1706381.1	UGGCAGUGGUGUCUGCUGUCU		121-141	AGACAGCAGACACCACUGCCACA		119-141
AD-1706382.1	GGCAGUGGUGUCUGCUGUCAU		122-142	ATGACAGCAGACACCACUGCCAC		120-142
AD-1706383.1	GCAGUGGUGUCUGCUGUCACU		123-143	AGUGACAGCAGACACCACUGCCA		121-143
AD-1706384.1	CAGUGGUGUCUGCUGUCACUU		124-144	AAGUGACAGCAGACACCACUGCC		122-144

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO.	Range in NM_031479.5	Antisense Strand Sequence 5' to 3'	SEQ ID NO.	Range in NM_031479.5
AD-1706385.1	AGUGGUGUCUGCUGUCACUGU		125-145	ACAGTGACAGCAGACACCACUGC		123-145
AD-1706386.1	GUGGUGUCUGCUGUCACUGUU		126-146	AACAGUGACAGCAGACACCACUG		124-146
AD-1706387.1	UGGUGUCUGCUGUCACUGUGU		127-147	ACACAGTGACAGCAGACACCACU		125-147
AD-1706388.1	GGUGUCUGCUGUCACUGUGCU		128-148	AGCACAGUGACAGCAGACACCAC		126-148
AD-1706407.1	CAGACUCAACAGACGGAGCAU		168-188	ATGCTCCGUCUGUUGAGUCUGAU		166-188
AD-1706408.1	AGACUCAACAGACGGAGCAAU		169-189	ATUGCUCCGUCTGUUGAGUCUGA		167-189
AD-1706409.1	GACUCAACAGACGGAGCAACU		170-190	AGUUGCTCCGUCUGUUGAGUCUG		168-190
AD-1706410.1	ACUCAACAGACGGAGCAACUU		171-191	AAGUTGCUCCGTCUGUUGAGUCU		169-191
AD-1706411.1	CUCAACAGACGGAGCAACUGU		172-192	ACAGTUGCUCCGUCUGUUGAGUC		170-192
AD-1706412.1	UCAACAGACGGAGCAACUGCU		173-193	AGCAGUTGCUCCGUCUGUUGAGU		171-193
AD-1706413.1	CAACAGACGGAGCAACUGCCU		174-194	AGGCAGTUGCUCCGUCUGUUGAG		172-194
AD-1706414.1	AACAGACGGAGCAACUGCCAU		175-195	ATGGCAGUUGCTCCGUCUGUUGA		173-195
AD-1706415.1	ACAGACGGAGCAACUGCCAUU		176-196	AAUGGCAGUUGCUCCGUCUGUUG		174-196
AD-1706416.1	CAGACGGAGCAACUGCCAUCU		177-197	AGAUGGCAGUUGCUCCGUCUGUU		175-197
AD-1706417.1	AGACGGAGCAACUGCCAUCCU		178-198	AGGATGGCAGUTGCUCCGUCUGU		176-198
AD-1706418.1	GACGGAGCAACUGCCAUCCGU		179-199	ACGGAUGGCAGTUGCUCCGUCUG		177-199
AD-1706419.1	ACGGAGCAACUGCCAUCCGAU		180-200	ATCGGATGGCAGUUGCUCCGUCU		178-200
AD-1706420.1	CGGAGCAACUGCCAUCCGAGU		181-201	ACUCGGAUGGCAGUUGCUCCGUC		179-201
AD-1706421.1	GGAGCAACUGCCAUCCGAGGU		182-202	ACCUCGGAUGGCAGUUGCUCCGU		180-202
AD-1706423.1	AGCAACUGCCAUCCGAGGCUU		184-204	AAGCCUCGGAUGGCAGUUGCUCC		182-204
AD-1706424.1	GCAACUGCCAUCCGAGGCUCU		185-205	AGAGCCTCGGATGGCAGUUGCUC		183-205
AD-1706425.1	CAACUGCCAUCCGAGGCUCCU		186-206	AGGAGCCUCGGAUGGCAGUUGCU		184-206
AD-1706520.1	CAAGCAGAACGAGCUCUGGUU		339-359	AACCAGAGCUCGUUCUGCUUGGG		337-359
AD-1706521.1	AAGCAGAACGAGCUCUGGUGU		340-360	ACACCAGAGCUCGUUCUGCUUGG		338-360
AD-1706522.1	AGCAGAACGAGCUCUGGUGCU		341-361	AGCACCAGAGCTCGUUCUGCUUG		339-361
AD-1706523.1	GCAGAACGAGCUCUGGUGCUU		342-362	AAGCACCAGAGCUCGUUCUGCUU		340-362
AD-1706524.1	CAGAACGAGCUCUGGUGCUGU		343-363	ACAGCACCAGAGCUCGUUCUGCU		341-363

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO.	Range in NM_031479.5	Antisense Strand Sequence 5' to 3'	SEQ ID NO.	Range in NM_031479.5
AD-1706525.1	AGAACGAGCUCUGGUGCUGGU		344-364	ACCAGCACCAGAGCUCGUUCUGC		342-364
AD-1706526.1	GAACGAGCUCUGGUGCUGGAU		345-365	ATCCAGCACCAGAGCUCGUUCUG		343-365
AD-1706527.1	AACGAGCUCUGGUGCUGGAGU		346-366	ACUCCAGCACCAGAGCUCGUUCU		344-366
AD-1706528.1	ACGAGCUCUGGUGCUGGAGCU		347-367	AGCUCCAGCACCAGAGCUCGUUC		345-367
AD-1706530.1	GAGCUCUGGUGCUGGAGCUAU		349-369	ATAGCUCCAGCACCAGAGCUCGU		347-369
AD-1706532.1	GCUCUGGUGCUGGAGCUAGCU		351-371	AGCUAGCUCCAGCACCAGAGCUC		349-371
AD-1706533.1	CUCUGGUGCUGGAGCUAGCCU		352-372	AGGCTAGCUCCAGCACCAGAGCU		350-372
AD-1706534.1	UCUGGUGCUGGAGCUAGCCAU		353-373	ATGGCUAGCUCCAGCACCAGAGC		351-373
AD-1706535.1	CUGGUGCUGGAGCUAGCCAAU		354-374	ATUGGCTAGCUCCAGCACCAGAG		352-374
AD-1706536.1	UGGUGCUGGAGCUAGCCAAGU		355-375	ACUUGGCUAGCTCCAGCACCAGA		353-375
AD-1706537.1	GGUGCUGGAGCUAGCCAAGCU		356-376	AGCUTGGCUAGCUCCAGCACCAG		354-376
AD-1706538.1	GUGCUGGAGCUAGCCAAGCAU		357-377	ATGCTUGGCUAGCUCCAGCACCA		355-377
AD-1706539.1	UGCUGGAGCUAGCCAAGCAGU		358-378	ACUGCUTGGCUAGCUCCAGCACC		356-378
AD-1706543.1	GGAGCUAGCCAAGCAGCAAAU		362-382	ATUUGCTGCUUGGCUAGCUCCAG		360-382
AD-1706544.1	GAGCUAGCCAAGCAGCAAAUU		363-383	AAUUTGCUGCUTGGCUAGCUCCA		361-383
AD-1706545.1	AGCUAGCCAAGCAGCAAAUCU		364-384	AGAUTUGCUGCTUGGCUAGCUCC		362-384
AD-1706546.1	GCUAGCCAAGCAGCAAAUCCU		365-385	AGGATUTGCUGCUUGGCUAGCUC		363-385
AD-1706547.1	CUAGCCAAGCAGCAAAUCCUU		366-386	AAGGAUTUGCUGCUUGGCUAGCU		364-386
AD-1706548.1	UAGCCAAGCAGCAAAUCCUGU		367-387	ACAGGATUUGCTGCUUGGCUAGC		365-387
AD-1706549.1	AGCCAAGCAGCAAAUCCUGGU		368-388	ACCAGGAUUUGCUGCUUGGCUAG		366-388
AD-1706550.1	GCCAAGCAGCAAAUCCUGGAU		369-389	ATCCAGGAUUUGCUGCUUGGCUA		367-389
AD-1706578.1	ACCUGACCAGUCGUCCCAGAU		397-417	ATCUGGGACGACUGGUCAGGUGC		395-417
AD-1706579.1	CCUGACCAGUCGUCCCAGAAU		398-418	ATUCTGGGACGACUGGUCAGGUG		396-418
AD-1706580.1	CUGACCAGUCGUCCCAGAAUU		399-419	AAUUCUGGGACGACUGGUCAGGU		397-419
AD-1706581.1	UGACCAGUCGUCCCAGAAUAU		400-420	ATAUTCTGGGACGACUGGUCAGG		398-420
AD-1706582.1	GACCAGUCGUCCCAGAAUAAU		401-421	ATUATUCUGGGACGACUGGUCAG		399-421
AD-1706583.1	ACCAGUCGUCCCAGAAUAACU		402-422	AGUUAUTCUGGGACGACUGGUCA		400-422

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO.	Range in NM_031479.5	Antisense Strand Sequence 5' to 3'	SEQ ID NO.	Range in NM_031479.5
AD-1706584.1	CCAGUCGUCCCAGAAUAACUU		403-423	AAGUTATUCUGGGACGACUGGUC		401-423
AD-1706585.1	CAGUCGUCCCAGAAUAACUCU		404-424	AGAGTUAUUCUGGGACGACUGGU		402-424
AD-1706586.1	AGUCGUCCCAGAAUAACUCAU		405-425	ATGAGUTAUUCTGGGACGACUGG		403-425
AD-1706587.1	GUCGUCCCAGAAUAACUCAUU		406-426	AAUGAGTUAUUCUGGGACGACUG		404-426
AD-1706588.1	UCGUCCCAGAAUAACUCAUCU		407-427	AGAUGAGUUAUTCUGGGACGACU		405-427
AD-1706589.1	CGUCCCAGAAUAACUCAUCCU		408-428	AGGATGAGUUATUCUGGGACGAC		406-428
AD-1706590.1	GUCCCAGAAUAACUCAUCCUU		409-429	AAGGAUGAGUUAUUCUGGGACGA		407-429
AD-1706591.1	UCCCAGAAUAACUCAUCCUCU		410-430	AGAGGATGAGUTAUUCUGGGACG		408-430
AD-1706592.1	CCCAGAAUAACUCAUCCUCCU		411-431	AGGAGGAUGAGTUAUUCUGGGAC		409-431
AD-1706593.1	CCAGAAUAACUCAUCCUCCAU		412-432	ATGGAGGAUGAGUUAUUCUGGGA		410-432
AD-1706594.1	CAGAAUAACUCAUCCUCCACU		413-433	AGUGGAGGAUGAGUUAUUCUGGG		411-433
AD-1706635.1	GGGAGUGUGGCUCCAGGGAAU		474-494	ATUCCCTGGAGCCACACUCCCUG		472-494
AD-1706636.1	GGAGUGUGGCUCCAGGGAAUU		475-495	AAUUCCCUGGAGCCACACUCCCU		473-495
AD-1706637.1	GAGUGUGGCUCCAGGGAAUGU		476-496	ACAUTCCCUGGAGCCACACUCCC		474-496
AD-1706638.1	AGUGUGGCUCCAGGGAAUGGU		477-497	ACCATUCCCUGGAGCCACACUCC		475-497
AD-1706639.1	GAGGAGGUCAUCAGCUUUGCU		498-518	AGCAAAGCUGATGACCUCCUCCC		496-518
AD-1706640.1	AGGAGGUCAUCAGCUUUGCUU		499-519	AAGCAAAGCUGAUGACCUCCUCC		497-519
AD-1706641.1	GGAGGUCAUCAGCUUUGCUAU		500-520	ATAGCAAAGCUGAUGACCUCCUC		498-520
AD-1706642.1	GAGGUCAUCAGCUUUGCUACU		501-521	AGUAGCAAAGCTGAUGACCUCCU		499-521
AD-1706643.1	AGGUCAUCAGCUUUGCUACUU		502-522	AAGUAGCAAAGCUGAUGACCUCC		500-522
AD-1706644.1	GGUCAUCAGCUUUGCUACUGU		503-523	ACAGTAGCAAAGCUGAUGACCUC		501-523
AD-1706645.1	GUCAUCAGCUUUGCUACUGUU		504-524	AACAGUAGCAAAGCUGAUGACCU		502-524
AD-1706646.1	UCAUCAGCUUUGCUACUGUCU		505-525	AGACAGTAGCAAAGCUGAUGACC		503-525
AD-1706649.1	UCAGCUUUGCUACUGUCACAU		508-528	ATGUGACAGUAGCAAAGCUGAUG		506-528
AD-1706650.1	CAGCUUUGCUACUGUCACAGU		509-529	ACUGTGACAGUAGCAAAGCUGAU		507-529
AD-1706651.1	AGCUUUGCUACUGUCACAGAU		510-530	ATCUGUGACAGTAGCAAAGCUGA		508-530
AD-1706652.1	GCUUUGCUACUGUCACAGACU		511-531	AGUCTGTGACAGUAGCAAAGCUG		509-531

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO.	Range in NM_031479.5	Antisense Strand Sequence 5' to 3'	SEQ ID NO.	Range in NM_031479.5
AD-1706653.1	CUUUGCUACUGUCACAGACUU		512-532	AAGUCUGUGACAGUAGCAAAGCU		510-532
AD-1706654.1	UUUGCUACUGUCACAGACUCU		513-533	AGAGUCUGUGACAGUAGCAAAGC		511-533
AD-1706655.1	UUGCUACUGUCACAGACUCCU		514-534	AGGAGUCUGUGACAGUAGCAAAG		512-534
AD-1706656.1	UGCUACUGUCACAGACUCCAU		515-535	ATGGAGUCUGUGACAGUAGCAAA		513-535
AD-1706660.1	ACUGUCACAGACUCCACUUCU		519-539	AGAAGUGGAGUCUGUGACAGUAG		517-539
AD-1706661.1	CUGUCACAGACUCCACUUCAU		520-540	ATGAAGUGGAGUCUGUGACAGUA		518-540
AD-1706662.1	UGUCACAGACUCCACUUCAGU		521-541	ACUGAAGUGGAGUCUGUGACAGU		519-541
AD-1706664.1	UCACAGACUCCACUUCAGCCU		523-543	AGGCUGAAGUGGAGUCUGUGACA		521-543
AD-1706665.1	CACAGACUCCACUUCAGCCUU		524-544	AAGGCUGAAGUGGAGUCUGUGAC		522-544
AD-1706666.1	ACAGACUCCACUUCAGCCUAU		525-545	ATAGGCUGAAGUGGAGUCUGUGA		523-545
AD-1706667.1	CAGACUCCACUUCAGCCUACU		526-546	AGUAGGCUGAAGUGGAGUCUGUG		524-546
AD-1706668.1	AGACUCCACUUCAGCCUACAU		527-547	ATGUAGGCUGAAGUGGAGUCUGU		525-547
AD-1706669.1	GACUCCACUUCAGCCUACAGU		528-548	ACUGTAGGCUGAAGUGGAGUCUG		526-548
AD-1706670.1	ACUCCACUUCAGCCUACAGCU		529-549	AGCUGUAGGCUGAAGUGGAGUCU		527-549
AD-1706671.1	CUCCACUUCAGCCUACAGCUU		530-550	AAGCTGTAGGCTGAAGUGGAGUC		528-550
AD-1706672.1	UCCACUUCAGCCUACAGCUCU		531-551	AGAGCUGUAGGCUGAAGUGGAGU		529-551
AD-1706673.1	CCACUUCAGCCUACAGCUCCU		532-552	AGGAGCTGTAGGCUGAAGUGGAG		530-552
AD-1706674.1	CACUUCAGCCUACAGCUCCCU		533-553	AGGGAGCUGUAGGCUGAAGUGGA		531-553
AD-1706675.1	ACUUCAGCCUACAGCUCCCUU		534-554	AAGGGAGCUGUAGGCUGAAGUGG		532-554
AD-1706678.1	UCAGCCUACAGCUCCCUGCUU		537-557	AAGCAGGGAGCTGUAGGCUGAAG		535-557
AD-1706729.1	CACCUGUACCAUGCCCGCCUU		588-608	AAGGCGGGCAUGGUACAGGUGGU		586-608
AD-1706731.1	CCUGUACCAUGCCCGCCUGUU		590-610	AACAGGCGGGCAUGGUACAGGUG		588-610
AD-1706732.1	CUGUACCAUGCCCGCCUGUGU		591-611	ACACAGGCGGGCAUGGUACAGGU		589-611
AD-1706735.1	UACCAUGCCCGCCUGUGGCUU		594-614	AAGCCACAGGCGGGCAUGGUACA		592-614
AD-1706745.1	CACCCUUCCUGGCACUCUUUU		626-646	AAAAGAGUGCCAGGAAGGGUGGG		624-646
AD-1706746.1	ACCCUUCCUGGCACUCUUUGU		627-647	ACAAAGAGUGCCAGGAAGGGUGG		625-647
AD-1706747.1	CCCUUCCUGGCACUCUUUGCU		628-648	AGCAAAGAGUGCCAGGAAGGGUG		626-648

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO.	Range in NM_031479.5	Antisense Strand Sequence 5' to 3'	SEQ ID NO.	Range in NM_031479.5
AD-1706748.1	CCUUCCUGGCACUCUUUGCUU		629-649	AAGCAAAGAGUGCCAGGAAGGGU		627-649
AD-1706749.1	CUUCCUGGCACUCUUUGCUUU		630-650	AAAGCAAAGAGUGCCAGGAAGGG		628-650
AD-1706750.1	UUCCUGGCACUCUUUGCUUGU		631-651	ACAAGCAAAGAGUGCCAGGAAGG		629-651
AD-1706751.1	UCCUGGCACUCUUUGCUUGAU		632-652	ATCAAGCAAAGAGUGCCAGGAAG		630-652
AD-1706752.1	CCUGGCACUCUUUGCUUGAGU		633-653	ACUCAAGCAAAGAGUGCCAGGAA		631-653
AD-1706753.1	CUGGCACUCUUUGCUUGAGGU		634-654	ACCUCAAGCAAAGAGUGCCAGGA		632-654
AD-1706754.1	UGGCACUCUUUGCUUGAGGAU		635-655	ATCCTCAAGCAAAGAGUGCCAGG		633-655
AD-1706755.1	GGCACUCUUUGCUUGAGGAUU		636-656	AAUCCUCAAGCAAAGAGUGCCAG		634-656
AD-1706756.1	GCACUCUUUGCUUGAGGAUCU		637-657	AGAUCCTCAAGCAAAGAGUGCCA		635-657
AD-1706758.1	ACUCUUUGCUUGAGGAUCUUU		639-659	AAAGAUCCUCAAGCAAAGAGUGC		637-659
AD-1706759.1	CUCUUUGCUUGAGGAUCUUCU		640-660	AGAAGATCCUCAAGCAAAGAGUG		638-660
AD-1706760.1	UCUUUGCUUGAGGAUCUUCCU		641-661	AGGAAGAUCCUCAAGCAAAGAGU		639-661
AD-1706761.1	CUUUGCUUGAGGAUCUUCCGU		642-662	ACGGAAGAUCCTCAAGCAAAGAG		640-662
AD-1706762.1	UUUGCUUGAGGAUCUUCCGAU		643-663	ATCGGAAGAUCCUCAAGCAAAGA		641-663
AD-1706763.1	UUGCUUGAGGAUCUUCCGAUU		644-664	AAUCGGAAGAUCCUCAAGCAAAG		642-664
AD-1706764.1	UGCUUGAGGAUCUUCCGAUGU		645-665	ACAUCGGAAGATCCUCAAGCAAA		643-665
AD-1706765.1	GCUUGAGGAUCUUCCGAUGGU		646-666	ACCATCGGAAGAUCCUCAAGCAA		644-666
AD-1706796.1	CUGGCUGAGCACCACAUCACU		702-722	AGUGAUGUGGUGCUCAGCCAGGA		700-722
AD-1706797.1	UGGCUGAGCACCACAUCACCU		703-723	AGGUGATGUGGTGCUCAGCCAGG		701-723
AD-1706798.1	GGCUGAGCACCACAUCACCAU		704-724	ATGGTGAUGUGGUGCUCAGCCAG		702-724
AD-1706799.1	GCUGAGCACCACAUCACCAAU		705-725	ATUGGUGAUGUGGUGCUCAGCCA		703-725
AD-1706800.1	CUGAGCACCACAUCACCAACU		706-726	AGUUGGTGAUGTGGUGCUCAGCC		704-726
AD-1706801.1	UGAGCACCACAUCACCAACCU		707-727	AGGUTGGUGAUGUGGUGCUCAGC		705-727
AD-1706802.1	GAGCACCACAUCACCAACCUU		708-728	AAGGTUGGUGATGUGGUGCUCAG		706-728
AD-1706803.1	AGCACCACAUCACCAACCUGU		709-729	ACAGGUTGGUGAUGUGGUGCUCA		707-729
AD-1706804.1	GCACCACAUCACCAACCUGGU		710-730	ACCAGGTUGGUGAUGUGGUGCUC		708-730
AD-1706807.1	CCACAUCACCAACCUGGGCUU		713-733	AAGCCCAGGUUGGUGAUGUGGUG		711-733

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO.	Range in NM_031479.5	Antisense Strand Sequence 5' to 3'	SEQ ID NO.	Range in NM_031479.5
AD-1706808.1	CACAUCACCAACCUGGGCUGU		714-734	ACAGCCCAGGUTGGUGAUGUGGU		712-734
AD-1706809.1	ACAUCACCAACCUGGGCUGGU		715-735	ACCAGCCCAGGTUGGUGAUGUGG		713-735
AD-1706811.1	AUCACCAACCUGGGCUGGCAU		717-737	ATGCCAGCCCAGGUUGGUGAUGU		715-737
AD-1706812.1	UCACCAACCUGGGCUGGCAUU		718-738	AAUGCCAGCCCAGGUUGGUGAUG		716-738
AD-1706831.1	UACCUUAACUCUGCCCUCUAU		737-757	ATAGAGGGCAGAGUUAAGGUAUG		735-757
AD-1706832.1	ACCUUAACUCUGCCCUCUAGU		738-758	ACUAGAGGGCAGAGUUAAGGUAU		736-758
AD-1706833.1	CCUUAACUCUGCCCUCUAGUU		739-759	AACUAGAGGGCAGAGUUAAGGUA		737-759
AD-1706834.1	CUUAACUCUGCCCUCUAGUGU		740-760	ACACTAGAGGGCAGAGUUAAGGU		738-760
AD-1706835.1	UUAACUCUGCCCUCUAGUGGU		741-761	ACCACUAGAGGGCAGAGUUAAGG		739-761
AD-1706836.1	UAACUCUGCCCUCUAGUGGCU		742-762	AGCCACTAGAGGGCAGAGUUAAG		740-762
AD-1706848.1	AAGUCUGGUGUCCUGAAACUU		774-794	AAGUTUCAGGACACCAGACUUCU		772-794
AD-1706849.1	AGUCUGGUGUCCUGAAACUGU		775-795	ACAGTUTCAGGACACCAGACUUC		773-795
AD-1706850.1	GUCUGGUGUCCUGAAACUGCU		776-796	AGCAGUTUCAGGACACCAGACUU		774-796
AD-1706851.1	UCUGGUGUCCUGAAACUGCAU		777-797	ATGCAGTUUCAGGACACCAGACU		775-797
AD-1706852.1	CUGGUGUCCUGAAACUGCAAU		778-798	ATUGCAGUUUCAGGACACCAGAC		776-798
AD-1706853.1	UGGUGUCCUGAAACUGCAACU		779-799	AGUUGCAGUUUCAGGACACCAGA		777-799
AD-1706854.1	GGUGUCCUGAAACUGCAACUU		780-800	AAGUTGCAGUUTCAGGACACCAG		778-800
AD-1706855.1	GUGUCCUGAAACUGCAACUAU		781-801	ATAGTUGCAGUTUCAGGACACCA		779-801
AD-1706856.1	UGUCCUGAAACUGCAACUAGU		782-802	ACUAGUTGCAGTUUCAGGACACC		780-802
AD-1706857.1	GUCCUGAAACUGCAACUAGAU		783-803	ATCUAGTUGCAGUUUCAGGACAC		781-803
AD-1706858.1	UCCUGAAACUGCAACUAGACU		784-804	AGUCTAGUUGCAGUUUCAGGACA		782-804
AD-1706859.1	CCUGAAACUGCAACUAGACUU		785-805	AAGUCUAGUUGCAGUUUCAGGAC		783-805
AD-1706860.1	CUGAAACUGCAACUAGACUGU		786-806	ACAGTCTAGUUGCAGUUUCAGGA		784-806
AD-1706861.1	UGAAACUGCAACUAGACUGCU		787-807	AGCAGUCUAGUTGCAGUUUCAGG		785-807
AD-1706862.1	GAAACUGCAACUAGACUGCAU		788-808	ATGCAGTCUAGTUGCAGUUUCAG		786-808
AD-1706863.1	AAACUGCAACUAGACUGCAGU		789-809	ACUGCAGUCUAGUUGCAGUUUCA		787-809
AD-1706864.1	AACUGCAACUAGACUGCAGAU		790-810	ATCUGCAGUCUAGUUGCAGUUUC		788-810

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AD-1706866.1	CUGCAACUAGACUGCAGACCU		792-812	AGGUCUGCAGUCUAGUUGCAGUU		790-812
AD-1706873.1	GGCAACAGCACAGUUACUGGU		819-839	ACCAGUAACUGTGCUGUUGCCUU		817-839
AD-1706874.1	GCAACAGCACAGUUACUGGAU		820-840	ATCCAGTAACUGUGCUGUUGCCU		818-840
AD-1706875.1	CAACAGCACAGUUACUGGACU		821-841	AGUCCAGUAACTGUGCUGUUGCC		819-841
AD-1706876.1	AACAGCACAGUUACUGGACAU		822-842	ATGUCCAGUAACUGUGCUGUUGC		820-842
AD-1706877.1	ACAGCACAGUUACUGGACAAU		823-843	ATUGTCCAGUAACUGUGCUGUUG		821-843
AD-1706878.1	CAGCACAGUUACUGGACAACU		824-844	AGUUGUCCAGUAACUGUGCUGUU		822-844
AD-1706879.1	AGCACAGUUACUGGACAACCU		825-845	AGGUTGTCCAGTAACUGUGCUGU		823-845
AD-1706908.1	CUUGGACACAGCAGGACACCU		854-874	AGGUGUCCUGCTGUGUCCAAGAG		852-874
AD-1706909.1	UUGGACACAGCAGGACACCAU		855-875	ATGGTGTCCUGCUGUGUCCAAGA		853-875
AD-1706910.1	UGGACACAGCAGGACACCAGU		856-876	ACUGGUGUCCUGCUGUGUCCAAG		854-876
AD-1706911.1	GGACACAGCAGGACACCAGCU		857-877	AGCUGGTGUCCTGCUGUGUCCAA		855-877
AD-1706912.1	GACACAGCAGGACACCAGCAU		858-878	ATGCTGGUGUCCUGCUGUGUCCA		856-878
AD-1706913.1	ACACAGCAGGACACCAGCAGU		859-879	ACUGCUGGUGUCCUGCUGUGUCC		857-879
AD-1706914.1	CACAGCAGGACACCAGCAGCU		860-880	AGCUGCTGGUGTCCUGCUGUGUC		858-880
AD-1706918.1	GCAGGACACCAGCAGCCCUUU		864-884	AAAGGGCUGCUGGUGUCCUGCUG		862-884
AD-1706921.1	GGACACCAGCAGCCCUUCCUU		867-887	AAGGAAGGGCUGCUGGUGUCCUG		865-887
AD-1706922.1	GACACCAGCAGCCCUUCCUAU		868-888	ATAGGAAGGGCTGCUGGUGUCCU		866-888
AD-1706923.1	ACACCAGCAGCCCUUCCUAGU		869-889	ACUAGGAAGGGCUGCUGGUGUCC		867-889
AD-1706925.1	ACCAGCAGCCCUUCCUAGAGU		871-891	ACUCTAGGAAGGGCUGCUGGUGU		869-891
AD-1706926.1	CCAGCAGCCCUUCCUAGAGCU		872-892	AGCUCUAGGAAGGGCUGCUGGUG		870-892
AD-1706927.1	CAGCAGCCCUUCCUAGAGCUU		873-893	AAGCTCTAGGAAGGGCUGCUGGU		871-893
AD-1706929.1	GCAGCCCUUCCUAGAGCUUAU		875-895	ATAAGCTCUAGGAAGGGCUGCUG		873-895
AD-1706930.1	CAGCCCUUCCUAGAGCUUAAU		876-896	ATUAAGCUCUAGGAAGGGCUGCU		874-896
AD-1706931.1	AGCCCUUCCUAGAGCUUAAGU		877-897	ACUUAAGCUCUAGGAAGGGCUGC		875-897
AD-1706932.1	GCCCUUCCUAGAGCUUAAGAU		878-898	ATCUTAAGCUCTAGGAAGGGCUG		876-898
AD-1706933.1	CCCUUCCUAGAGCUUAAGAUU		879-899	AAUCTUAAGCUCUAGGAAGGGCU		877-899

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO.	Range in NM_031479.5	Antisense Strand Sequence 5' to 3'	SEQ ID NO.	Range in NM_031479.5
AD-1706934.1	CCUUCCUAGAGCUUAAGAUCU		880-900	AGAUCUTAAGCTCUAGGAAGGGC		878-900
AD-1706982.1	UUACGUAGACUUCCAGGAACU		986-1006	AGUUCCTGGAAGUCUACGUAAUG		984-1006
AD-1706983.1	UACGUAGACUUCCAGGAACUU		987-1007	AAGUTCCUGGAAGUCUACGUAAU		985-1007
AD-1706984.1	ACGUAGACUUCCAGGAACUGU		988-1008	ACAGTUCCUGGAAGUCUACGUAA		986-1008
AD-1706985.1	CGUAGACUUCCAGGAACUGGU		989-1009	ACCAGUTCCUGGAAGUCUACGUA		987-1009
AD-1706987.1	UAGACUUCCAGGAACUGGGAU		991-1011	ATCCCAGUUCCTGGAAGUCUACG		989-1011
AD-1706988.1	AGACUUCCAGGAACUGGGAUU		992-1012	AAUCCCAGUUCCUGGAAGUCUAC		990-1012
AD-1706989.1	GACUUCCAGGAACUGGGAUGU		993-1013	ACAUCCCAGUUCCUGGAAGUCUA		991-1013
AD-1706990.1	ACUUCCAGGAACUGGGAUGGU		994-1014	ACCATCCCAGUTCCUGGAAGUCU		992-1014
AD-1706991.1	CUUCCAGGAACUGGGAUGGCU		995-1015	AGCCAUCCCCAGTUCCUGGGAAGUC		993-1015
AD-1707013.1	GACUGGAUACUGCAGCCCGAU		1017-1037	ATCGGGCUGCAGUAUCCCAGUCCC		1015-1037
AD-1707014.1	ACUGGAUACUGCAGCCCGAGU		1018-1038	ACUCGGGCUGCAGUAUCCCAGUCC		1016-1038
AD-1707015.1	CUGGAUACUGCAGCCCGAGGU		1019-1039	ACCUCGGGCUGCAGUAUCCCAGUC		1017-1039
AD-1707016.1	GUACCAGCUGAAUUACUGCAU		1040-1060	ATGCAGTAAUUCAGCUGGUACCC		1038-1060
AD-1707017.1	UACCAGCUGAAUUACUGCAGU		1041-1061	ACUGCAGUAAUTCAGCUGGUACC		1039-1061
AD-1707018.1	ACCAGCUGAAUUACUGCAGUU		1042-1062	AACUGCAGUAATUCAGCUGGUAC		1040-1062
AD-1707019.1	CCAGCUGAAUUACUGCAGUGU		1043-1063	ACACTGCAGUAAUUCAGCUGGUA		1041-1063
AD-1707020.1	CAGCUGAAUUACUGCAGUGGU		1044-1064	ACCACUGCAGUAAUUCAGCUGGU		1042-1064
AD-1707021.1	AGCUGAAUUACUGCAGUGGGU		1045-1065	ACCCACTGCAGTAAUUCAGCUGG		1043-1065
AD-1707022.1	GCUGAAUUACUGCAGUGGGCU		1046-1066	AGCCCACUGCAGUAAUUCAGCUG		1044-1066
AD-1707023.1	CUGAAUUACUGCAGUGGGCAU		1047-1067	ATGCCCACUGCAGUAAUUCAGCU		1045-1067
AD-1707024.1	UGAAUUACUGCAGUGGGCAGU		1048-1068	ACUGCCCACUGCAGUAAUUCAGC		1046-1068
AD-1707025.1	GAAUUACUGCAGUGGGCAGUU		1049-1069	AACUGCCCACUGCAGUAAUUCAG		1047-1069
AD-1707030.1	ACUGCAGUGGGCAGUGCCCUU		1054-1074	AAGGGCACUGCCCACUGCAGUAA		1052-1074
AD-1707047.1	CAGGCAUUGCUGCCUCUUUCU		1093-1113	AGAAAGAGGCAGCAAUGCCUGGG		1091-1113
AD-1707048.1	AGGCAUUGCUGCCUCUUUCCU		1094-1114	AGGAAAGAGGCAGCAAUGCCUGG		1092-1114
AD-1707049.1	GGCAUUGCUGCCUCUUUCCAU		1095-1115	ATGGAAAGAGGCAGCAAUGCCUG		1093-1115

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO.	Range in NM_031479.5	Antisense Strand Sequence 5' to 3'	SEQ ID NO.	Range in NM_031479.5
AD-1707050.1	GCAUUGCUGCCUCUUUCCAUU		1096-1116	AAUGGAAAGAGGCAGCAAUGCCU		1094-1116
AD-1707051.1	CAUUGCUGCCUCUUUCCAUUU		1097-1117	AAAUGGAAAGAGGCAGCAAUGCC		1095-1117
AD-1707052.1	AUUGCUGCCUCUUUCCAUUCU		1098-1118	AGAATGGAAAGAGGCAGCAAUGC		1096-1118
AD-1707053.1	UUGCUGCCUCUUUCCAUUCUU		1099-1119	AAGAAUGGAAAGAGGCAGCAAUG		1097-1119
AD-1707054.1	UGCUGCCUCUUUCCAUUCUGU		1100-1120	ACAGAATGGAAAGAGGCAGCAAU		1098-1120
AD-1707055.1	GCUGCCUCUUUCCAUUCUGCU		1101-1121	AGCAGAAUGGAAAGAGGCAGCAA		1099-1121
AD-1707056.1	CUGCCUCUUUCCAUUCUGCCU		1102-1122	AGGCAGAAUGGAAAGAGGCAGCA		1100-1122
AD-1707057.1	UGCCUCUUUCCAUUCUGCCGU		1103-1123	ACGGCAGAAUGGAAAGAGGCAGC		1101-1123
AD-1707058.1	GCCUCUUUCCAUUCUGCCGUU		1104-1124	AACGGCAGAAUGGAAAGAGGCAG		1102-1124
AD-1707059.1	CCUCUUUCCAUUCUGCCGUCU		1105-1125	AGACGGCAGAATGGAAAGAGGCA		1103-1125
AD-1707060.1	CUCUUUCCAUUCUGCCGUCUU		1106-1126	AAGACGGCAGAAUGGAAAGAGGC		1104-1126
AD-1707061.1	UCUUUCCAUUCUGCCGUCUUU		1107-1127	AAAGACGGCAGAAUGGAAAGAGG		1105-1127
AD-1707062.1	CUUUCCAUUCUGCCGUCUUCU		1108-1128	AGAAGACGGCAGAAUGGAAAGAG		1106-1128
AD-1707063.1	UUUCCAUUCUGCCGUCUUCAU		1109-1129	ATGAAGACGGCAGAAUGGAAAGA		1107-1129
AD-1707064.1	UUCCAUUCUGCCGUCUUCAGU		1110-1130	ACUGAAGACGGCAGAAUGGAAAG		1108-1130
AD-1707065.1	UCCAUUCUGCCGUCUUCAGCU		1111-1131	AGCUGAAGACGGCAGAAUGGAAA		1109-1131
AD-1707066.1	CCAUUCUGCCGUCUUCAGCCU		1112-1132	AGGCTGAAGACGGCAGAAUGGAA		1110-1132
AD-1707067.1	CAUUCUGCCGUCUUCAGCCUU		1113-1133	AAGGCUGAAGACGGCAGAAUGGA		1111-1133
AD-1707070.1	UCUGCCGUCUUCAGCCUCCUU		1116-1136	AAGGAGGCUGAAGACGGCAGAAU		1114-1136
AD-1707074.1	CCGUCUUCAGCCUCCUCAAAU		1120-1140	ATUUGAGGAGGCUGAAGACGGCA		1118-1140
AD-1707075.1	CGUCUUCAGCCUCCUCAAAGU		1121-1141	ACUUTGAGGAGGCUGAAGACGGC		1119-1141
AD-1707076.1	GUCUUCAGCCUCCUCAAAGCU		1122-1142	AGCUTUGAGGAGGCUGAAGACGG		1120-1142
AD-1707077.1	UCUUCAGCCUCCUCAAAGCCU		1123-1143	AGGCTUTGAGGAGGCUGAAGACG		1121-1143
AD-1707078.1	CUUCAGCCUCCUCAAAGCCAU		1124-1144	ATGGCUTUGAGGAGGCUGAAGAC		1122-1144
AD-1707080.1	UCAGCCUCCUCAAAGCCAACU		1126-1146	AGUUGGCUUUGAGGAGGCUGAAG		1124-1146
AD-1707081.1	CAGCCUCCUCAAAGCCAACAU		1127-1147	ATGUTGGCUUUGAGGAGGCUGAA		1125-1147
AD-1707082.1	AGCCUCCUCAAAGCCAACAAU		1128-1148	ATUGTUGGCUUTGAGGAGGCUGA		1126-1148

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AD-1707083.1	GCCUCCUCAAAGCCAACAAUU		1129-1149	AAUUGUTGGCUTUGAGGAGGCUG		1127-1149
AD-1707084.1	CCUCCUCAAAGCCAACAAUCU		1130-1150	AGAUTGTUGGCTUUGAGGAGGCU		1128-1150
AD-1707085.1	CUCCUCAAAGCCAACAAUCCU		1131-1151	AGGATUGUUGGCUUUGAGGAGGC		1129-1151
AD-1707086.1	UCCUCAAAGCCAACAAUCCUU		1132-1152	AAGGAUTGUUGGCUUUGAGGAGG		1130-1152
AD-1707087.1	CCUCAAAGCCAACAAUCCUUU		1133-1153	AAAGGATUGUUGGCUUUGAGGAG		1131-1153
AD-1707088.1	CUCAAAGCCAACAAUCCUUGU		1134-1154	ACAAGGAUUGUTGGCUUUGAGGA		1132-1154
AD-1707092.1	AAGCCAACAAUCCUUGGCCUU		1138-1158	AAGGCCAAGGATUGUUGGCUUUG		1136-1158
AD-1707093.1	AGCCAACAAUCCUUGGCCUGU		1139-1159	ACAGGCCAAGGAUUGUUGGCUUU		1137-1159
AD-1707094.1	GCCAACAAUCCUUGGCCUGCU		1140-1160	AGCAGGCCAAGGAUUGUUGGCUU		1138-1160
AD-1707095.1	CCAACAAUCCUUGGCCUGCCU		1141-1161	AGGCAGGCCAAGGAUUGUUGGCU		1139-1161
AD-1707097.1	AACAAUCCUUGGCCUGCCAGU		1143-1163	ACUGGCAGGCCAAGGAUUGUUGG		1141-1163
AD-1707098.1	ACAAUCCUUGGCCUGCCAGUU		1144-1164	AACUGGCAGGCCAAGGAUUGUUG		1142-1164
AD-1707105.1	UUGGCCUGCCAGUACCUCCUU		1151-1171	AAGGAGGUACUGGCAGGCCAAGG		1149-1171
AD-1707125.1	GUUGUGUCCCUACUGCCCGAU		1171-1191	ATCGGGCAGUAGGGACACAACAG		1169-1191
AD-1707126.1	UUGUGUCCCUACUGCCCGAAU		1172-1192	ATUCGGGCAGUAGGGACACAACA		1170-1192
AD-1707127.1	UGUGUCCCUACUGCCCGAAGU		1173-1193	ACUUCGGGCAGTAGGGACACAAC		1171-1193
AD-1707128.1	GUGUCCCUACUGCCCGAAGGU		1174-1194	ACCUTCGGGCAGUAGGGACACAA		1172-1194
AD-1707129.1	UGUCCCUACUGCCCGAAGGCU		1175-1195	AGCCTUCGGGCAGUAGGGACACA		1173-1195
AD-1707132.1	UCUCUCCCUCUACCUGGAUU		1198-1218	AAUCCAGGUAGAGGAGAGAGAGG		1196-1218
AD-1707133.1	CUCUCUCCUCUACCUGGAUCU		1199-1219	AGAUCCAGGUAGAGGAGAGAGAG		1197-1219
AD-1707134.1	UCUCUCCUCUACCUGGAUCAU		1200-1220	ATGATCCAGGUAGAGGAGAGAGA		1198-1220
AD-1707135.1	CUCUCCUCUACCUGGAUCAUU		1201-1221	AAUGAUCCAGGTAGAGGAGAGAG		1199-1221
AD-1707136.1	UCUCCUCUACCUGGAUCAUAU		1202-1222	ATAUGATCCAGGUAGAGGAGAGA		1200-1222
AD-1707137.1	CUCCUCUACCUGGAUCAUAAU		1203-1223	ATUATGAUCCAGGUAGAGGAGAG		1201-1223
AD-1707138.1	UCCUCUACCUGGAUCAUAAUU		1204-1224	AAUUAUGAUCCAGGUAGAGGAGA		1202-1224
AD-1707139.1	CCUCUACCUGGAUCAUAAUGU		1205-1225	ACAUTATGAUCCAGGUAGAGGAG		1203-1225
AD-1707140.1	CUCUACCUGGAUCAUAAUGGU		1206-1226	ACCATUAUGAUCCAGGUAGAGGA		1204-1226

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AD-1707141.1	UCUACCUGGAUCAUAAUGGCU		1207-1227	AGCCAUTAUGATCCAGGUAGAGG		1205-1227
AD-1707142.1	CUACCUGGAUCAUAAUGGCAU		1208-1228	ATGCCATUAUGAUCCAGGUAGAG		1206-1228
AD-1707143.1	UACCUGGAUCAUAAUGGCAAU		1209-1229	ATUGCCAUUAUGAUCCAGGUAGA		1207-1229
AD-1707144.1	ACCUGGAUCAUAAUGGCAAUU		1210-1230	AAUUGCCAUUATGAUCCAGGUAG		1208-1230
AD-1707145.1	CCUGGAUCAUAAUGGCAAUGU		1211-1231	ACAUTGCCAUUAUGAUCCAGGUA		1209-1231
AD-1707146.1	CUGGAUCAUAAUGGCAAUGUU		1212-1232	AACATUGCCAUTAUGAUCCAGGU		1210-1232
AD-1707147.1	UGGAUCAUAAUGGCAAUGUGU		1213-1233	ACACAUTGCCATUAUGAUCCAGG		1211-1233
AD-1707148.1	GGAUCAUAAUGGCAAUGUGGU		1214-1234	ACCACATUGCCAUUAUGAUCCAG		1212-1234
AD-1707149.1	GAUCAUAAUGGCAAUGUGGUU		1215-1235	AACCACAUUGCCAUUAUGAUCCA		1213-1235
AD-1707150.1	AUCAUAAUGGCAAUGUGGUCU		1216-1236	AGACCACAUUGCCAUUAUGAUCC		1214-1236
AD-1707151.1	UCAUAAUGGCAAUGUGGUCAU		1217-1237	ATGACCACAUUGCCAUUAUGAUC		1215-1237
AD-1707152.1	CAUAAUGGCAAUGUGGUCAAU		1218-1238	ATUGACCACAUTGCCAUUAUGAU		1216-1238
AD-1707153.1	AUAAUGGCAAUGUGGUCAAGU		1219-1239	ACUUGACCACATUGCCAUUAUGA		1217-1239
AD-1707154.1	UAAUGGCAAUGUGGUCAAGAU		1220-1240	ATCUTGACCACAUUGCCAUUAUG		1218-1240
AD-1707155.1	AAUGGCAAUGUGGUCAAGACU		1221-1241	AGUCTUGACCACAUUGCCAUUAU		1219-1241
AD-1707156.1	AUGGCAAUGUGGUCAAGACGU		1222-1242	ACGUCUTGACCACAUUGCCAUUA		1220-1242
AD-1707157.1	UGGCAAUGUGGUCAAGACGGU		1223-1243	ACCGTCTUGACCACAUUGCCAUU		1221-1243
AD-1707158.1	GGCAAUGUGGUCAAGACGGAU		1224-1244	ATCCGUCUUGACCACAUUGCCAU		1222-1244
AD-1707159.1	GCAAUGUGGUCAAGACGGAUU		1225-1245	AAUCCGTCUUGACCACAUUGCCA		1223-1245
AD-1707160.1	CAAUGUGGUCAAGACGGAUGU		1226-1246	ACAUCCGUCUUGACCACAUUGCC		1224-1246
AD-1707161.1	AAUGUGGUCAAGACGGAUGUU		1227-1247	AACATCCGUCUTGACCACAUUGC		1225-1247
AD-1707162.1	AUGUGGUCAAGACGGAUGUGU		1228-1248	ACACAUCCGUCTUGACCACAUUG		1226-1248
AD-1707163.1	UGUGGUCAAGACGGAUGUGCU		1229-1249	AGCACATCCGUCUUGACCACAUU		1227-1249
AD-1707164.1	GUGGUCAAGACGGAUGUGCCU		1230-1250	AGGCACAUCCGTCUUGACCACAU		1228-1250
AD-1707165.1	UGGUCAAGACGGAUGUGCCAU		1231-1251	ATGGCACAUCCGUCUUGACCACA		1229-1251
AD-1707166.1	GGUCAAGACGGAUGUGCCAGU		1232-1252	ACUGGCACAUCCGUCUUGACCAC		1230-1252
AD-1707167.1	GUCAAGACGGAUGUGCCAGAU		1233-1253	ATCUGGCACAUCCGUCUUGACCA		1231-1253

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AD-1707168.1	UCAAGACGGAUGUGCCAGAUU		1234-1254	AAUCUGGCACATCCGUCUUGACC		1232-1254
AD-1707169.1	CAAGACGGAUGUGCCAGAUAU		1235-1255	ATAUCUGGCACAUCCGUCUUGAC		1233-1255
AD-1707170.1	AAGACGGAUGUGCCAGAUAUU		1236-1256	AAUATCTGGCACAUCCGUCUUGA		1234-1256
AD-1707171.1	AGACGGAUGUGCCAGAUAUGU		1237-1257	ACAUAUCUGGCACAUCCGUCUUG		1235-1257
AD-1707172.1	GACGGAUGUGCCAGAUAUGGU		1238-1258	ACCATATCUGGCACAUCCGUCUU		1236-1258
AD-1707173.1	ACGGAUGUGCCAGAUAUGGUU		1239-1259	AACCAUAUCUGGCACAUCCGUCU		1237-1259
AD-1707174.1	CGGAUGUGCCAGAUAUGGUGU		1240-1260	ACACCATAUCUGGCACAUCCGUC		1238-1260
AD-1707176.1	GAUGUGCCAGAUAUGGUGGUU		1242-1262	AACCACCAUAUCUGGCACAUCCG		1240-1262
AD-1707177.1	AUGUGCCAGAUAUGGUGGUGU		1243-1263	ACACCACCAUATCUGGCACAUCC		1241-1263
AD-1707178.1	UGUGCCAGAUAUGGUGGUGGU		1244-1264	ACCACCACCAUAUCUGGCACAUC		1242-1264
AD-1707179.1	GUGCCAGAUAUGGUGGUGGAU		1245-1265	ATCCACCACCATAUCUGGCACAU		1243-1265
AD-1707180.1	UGCCAGAUAUGGUGGUGGAGU		1246-1266	ACUCCACCACCAUAUCUGGCACA		1244-1266
AD-1707182.1	CCAGAUAUGGUGGUGGAGGCU		1248-1268	AGCCTCCACCACCAUAUCUGGCA		1246-1268
AD-1707189.1	UGGUGGUGGAGGCCUGUGGCU		1255-1275	AGCCACAGGCCTCCACCACCAUA		1253-1275
AD-1707190.1	GGUGGUGGAGGCCUGUGGCUU		1256-1276	AAGCCACAGGCCUCCACCACCAU		1254-1276
AD-1707197.1	GAGGCCUGUGGCUGCAGCUAU		1263-1283	ATAGCUGCAGCCACAGGCCUCCA		1261-1283
AD-1707200.1	GCCUGUGGCUGCAGCUAGCAU		1266-1286	ATGCTAGCUGCAGCCACAGGCCU		1264-1286
AD-1707201.1	CCUGUGGCUGCAGCUAGCAAU		1267-1287	ATUGCUAGCUGCAGCCACAGGCC		1265-1287
AD-1707202.1	CUGUGGCUGCAGCUAGCAAGU		1268-1288	ACUUGCTAGCUGCAGCCACAGGC		1266-1288
AD-1707203.1	UGUGGCUGCAGCUAGCAAGAU		1269-1289	ATCUTGCUAGCTGCAGCCACAGG		1267-1289
AD-1707204.1	GUGGCUGCAGCUAGCAAGAGU		1270-1290	ACUCTUGCUAGCUGCAGCCACAG		1268-1290
AD-1707205.1	UGGCUGCAGCUAGCAAGAGGU		1271-1291	ACCUCUTGCUAGCUGCAGCCACA		1269-1291
AD-1707206.1	GGCUGCAGCUAGCAAGAGGAU		1272-1292	ATCCTCTUGCUAGCUGCAGCCAC		1270-1292
AD-1707207.1	GCUGCAGCUAGCAAGAGGACU		1273-1293	AGUCCUCUUGCTAGCUGCAGCCA		1271-1293
AD-1707208.1	CUGCAGCUAGCAAGAGGACCU		1274-1294	AGGUCCTCUUGCUAGCUGCAGCC		1272-1294
AD-1707209.1	UGCAGCUAGCAAGAGGACCUU		1275-1295	AAGGTCCUCUUGCUAGCUGCAGC		1273-1295
AD-1707210.1	GCAGCUAGCAAGAGGACCUGU		1276-1296	ACAGGUCCUCUTGCUAGCUGCAG		1274-1296

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AD-1707211.1	CAGCUAGCAAGAGGACCUGGU		1277-1297	ACCAGGTCCUCTUGCUAGCUGCA		1275-1297
AD-1707212.1	GCUUUGGAGUGAAGAGACCAU		1298-1318	ATGGTCTCUUCACUCCAAAGCCC		1296-1318
AD-1707213.1	CUUUGGAGUGAAGAGACCAAU		1299-1319	ATUGGUCUCUUCACUCCAAAGCC		1297-1319
AD-1707214.1	UUUGGAGUGAAGAGACCAAGU		1300-1320	ACUUGGTCUCUTCACUCCAAAGC		1298-1320
AD-1707216.1	UGGAGUGAAGAGACCAAGAUU		1302-1322	AAUCTUGGUCUCUUCACUCCAAA		1300-1322
AD-1707217.1	GGAGUGAAGAGACCAAGAUGU		1303-1323	ACAUCUTGGUCTCUUCACUCCAA		1301-1323
AD-1707218.1	GAGUGAAGAGACCAAGAUGAU		1304-1324	ATCATCTUGGUCUCUUCACUCCA		1302-1324
AD-1707221.1	UGAAGAGACCAAGAUGAAGUU		1307-1327	AACUTCAUCUUGGUCUCUUCACU		1305-1327
AD-1707223.1	AAGAGACCAAGAUGAAGUUUU		1309-1329	AAAACUTCAUCTUGGUCUCUUCA		1307-1329
AD-1707224.1	AGAGACCAAGAUGAAGUUUCU		1310-1330	AGAAACTUCAUCUUGGUCUCUUC		1308-1330
AD-1707225.1	GAGACCAAGAUGAAGUUUCCU		1311-1331	AGGAAACUUCATCUUGGUCUCUU		1309-1331
AD-1707226.1	AGACCAAGAUGAAGUUUCCCU		1312-1332	AGGGAAACUUCAUCUUGGUCUCU		1310-1332
AD-1707227.1	GACCAAGAUGAAGUUUCCCAU		1313-1333	ATGGGAAACUUCAUCUUGGUCUC		1311-1333
AD-1707228.1	ACCAAGAUGAAGUUUCCCAGU		1314-1334	ACUGGGAAACUTCAUCUUGGUCU		1312-1334
AD-1707229.1	CCAAGAUGAAGUUUCCCAGGU		1315-1335	ACCUGGGAAACTUCAUCUUGGUC		1313-1335
AD-1707230.1	CAAGAUGAAGUUUCCCAGGCU		1316-1336	AGCCTGGGAAACUUCAUCUUGGU		1314-1336
AD-1707231.1	AAGAUGAAGUUUCCCAGGCAU		1317-1337	ATGCCUGGGAAACUUCAUCUUGG		1315-1337
AD-1707232.1	AGAUGAAGUUUCCCAGGCACU		1318-1338	AGUGCCTGGGAAACUUCAUCUUG		1316-1338
AD-1707233.1	GAUGAAGUUUCCCAGGCACAU		1319-1339	ATGUGCCUGGGAAACUUCAUCUU		1317-1339
AD-1707234.1	AUGAAGUUUCCCAGGCACAGU		1320-1340	ACUGTGCCUGGGAAACUUCAUCU		1318-1340
AD-1707236.1	GAAGUUUCCCAGGCACAGGGU		1322-1342	ACCCTGTGCCUGGGAAACUUCAU		1320-1342
AD-1707237.1	AAGUUUCCCAGGCACAGGGCU		1323-1343	AGCCCUGTGCCTGGGAAACUUCA		1321-1343
AD-1707239.1	GUUUCCCAGGCACAGGGCAUU		1325-1345	AAUGCCCUGTGCCUGGGAAACUU		1323-1345
AD-1707240.1	UUUCCCAGGCACAGGGCAUCU		1326-1346	AGAUGCCCUGTGCCUGGGAAACU		1324-1346
AD-1707241.1	UUCCCAGGCACAGGGCAUCUU		1327-1347	AAGATGCCCUGTGCCUGGGAAAC		1325-1347
AD-1707242.1	UCCCAGGCACAGGGCAUCUGU		1328-1348	ACAGAUGCCCUGTGCCUGGGAAA		1326-1348
AD-1707275.1	CAACCCAACAACCACCUGGCU		1381-1401	AGCCAGGTGGGUTGTUGGGUUGGG		1379-1401

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AD-1707276.1	AACCCAACAACCACCUGGCAU		1382-1402	ATGCCAGGUGGTUGUUGGGUUGG		1380-1402
AD-1707277.1	ACCCAACAACCACCUGGCAAU		1383-1403	ATUGCCAGGUGGUUGUUGGGUUG		1381-1403
AD-1707278.1	CCCAACAACCACCUGGCAAUU		1384-1404	AAUUGCCAGGUGGUUGUUGGGUU		1382-1404
AD-1707279.1	CCAACAACCACCUGGCAAUAU		1385-1405	ATAUTGCCAGGTGGUUGUUGGGU		1383-1405
AD-1707280.1	CAACAACCACCUGGCAAUAUU		1386-1406	AAUATUGCCAGGUGGUUGUUGGG		1384-1406
AD-1707281.1	AACAACCACCUGGCAAUAUGU		1387-1407	ACAUAUTGCCAGGUGGUUGUUGG		1385-1407
AD-1707282.1	ACAACCACCUGGCAAUAUGAU		1388-1408	ATCATATUGCCAGGUGGUUGUUG		1386-1408
AD-1707283.1	CAACCACCUGGCAAUAUGACU		1389-1409	AGUCAUAUUGCCAGGUGGUUGUU		1387-1409
AD-1707284.1	AACCACCUGGCAAUAUGACUU		1390-1410	AAGUCATAUUGCCAGGUGGUUGU		1388-1410
AD-1707285.1	ACCACCUGGCAAUAUGACUCU		1391-1411	AGAGTCAUAUUGCCAGGUGGUUG		1389-1411
AD-1707286.1	CCACCUGGCAAUAUGACUCAU		1392-1412	ATGAGUCAUAUTGCCAGGUGGUU		1390-1412
AD-1707287.1	CACCUGGCAAUAUGACUCACU		1393-1413	AGUGAGTCAUATUGCCAGGUGGU		1391-1413
AD-1707288.1	ACCUGGCAAUAUGACUCACUU		1394-1414	AAGUGAGUCAUAUUGCCAGGUGG		1392-1414
AD-1707289.1	CCUGGCAAUAUGACUCACUUU		1395-1415	AAAGTGAGUCATAUUGCCAGGUG		1393-1415
AD-1707290.1	CUGGCAAUAUGACUCACUUGU		1396-1416	ACAAGUGAGUCAUAUUGCCAGGU		1394-1416
AD-1707291.1	UGGCAAUAUGACUCACUUGAU		1397-1417	ATCAAGTGAGUCAUAUUGCCAGG		1395-1417
AD-1707292.1	GGCAAUAUGACUCACUUGACU		1398-1418	AGUCAAGUGAGTCAUAUUGCCAG		1396-1418
AD-1707293.1	GCAAUAUGACUCACUUGACCU		1399-1419	AGGUCAAGUGAGUCAUAUUGCCA		1397-1419
AD-1707299.1	GGACCCAAAUGGGCACUUUCU		1425-1445	AGAAAGTGCCCAUUUGGGUCCCA		1423-1445
AD-1707301.1	ACCCAAAUGGGCACUUUCUUU		1427-1447	AAAGAAAGUGCCCAUUUGGGUCC		1425-1447
AD-1707302.1	CCCAAAUGGGCACUUUCUUGU		1428-1448	ACAAGAAAGUGCCCAUUUGGGUC		1426-1448
AD-1707303.1	CCAAAUGGGCACUUUCUUGUU		1429-1449	AACAAGAAAGUGCCCAUUUGGGU		1427-1449
AD-1707304.1	CAAAUGGGCACUUUCUUGUCU		1430-1450	AGACAAGAAAGTGCCCAUUUGGG		1428-1450
AD-1707305.1	AAAUGGGCACUUUCUUGUCUU		1431-1451	AAGACAAGAAAGUGCCCAUUUGG		1429-1451
AD-1707306.1	AAUGGGCACUUUCUUGUCUGU		1432-1452	ACAGACAAGAAAGUGCCCAUUUG		1430-1452
AD-1707307.1	AUGGGCACUUUCUUGUCUGAU		1433-1453	ATCAGACAAGAAAGUGCCCAUUU		1431-1453
AD-1707308.1	UGGGCACUUUCUUGUCUGAGU		1434-1454	ACUCAGACAAGAAAGUGCCCAUU		1432-1454

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AD-1707309.1	GGGCACUUUCUUGUCUGAGAU		1435-1455	ATCUCAGACAAGAAAGUGCCCAU		1433-1455
AD-1707310.1	GGCACUUUCUUGUCUGAGACU		1436-1456	AGUCTCAGACAAGAAAGUGCCCA		1434-1456
AD-1707311.1	GCACUUUCUUGUCUGAGACUU		1437-1457	AAGUCUCAGACAAGAAAGUGCCC		1435-1457
AD-1707312.1	CACUUUCUUGUCUGAGACUCU		1438-1458	AGAGTCTCAGACAAGAAAGUGCC		1436-1458
AD-1707313.1	ACUUUCUUGUCUGAGACUCUU		1439-1459	AAGAGUCUCAGACAAGAAAGUGC		1437-1459
AD-1707314.1	CUUUCUUGUCUGAGACUCUGU		1440-1460	ACAGAGTCUCAGACAAGAAAGUG		1438-1460
AD-1707315.1	UUUCUUGUCUGAGACUCUGGU		1441-1461	ACCAGAGUCUCAGACAAGAAAGU		1439-1461
AD-1707316.1	UUCUUGUCUGAGACUCUGGCU		1442-1462	AGCCAGAGUCUCAGACAAGAAAG		1440-1462
AD-1707317.1	UCUUGUCUGAGACUCUGGCUU		1443-1463	AAGCCAGAGUCTCAGACAAGAAA		1441-1463
AD-1707318.1	CUUGUCUGAGACUCUGGCUUU		1444-1464	AAAGCCAGAGUCUCAGACAAGAA		1442-1464
AD-1707337.1	UAUUCCAGGUUGGCUGAUGUU		1463-1483	AACATCAGCCAACCUGGAAUAAG		1461-1483
AD-1707338.1	AUUCCAGGUUGGCUGAUGUGU		1464-1484	ACACAUCAGCCAACCUGGAAUAA		1462-1484
AD-1707339.1	UUCCAGGUUGGCUGAUGUGUU		1465-1485	AACACATCAGCCAACCUGGAAUA		1463-1485
AD-1707340.1	UCCAGGUUGGCUGAUGUGUUU		1466-1486	AAACACAUCAGCCAACCUGGAAU		1464-1486
AD-1707341.1	CCAGGUUGGCUGAUGUGUUGU		1467-1487	ACAACACAUCAGCCAACCUGGAA		1465-1487
AD-1707342.1	CAGGUUGGCUGAUGUGUUGGU		1468-1488	ACCAACACAUCAGCCAACCUGGA		1466-1488
AD-1707388.1	GAUUUCCUGCCCUAAGUCCUU		1534-1554	AAGGACTUAGGGCAGGAAAUCAU		1532-1554
AD-1707390.1	UUUCCUGCCCUAAGUCCUGUU		1536-1556	AACAGGACUUAGGGCAGGAAAUC		1534-1556
AD-1707411.1	AGAAGAUGUCAGGGACUAGGU		1557-1577	ACCUAGTCCCUGACAUCUUCUCA		1555-1577
AD-1707412.1	GAAGAUGUCAGGGACUAGGGU		1558-1578	ACCCTAGUCCCTGACAUCUUCUC		1556-1578
AD-1707415.1	AAGAUGUCAGGGACUAGGGAU		1559-1579	ATCCCUAGUCCCUGACAUCUUCU		1557-1579
AD-1707416.1	AGAUGUCAGGGACUAGGGAGU		1560-1580	ACUCCCTAGUCCCUGACAUCUUC		1558-1580
AD-1707417.1	GAUGUCAGGGACUAGGGAGGU		1561-1581	ACCUCCCUAGUCCCUGACAUCUU		1559-1581
AD-1707418.1	AUGUCAGGGACUAGGGAGGGU		1562-1582	ACCCTCCCUAGTCCCUGACAUCU		1560-1582
AD-1707466.1	GAGGAGGAAGCAGAUAGAUGU		1646-1666	ACAUCUAUCUGCUUCCUCCUCCC		1644-1666
AD-1707467.1	AGGAGGAAGCAGAUAGAUGGU		1647-1667	ACCATCTAUCUGCUUCCUCCUCC		1645-1667
AD-1707468.1	GGAGGAAGCAGAUAGAUGGUU		1648-1668	AACCAUCUAUCTGCUUCCUCCUC		1646-1668

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AD-1707469.1	GAGGAAGCAGAUAGAUGGUCU		1649-1669	AGACCATCUAUCUGCUUCCUCCU		1647-1669
AD-1707470.1	AGGAAGCAGAUAGAUGGUCCU		1650-1670	AGGACCAUCUATCUGCUUCCUCC		1648-1670
AD-1707471.1	GGAAGCAGAUAGAUGGUCCAU		1651-1671	ATGGACCAUCUAUCUGCUUCCUC		1649-1671
AD-1707472.1	GAAGCAGAUAGAUGGUCCAGU		1652-1672	ACUGGACCAUCTAUCUGCUUCCU		1650-1672
AD-1707473.1	AAGCAGAUAGAUGGUCCAGCU		1653-1673	AGCUGGACCAUCUAUCUGCUUCC		1651-1673
AD-1707474.1	AGCAGAUAGAUGGUCCAGCAU		1654-1674	ATGCTGGACCATCUAUCUGCUUC		1652-1674
AD-1707475.1	GCAGAUAGAUGGUCCAGCAGU		1655-1675	ACUGCUGGACCAUCUAUCUGCUU		1653-1675
AD-1707476.1	CAGAUAGAUGGUCCAGCAGGU		1656-1676	ACCUGCTGGACCAUCUAUCUGCU		1654-1676
AD-1707477.1	AGAUAGAUGGUCCAGCAGGCU		1657-1677	AGCCTGCUGGACCAUCUAUCUGC		1655-1677
AD-1707478.1	GAUAGAUGGUCCAGCAGGCUU		1658-1678	AAGCCUGCUGGACCAUCUAUCUG		1656-1678
AD-1707479.1	AUAGAUGGUCCAGCAGGCUUU		1659-1679	AAAGCCTGCUGGACCAUCUAUCU		1657-1679
AD-1707480.1	UAGAUGGUCCAGCAGGCUUGU		1660-1680	ACAAGCCUGCUGGACCAUCUAUC		1658-1680
AD-1707481.1	AGAUGGUCCAGCAGGCUUGAU		1661-1681	ATCAAGCCUGCTGGACCAUCUAU		1659-1681
AD-1707482.1	GAUGGUCCAGCAGGCUUGAAU		1662-1682	ATUCAAGCCUGCUGGACCAUCUA		1660-1682
AD-1707483.1	AUGGUCCAGCAGGCUUGAAGU		1663-1683	ACUUCAAGCCUGCUGGACCAUCU		1661-1683
AD-1707484.1	UGGUCCAGCAGGCUUGAAGCU		1664-1684	AGCUTCAAGCCTGCUGGACCAUC		1662-1684
AD-1707485.1	GGUCCAGCAGGCUUGAAGCAU		1665-1685	ATGCTUCAAGCCUGCUGGACCAU		1663-1685
AD-1707486.1	GUCCAGCAGGCUUGAAGCAGU		1666-1686	ACUGCUTCAAGCCUGCUGGACCA		1664-1686
AD-1707553.1	AAGGUCAAGAGGGAGAUGGGU		1733-1753	ACCCAUCUCCCTCUUGACCUUCC		1731-1753
AD-1707554.1	AGGUCAAGAGGGAGAUGGGCU		1734-1754	AGCCCATCUCCCUCUUGACCUUC		1732-1754
AD-1707555.1	GGUCAAGAGGGAGAUGGGCAU		1735-1755	ATGCCCAUCUCCCUCUUGACCUU		1733-1755
AD-1707556.1	GUCAAGAGGGAGAUGGGCAAU		1736-1756	ATUGCCCAUCUCCCUCUUGACCU		1734-1756
AD-1707557.1	UCAAGAGGGAGAUGGGCAAGU		1737-1757	ACUUGCCCAUCTCCCUCUUGACC		1735-1757
AD-1707577.1	GCGCUGAGGGAGGAUGCUUAU		1757-1777	ATAAGCAUCCUCCCUCAGCGCCU		1755-1777
AD-1707578.1	CGCUGAGGGAGGAUGCUUAGU		1758-1778	ACUAAGCAUCCTCCCUCAGCGCC		1756-1778
AD-1707605.1	GCACUAAGCCUAAGAAGUUCU		1811-1831	AGAACUTCUUAGGCUUAGUGCCU		1809-1831
AD-1707606.1	CACUAAGCCUAAGAAGUUCCU		1812-1832	AGGAACTUCUUAGGCUUAGUGCC		1810-1832

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AD-1707623.1	ACAGGACCCACUGGGAGACAU		1849-1869	ATGUCUCCCAGTGGGUCCUGUCC		1847-1869
AD-1707624.1	CAGGACCCACUGGGAGACAAU		1850-1870	ATUGTCTCCCAGUGGGUCCUGUC		1848-1870
AD-1707625.1	AGGACCCACUGGGAGACAAGU		1851-1871	ACUUGUCUCCCAGUGGGUCCUGU		1849-1871
AD-1707626.1	GGACCCACUGGGAGACAAGCU		1852-1872	AGCUTGTCUCCCAGUGGGUCCUG		1850-1872
AD-1707627.1	GACCCACUGGGAGACAAGCAU		1853-1873	ATGCTUGUCUCCCAGUGGGUCCU		1851-1873
AD-1707628.1	ACCCACUGGGAGACAAGCAUU		1854-1874	AAUGCUTGUCUCCCAGUGGGUCC		1852-1874
AD-1707629.1	CCCACUGGGAGACAAGCAUUU		1855-1875	AAAUGCTUGUCTCCCAGUGGGUC		1853-1875
AD-1707630.1	CCACUGGGAGACAAGCAUUUU		1856-1876	AAAATGCUUGUCUCCCAGUGGGU		1854-1876
AD-1707631.1	CACUGGGAGACAAGCAUUUAU		1857-1877	ATAAAUGCUUGTCUCCCAGUGGG		1855-1877
AD-1707632.1	ACUGGGAGACAAGCAUUUAUU		1858-1878	AAUAAATGCUUGUCUCCCAGUGG		1856-1878
AD-1707633.1	CUGGGAGACAAGCAUUUAUAU		1859-1879	ATAUAAAUGCUTGUCUCCCAGUG		1857-1879
AD-1707634.1	UGGGAGACAAGCAUUUAUACU		1860-1880	AGUATAAAUGCTUGUCUCCCAGU		1858-1880
AD-1707636.1	GGAGACAAGCAUUUAUACUUU		1862-1882	AAAGTATAAAUGCUUGUCUCCCA		1860-1882
AD-1707637.1	GAGACAAGCAUUUAUACUUUU		1863-1883	AAAAGUAUAAATGCUUGUCUCCC		1861-1883
AD-1707638.1	AGACAAGCAUUUAUACUUUCU		1864-1884	AGAAAGTAUAAAUGCUUGUCUCC		1862-1884
AD-1707639.1	GACAAGCAUUUAUACUUUCUU		1865-1885	AAGAAAGUAUAAAUGCUUGUCUC		1863-1885
AD-1707640.1	ACAAGCAUUUAUACUUUCUUU		1866-1886	AAAGAAAGUAUAAAUGCUUGUCU		1864-1886
AD-1707641.1	CAAGCAUUUAUACUUUCUUUU		1867-1887	AAAAGAAAGUATAAAUGCUUGUC		1865-1887
AD-1708118.1	CCAGACAUGAGCUGUGAGGGU		44373	ACCCTCACAGCUCAUGUCUGGCU		44312
AD-1708120.1	AGACAUGAGCUGUGAGGGUCU		860-880	AGACCCTCACAGCUCAUGUCUGG		858-880
AD-1708124.1	AUGAGCUGUGAGGGUCAAGCU		864-884	AGCUTGACCCUCACAGCUCAUGU		862-884
AD-1708126.1	GAGCUGUGAGGGUCAAGCACU		866-886	AGUGCUTGACCCUCACAGCUCAU		864-886
AD-1708127.1	AGCUGUGAGGGUCAAGCACAU		15-35	AUGUGCTUGACCCUCACAGCUCA		13-35
AD-1708130.1	UGUGAGGGUCAAGCACAGCUU		870-890	AAGCTGTGCUUGACCCUCACAGC		868-890
AD-1708132.1	UGAGGGUCAAGCACAGCUAUU		20-40	AAUAGCTGUGCUUGACCCUCACA		18-40
AD-1708135.1	GGGUCAAGCACAGCUAUCCAU		23-43	AUGGAUAGCUGUGCUUGACCCUC		21-43
AD-1708140.1	AAGCACAGCUAUCCAUCAGAU		28-48	AUCUGATGGAUAGCUGUGCUUGA		26-48

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AD-1708143.1	CACAGCUAUCCAUCAGAUGAU		31-51	AUCATCTGAUGGAUAGCUGUGCU		29-51
AD-1708145.1	CAGCUAUCCAUCAGAUGAUCU		33-53	AGAUCATCUGAUGGAUAGCUGUG		31-53
AD-1708146.1	AGCUAUCCAUCAGAUGAUCUU		886-906	AAGATCAUCUGAUGGAUAGCUGU		884-906
AD-1708148.1	CUAUCCAUCAGAUGAUCUACU		36-56	AGUAGATCAUCUGAUGGAUAGCU		34-56
AD-1708149.1	UAUCCAUCAGAUGAUCUACUU		37-57	AAGUAGAUCAUCUGAUGGAUAGC		35-57
AD-1708151.1	UCCAUCAGAUGAUCUACUUUU		891-911	AAAAGUAGAUCAUCUGAUGGAUA		889-911
AD-1708152.1	CCAUCAGAUGAUCUACUUUCU		892-912	AGAAAGTAGAUCAUCUGAUGGAU		890-912
AD-1708156.1	CAGAUGAUCUACUUUCAGCCU		44-64	AGGCTGAAAGUAGAUCAUCUGAU		42-64
AD-1708158.1	GAUGAUCUACUUUCAGCCUUU		46-66	AAAGGCTGAAAGUAGAUCAUCUG		44-66
AD-1708163.1	UCUACUUUCAGCCUUCCUGAU		51-71	AUCAGGAAGGCUGAAAGUAGAUC		49-71
AD-1708166.1	ACUUUCAGCCUUCCUGAGUCU		54-74	AGACTCAGGAAGGCUGAAAGUAG		52-74
AD-1708170.1	UCAGCCUUCCUGAGUCCCAGU		910-930	ACUGGGACUCAGGAAGGCUGAAA		908-930
AD-1708220.1	GUGGCAGUGGUGUCUGCUGUU		120-140	AACAGCAGACACCACUGCCACAC		118-140
AD-1708223.1	GCAGUGGUGUCUGCUGUCACU		123-143	AGUGACAGCAGACACCACUGCCA		121-143
AD-1708225.1	AGUGGUGUCUGCUGUCACUGU		125-145	ACAGTGACAGCAGACACCACUGC		123-145
AD-1708227.1	UGGUGUCUGCUGUCACUGUGU		127-147	ACACAGTGACAGCAGACACCACU		125-147
AD-1708245.1	GACUCAACAGACGGAGCAACU		170-190	AGUUGCTCCGUCUGUUGAGUCUG		168-190
AD-1708248.1	UCAACAGACGGAGCAACUGCU		173-193	AGCAGUTGCUCCGUCUGUUGAGU		171-193
AD-1708249.1	CAACAGACGGAGCAACUGCCU		1026-1046	AGGCAGTUGCUCCGUCUGUUGAG		1024-1046
AD-1708251.1	ACAGACGGAGCAACUGCCAUU		176-196	AAUGGCAGUUGCUCCGUCUGUUG		174-196
AD-1708255.1	ACGGAGCAACUGCCAUCCGAU		180-200	AUCGGATGGCAGUUGCUCCGUCU		178-200
AD-1708260.1	GCAACUGCCAUCCGAGGCUCU		185-205	AGAGCCTCGGAUGGCAGUUGCUC		183-205
AD-1708342.1	CAAGCAGAACGAGCUCUGGUU		339-359	AACCAGAGCUCGUUCUGCUUGGG		337-359
AD-1708344.1	AGCAGAACGAGCUCUGGUGCU		341-361	AGCACCAGAGCUCGUUCUGCUUG		339-361
AD-1708347.1	AGAACGAGCUCUGGUGCUGGU		1196-1216	ACCAGCACCAGAGCUCGUUCUGC		1194-1216
AD-1708350.1	ACGAGCUCUGGUGCUGGAGCU		347-367	AGCUCCAGCACCAGAGCUCGUUC		345-367
AD-1708356.1	UCUGGUGCUGGAGCUAGCCAU		1205-1225	AUGGCUAGCUCCAGCACCAGAGC		1203-1225

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO.	Range in NM_031479.5	Antisense Strand Sequence 5' to 3'	SEQ ID NO.	Range in NM_031479.5
AD-1708357.1	CUGGUGCUGGAGCUAGCCAAU		354-374	AUUGGCTAGCUCCAGCACCAGAG		352-374
AD-1708361.1	UGCUGGAGCUAGCCAAGCAGU		358-378	ACUGCUTGGCUAGCUCCAGCACC		356-378
AD-1708365.1	GGAGCUAGCCAAGCAGCAAAU		362-382	AUUUGCTGCUUGGCUAGCUCCAG		360-382
AD-1708368.1	GCUAGCCAAGCAGCAAAUCCU		365-385	AGGATUTGCUGCUUGGCUAGCUC		363-385
AD-1708369.1	CUAGCCAAGCAGCAAAUCCUU		366-386	AAGGAUTUGCUGCUUGGCUAGCU		364-386
AD-1708397.1	UGACCAGUCGUCCCAGAAUAU		1252-1272	AUAUTCTGGGACGACUGGUCAGG		1250-1272
AD-1708399.1	ACCAGUCGUCCCAGAAUAACU		402-422	AGUUAUTCUGGGACGACUGGUCA		400-422
AD-1708401.1	CAGUCGUCCCAGAAUAACUCU		1256-1276	AGAGTUAUUCUGGGACGACUGGU		1254-1276
AD-1708402.1	AGUCGUCCCAGAAUAACUCAU		405-425	AUGAGUTAUUCUGGGACGACUGG		403-425
AD-1708403.1	GUCGUCCCAGAAUAACUCAUU		406-426	AAUGAGTUAUUCUGGGACGACUG		404-426
AD-1708405.1	CGUCCCAGAAUAACUCAUCCU		408-428	AGGATGAGUUAUUCUGGGACGAC		406-428
AD-1708407.1	UCCCAGAAUAACUCAUCCUCU		410-430	AGAGGATGAGUUAUUCUGGGACG		408-430
AD-1708408.1	CCCAGAAUAACUCAUCCUCCU		1263-1283	AGGAGGAUGAGUUAUUCUGGGAC		1261-1283
AD-1708447.1	GGGAGUGUGGGCUCCCAGGGAAU		474-494	AUUCCCTGGAGCCACACUCCCUG		472-494
AD-1708454.1	GAGGUCAUCAGCUUUGCUACU		501-521	AGUAGCAAAGCUGAUGACCUCCU		499-521
AD-1708457.1	GUCAUCAGCUUUGCUACUGUU		504-524	AACAGUAGCAAAGCUGAUGACCU		502-524
AD-1708458.1	UCAUCAGCUUUGCUACUGUCU		1357-1377	AGACAGTAGCAAAGCUGAUGACC		1355-1377
AD-1708462.1	CAGCUUUGCUACUGUCACAGU		1361-1381	ACUGTGACAGUAGCAAAGCUGAU		1359-1381
AD-1708464.1	GCUUUGCUACUGUCACAGACU		511-531	AGUCTGTGACAGUAGCAAAGCUG		509-531
AD-1708466.1	UUUGCUACUGUCACAGACUCU		513-533	AGAGTCTGUGACAGUAGCAAAGC		511-533
AD-1708468.1	UGCUACUGUCACAGACUCCAU		515-535	AUGGAGTCUGUGACAGUAGCAAA		513-535
AD-1708473.1	CUGUCACAGACUCCACUUCAU		520-540	AUGAAGTGGAGUCUGUGACAGUA		518-540
AD-1708476.1	UCACAGACUCCACUUCAGCCU		523-543	AGGCTGAAGUGGAGUCUGUGACA		521-543
AD-1708478.1	ACAGACUCCACUUCAGCCUAU		525-545	AUAGGCTGAAGUGGAGUCUGUGA		523-545
AD-1708482.1	ACUCCACUUCAGCCUACAGCU		529-549	AGCUGUAGGCUGAAGUGGAGUCU		527-549
AD-1708483.1	CUCCACUUCAGCCUACAGCUU		530-550	AAGCTGTAGGCUGAAGUGGAGUC		528-550
AD-1708485.1	CCACUUCAGCCUACAGCUCCU		532-552	AGGAGCTGUAGGCUGAAGUGGAG		530-552

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AD-1708559.1	UGGCACUCUUUGCUUGAGGAU		635-655	AUCCUCAAGCAAAGAGUGCCAGG		633-655
AD-1708561.1	GCACUCUUUGCUUGAGGAUCU		637-657	AGAUCCUCAAGCAAAGAGUGCCA		635-657
AD-1708564.1	CUCUUUGCUUGAGGAUCUUCU		640-660	AGAAGATCCUCAAGCAAAGAGUG		638-660
AD-1708565.1	UCUUUGCUUGAGGAUCUUCCU		641-661	AGGAAGAUCCUCAAGCAAAGAGU		639-661
AD-1708567.1	UUUGCUUGAGGAUCUUCCGAU		643-663	AUCGGAAGAUCCUCAAGCAAAGA		641-663
AD-1708647.1	UGGCUGAGCACCACACAUCACCU		1555-1575	AGGUGATGUGGUGCUCAGCCAGG		1553-1575
AD-1708648.1	GGCUGAGCACCACACAUCACCAU		1556-1576	AUGGTGAUGUGGUGCUCAGCCAG		1554-1576
AD-1708650.1	CUGAGCACCACACAUCACCAACU		706-726	AGUUGGTGAUGUGGUGCUCAGCC		704-726
AD-1708657.1	CCACAUCACCACAACCUGGGCUU		713-733	AAGCCCAGGUUGGUGAUGUGGUG		711-733
AD-1708662.1	UCACCAACCUGGGCUGGCAUU		1570-1590	AAUGCCAGCCCAGGUUGGUGAUG		1568-1590
AD-1708680.1	CCUUAACUCUGCCCUCUAGUU		739-759	AACUAGAGGGCAGAGUUAAGGUA		737-759
AD-1708683.1	UAACUCUGCCCUCUAGUGGCU		742-762	AGCCACTAGAGGGCAGAGUUAAG		740-762
AD-1708697.1	GUCUGGUGUCCUGAAACUGCU		1628-1648	AGCAGUTUCAGGACACCAGACUU		1626-1648
AD-1708698.1	UCUGGUGUCCUGAAACUGCAU		1629-1649	AUGCAGTUUCAGGACACCAGACU		1627-1649
AD-1708700.1	UGGUGUCCUGAAACUGCAACU		779-799	AGUUGCAGUUUCAGGACACCAGA		777-799
AD-1708704.1	GUCCUGAAACUGCAACUAGAU		783-803	AUCUAGTUGCAGUUUCAGGACAC		781-803
AD-1708706.1	CCUGAAACUGCAACUAGACUU		785-805	AAGUCUAGUUGCAGUUUCAGGAC		783-805
AD-1708707.1	CUGAAACUGCAACUAGACUGU		786-806	ACAGTCTAGUUGCAGUUUCAGGA		784-806
AD-1708709.1	GAAACUGCAACUAGACUGCAU		788-808	AUGCAGTCUAGUUGCAGUUUCAG		786-808
AD-1708711.1	AACUGCAACUAGACUGCAGAU		790-810	AUCUGCAGUCUAGUUGCAGUUUC		788-810
AD-1708719.1	GCAACAGCACAGUUACUGGAU		820-840	AUCCAGTAACUGUGCUGUUGCCU		818-840
AD-1708721.1	AACAGCACAGUUACUGGACAU		1677-1697	AUGUCCAGUAACUGUGCUGUUGC		1675-1697
AD-1708724.1	AGCACAGUUACUGGACAACCU		825-845	AGGUTGTCCAGUAACUGUGCUGU		823-845
AD-1708746.1	UUGGACACAGCAGGACACCAU		855-875	AUGGTGTCCUGCUGUGUCCAAGA		853-875
AD-1708748.1	GGACACAGCAGGACACCAGCU		1712-1732	AGCUGGTGUCCUGCUGUGUCCAA		1710-1732
AD-1708751.1	CACAGCAGGACACCAGCAGCU		860-880	AGCUGCTGGUGUCCUGCUGUGUC		858-880
AD-1708759.1	GACACCAGCAGCCCUUCCUAU		868-888	AUAGGAAGGGCUGCUGGUGUCCU		866-888

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AD-1708763.1	CCAGCAGCCCUUCCUAGAGCU		872-892	AGCUCUAGGAAGGGCUGCUGGUG		870-892
AD-1708764.1	CAGCAGCCCUUCCUAGAGCUU		873-893	AAGCTCTAGGAAGGGCUGCUGGU		871-893
AD-1708766.1	GCAGCCCUUCCUAGAGCUUAU		1730-1750	AUAAGCTCUAGGAAGGGCUGCUG		1728-1750
AD-1708771.1	CCUUCCUAGAGCUUAAGAUCU		880-900	AGAUCUTAAGCUCUAGGAAGGGC		878-900
AD-1708813.1	UUACGUAGACUUCCAGGAACU		986-1006	AGUUCCTGGAAGUCUACGUAAUG		984-1006
AD-1708819.1	AGACUUCCAGGAACUGGGAUU		992-1012	AAUCCCAGUUCCUGGAAGUCUAC		990-1012
AD-1708842.1	GUACCAGCUGAAUUACUGCAU		1040-1060	AUGCAGTAAUUCAGCUGGUACCC		1038-1060
AD-1708844.1	ACCAGCUGAAUUACUGCAGUU		1042-1062	AACUGCAGUAAUUCAGCUGGUAC		1040-1062
AD-1708849.1	CUGAAUUACUGCAGUGGGCAU		1047-1067	AUGCCCACUGCAGUAAUUCAGCU		1045-1067
AD-1708856.1	ACUGCAGUGGGCAGUGCCCUU		1054-1074	AAGGGCACUGCCCACUGCAGUAA		1052-1074
AD-1708872.1	CAGGCAUUGCUGCCUCUUUCU		1093-1113	AGAAAGAGGCAGCAAUGCCUGGG		1091-1113
AD-1708875.1	CAUUGCUGCCUCUUUCCAUUU		1097-1117	AAAUGGAAAGAGGCAGCAAUGCC		1095-1117
AD-1708882.1	GCCUCUUUCCAUUCUGCCGUU		1104-1124	AACGGCAGAAUGGAAAGAGGCAG		1102-1124
AD-1708887.1	UUUCCAUUCUGCCGUCUUCAU		1109-1129	AUGAAGACGGCAGAAUGGAAAGA		1107-1129
AD-1708889.1	UCCAUUCUGCCGUCUUCAGCU		1111-1131	AGCUGAAGACGGCAGAAUGGAAA		1109-1131
AD-1708890.1	CCAUUCUGCCGUCUUCAGCCU		1112-1132	AGGCTGAAGACGGCAGAAUGGAA		1110-1132
AD-1708899.1	CGUCUUCAGCCUCCUCAAAGU		1121-1141	ACUUTGAGGAGGCUGAAGACGGC		1119-1141
AD-1708901.1	UCUUCAGCCUCCUCAAAGCCU		1978-1998	AGGCTUTGAGGAGGCUGAAGACG		1976-1998
AD-1708902.1	CUUCAGCCUCCUCAAAGCCAU		1979-1999	AUGGCUTUGAGGAGGCUGAAGAC		1977-1999
AD-1708907.1	GCCUCCUCAAAGCCAACAAUU		1129-1149	AAUUGUTGGCUUUGAGGAGGCUG		1127-1149
AD-1708908.1	CCUCCUCAAAGCCAACAAUCU		1130-1150	AGAUTGTTGGCUUUGAGGAGGCU		1128-1150
AD-1708911.1	CCUCAAAGCCAACAAUCCUUU		1133-1153	AAAGGATUGUUGGCUUUGAGGAG		1131-1153
AD-1708921.1	AACAAUCCUUGGCCUGCCAGU		1143-1163	ACUGGCAGGCCAAGGAUUGUUGG		1141-1163
AD-1708956.1	UCUCCUCUACCUGGAUCAUAU		2057-2077	AUAUGATCCAGGUAGAGGAGAGA		2055-2077
AD-1708957.1	CUCCUCUACCUGGAUCAUAAU		1203-1223	AUUATGAUCCAGGUAGAGGAGAG		1201-1223
AD-1708962.1	CUACCUGGAUCAUAAUGGCAU		2063-2083	AUGCCATUAUGAUCCAGGUAGAG		2061-2083
AD-1708963.1	UACCUGGAUCAUAAUGGCAAU		1209-1229	AUUGCCAUUAUGAUCCAGGUAGA		1207-1229

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AD-1708971.1	UCAUAAUGGCAAUGUGGUCAU		2072-2092	AUGACCACAUUGCCAUUAUGAUC		2070-2092
AD-1708974.1	UAAUGGCAAUGUGGUCAAGAU		1220-1240	AUCUUGACCACAUUGCCAUUAUG		1218-1240
AD-1708976.1	AUGGCAAUGUGGUCAAGACGU		1222-1242	ACGUCUUGACCACAUUGCCAUUA		1220-1242
AD-1708977.1	UGGCAAUGUGGUCAAGACGGU		2078-2098	ACCGUCUUGACCACAUUGCCAUU		2076-2098
AD-1708984.1	GUGGUCAAGACGGAUGUGCCU		2085-2105	AGGCACAUCCGUCUUGACCACAU		2083-2105
AD-1708986.1	GGUCAAGACGGAUGUGCCAGU		2087-2107	ACUGGCACAUCCGUCUUGACCAC		2085-2107
AD-1708990.1	AAGACGGAUGUGCCAGAUAUU		1236-1256	AAUAUCUGGCACAUCCGUCUUGA		1234-1256
AD-1709009.1	UGGUGGUGGAGGCCUGUGGCU		1255-1275	AGCCACAGGCCUCCACCACCAUA		1253-1275
AD-1709021.1	CCUGUGGCUGCAGCUAGCAAU		1267-1287	AUUGCUAGCUGCAGCCACAGGCC		1265-1287
AD-1709022.1	CUGUGGCUGCAGCUAGCAAGU		2123-2143	ACUUGCUAGCUGCAGCCACAGGC		2121-2143
AD-1709026.1	GGCUGCAGCUAGCAAGAGGAU		1272-1292	AUCCUCUUGCUAGCUGCAGCCAC		1270-1292
AD-1709028.1	CUGCAGCUAGCAAGAGGACCU		1274-1294	AGGUCCUCUUGCUAGCUGCAGCC		1272-1294
AD-1709031.1	CAGCUAGCAAGAGGACCUGGU		1277-1297	ACCAGGUCCUCUUGCUAGCUGCA		1275-1297
AD-1709032.1	GCUUUGGAGUGAAGAGACCAU		2153-2173	AUGGUCUCUUCACUCCAAAGCCC		2151-2173
AD-1709034.1	UUUGGAGUGAAGAGACCAAGU		2155-2175	ACUUGGUCUCUUCACUCCAAAGC		2153-2175
AD-1709038.1	GAGUGAAGAGACCAAGAUGAU		2159-2179	AUCAUCUUGGUCUCUUCACUCCA		2157-2179
AD-1709041.1	UGAAGAGACCAAGAUGAAGUU		1307-1327	AACUUCAUCUUGGUCUCUUCACU		1305-1327
AD-1709044.1	AGAGACCAAGAUGAAGUUUCU		1310-1330	AGAAACUUCAUCUUGGUCUCUUC		1308-1330
AD-1709052.1	AGAUGAAGUUUCCCAGGCACU		2173-2193	AGUGCCUGGGAAACUUCAUCUUG		2171-2193
AD-1709056.1	GAAGUUUCCCAGGCACAGGGU		1322-1342	ACCCUGUGCCUGGGAAACUUCAU		1320-1342
AD-1709090.1	ACCCAACAACCACCUGGCAAU		1383-1403	AUUGCCAGGUGGUUGUUGGGUUG		1381-1403
AD-1709097.1	AACCACCUGGCAAUAUGACUU		1390-1410	AAGUCAUAUUGCCAGGUGGUUGU		1388-1410
AD-1709098.1	ACCACCUGGCAAUAUGACUCU		2246-2266	AGAGUCAUAUUGCCAGGUGGUUG		2244-2266
AD-1709100.1	CACCUGGCAAUAUGACUCACU		1393-1413	AGUGAGUCAUAUUGCCAGGUGGU		1391-1413
AD-1709102.1	CCUGGCAAUAUGACUCACUUU		1395-1415	AAAGUGAGUCAUAUUGCCAGGUG		1393-1415
AD-1709104.1	UGGCAAUAUGACUCACUUGAU		1397-1417	AUCAAGUGAGUCAUAUUGCCAGG		1395-1417
AD-1709106.1	GCAAUAUGACUCACUUGACCU		1399-1419	AGGUCAAGUGAGUCAUAUUGCCA		1397-1419

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AD-1709111.1	GGACCCAAAUGGGCACUUUCU		1425-1445	AGAAAGTGCCCAUUUGGGUCCCA		1423-1445
AD-1709120.1	UGGGCACUUUCUUGUCUGAGU		2289-2309	ACUCAGACAAGAAAGUGCCCAUU		2287-2309
AD-1709122.1	GGCACUUUCUUGUCUGAGACU		1436-1456	AGUCTCAGACAAGAAAGUGCCCA		1434-1456
AD-1709124.1	CACUUUCUUGUCUGAGACUCU		1438-1458	AGAGTCTCAGACAAGAAAGUGCC		1436-1458
AD-1709126.1	CUUUCUUGUCUGAGACUCUGU		1440-1460	ACAGAGTCUCAGACAAGAAAGUG		1438-1460
AD-1709128.1	UUCUUGUCUGAGACUCUGGCU		1442-1462	AGCCAGAGUCUCAGACAAGAAAG		1440-1462
AD-1709130.1	CUUGUCUGAGACUCUGGCUUU		2299-2319	AAAGCCAGAGUCUCAGACAAGAA		2297-2319
AD-1709148.1	UAUUCCAGGUUGGCUGAUGUU		1463-1483	AACATCAGCCAACCUGGAAUAAG		1461-1483
AD-1709151.1	UCCAGGUUGGCUGAUGUGUUU		1466-1486	AAACACAUCAGCCAACCUGGAAU		1464-1486
AD-1709201.1	CUCUCUCCUCUACCUGGAUCU		1199-1219	AGAUCCAGGUAGAGGAGAGAGAG		1197-1219
AD-1709237.1	GAUUUCCUGCCCUAAGUCCUU		1534-1554	AAGGACTUAGGGCAGGAAAUCAU		1532-1554
AD-1709239.1	UUUCCUGCCCUAAGUCCUGUU		1536-1556	AACAGGACUUAGGGCAGGAAAUC		1534-1556
AD-1709253.1	AGAAGAUGUCAGGGACUAGGU		1557-1577	ACCUAGTCCCUGACAUCUUCUCA		1555-1577
AD-1709254.1	AAGAUGUCAGGGACUAGGGAU		1559-1579	AUCCCUAGUCCCUGACAUCUUCU		1557-1579
AD-1709298.1	AGGAGGAAGCAGAUAGAUGGU		1647-1667	ACCATCTAUCUGCUUCCUCCUCC		1645-1667
AD-1709300.1	GAGGAAGCAGAUAGAUGGUCU		1649-1669	AGACCATCUAUCUGCUUCCUCCU		1647-1669
AD-1709301.1	AGGAAGCAGAUAGAUGGUCCU		2499-2519	AGGACCAUCUAUCUGCUUCCUCC		2497-2519
AD-1709304.1	AAGCAGAUAGAUGGUCCAGCU		2502-2522	AGCUGGACCAUCUAUCUGCUUCC		2500-2522
AD-1709307.1	CAGAUAGAUGGUCCAGCAGGU		1656-1676	ACCUGCTGGACCAUCUAUCUGCU		1654-1676
AD-1709310.1	AUAGAUGGUCCAGCAGGCUUU		1659-1679	AAAGCCTGCUGGACCAUCUAUCU		1657-1679
AD-1709314.1	AUGGUCCAGCAGGCUUGAAGU		1663-1683	ACUUCAAGCCUGCUGGACCAUCU		1661-1683
AD-1709315.1	UGGUCCAGCAGGCUUGAAGCU		2513-2533	AGCUTCAAGCCUGCUGGACCAUC		2511-2533
AD-1709317.1	GUCCAGCAGGCUUGAAGCAGU		1666-1686	ACUGCUTCAAGCCUGCUGGACCA		1664-1686
AD-1709372.1	GGUCAAGAGGGAGAUGGGCAU		2584-2604	AUGCCCAUCUCCCUCUUGACCUU		2582-2604
AD-1709390.1	GCGCUGAGGGAGGAUGCUUAU		1757-1777	AUAAGCAUCCUCCCUCAGCGCCU		1755-1777
AD-1709410.1	GCACUAAGCCUAAGAAGUUCU		1811-1831	AGAACUTCUUAGGCUUAGUGCCU		1809-1831
AD-1709411.1	CACUAAGCCUAAGAAGUUCCU		1812-1832	AGGAACTUCUUAGGCUUAGUGCC		1810-1832

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO.	Range in NM_031479.5	Antisense Strand Sequence 5' to 3'	SEQ ID NO.	Range in NM_031479.5
AD-1709429.1	CAGGACCCACUGGGAGACAAU		1850-1870	AUUGTCTCCCAGUGGGUCCUGUC		1848-1870
AD-1709431.1	GGACCCACUGGGAGACAAGCU		2701-2721	AGCUTGTCUCCCAGUGGGUCCUG		2699-2721
AD-1709433.1	ACCCACUGGGAGACAAGCAUU		1854-1874	AAUGCUTGUCUCCCAGUGGGUCC		1852-1874
AD-1709434.1	CCCACUGGGAGACAAGCAUUU		1855-1875	AAAUGCTUGUCUCCCAGUGGGUC		1853-1875
AD-1709442.1	GAGACAAGCAUUUAUACUUUU		2712-2732	AAAAGUAUAAAUGCUUGUCUCCC		2710-2732
AD-1709443.1	AGACAAGCAUUUAUACUUUCU		1864-1884	AGAAAGTAUAAAUGCUUGUCUCC		1862-1884
AD-1709502.1	AGGUCAAGAGGGAGAUGGGCU		1734-1754	AGCCCATCUCCCUCUUGACCUUC		1732-1754
AD-1711741.1	CAAGCACAGCUAUCCAUCAGU		27-47	ACUGAUGGAUAGCUGUGCUUGCU		25-47
AD-1711742.1	AUCUACUUUCAGCCUUCCUGU		50-70	ACAGGAAGGCUGAAAGUAGAUCU		48-70
AD-1711743.1	AGCCAAGCAGCAAAUCCUGGU		368-388	ACCAGGAUUUGCUGCUUGGCUCU		366-388
AD-1711744.1	ACCAGUCGUCCCAGAAUAACU		402-422	AGUUAUTCUGGGACGACUGGUCU		400-422
AD-1711745.1	CCUGGCACUCUUUGCUUGAGU		633-653	ACUCAAGCAAAGAGUGCCAGGCU		631-653
AD-1711746.1	CUGGCACUCUUUGCUUGAGGU		634-654	ACCUCAAGCAAAGAGUGCCAGCU		632-654
AD-1711747.1	CUUUGCUUGAGGAUCUUCCGU		642-662	ACGGAAGAUCCTCAAGCAAAGCU		640-662
AD-1711748.1	UUUGCUUGAGGAUCUUCCGAU		643-663	ATCGGAAGAUCCUCAAGCAAACU		641-663
AD-1711749.1	UUGCUUGAGGAUCUUCCGAUU		644-664	AAUCGGAAGAUCCUCAAGCAACU		642-664
AD-1711750.1	UGCUUGAGGAUCUUCCGAUGU		645-665	ACAUCGGAAGATCCUCAAGCACU		643-665
AD-1711751.1	GCUUGAGGAUCUUCCGAUGGU		646-666	ACCATCGGAAGAUCCUCAAGCCU		644-666
AD-1711752.1	AGCACCACAUCACCAACCUGU		709-729	ACAGGUTGGUGAUGUGGUGCUCU		707-729
AD-1711753.1	ACGUAGACUUCCAGGAACUGU		988-1008	ACAGTUCCUGGAAGUCUACGUCU		986-1008
AD-1711754.1	CGUAGACUUCCAGGAACUGGU		989-1009	ACCAGUTCCUGGAAGUCUACGCU		987-1009
AD-1711755.1	GACUUCCAGGAACUGGGAUGU		993-1013	ACAUCCCAGUUCCUGGAAGUCCU		991-1013
AD-1711756.1	UGCUGCCUCUUUCCAUUCUGU		1100-1120	ACAGAATGGAAAGAGGCAGCACU		1098-1120
AD-1711757.1	GCUGCCUCUUUCCAUUCUGCU		1101-1121	AGCAGAAUGGAAAGAGGCAGCCU		1099-1121
AD-1711758.1	CUGCCUCUUUCCAUUCUGCCU		1102-1122	AGGCAGAAUGGAAAGAGGCAGCU		1100-1122
AD-1711759.1	UUCCAUUCUGCCGUCUUCAGU		1110-1130	ACUGAAGACGGCAGAAUGGAACU		1108-1130
AD-1711760.1	CCUCAAAGCCAACAAUCCUUU		1133-1153	AAAGGATUGUUGGCUUUGAGGCU		1131-1153

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO.	Range in NM_031479.5	Antisense Strand Sequence 5' to 3'	SEQ ID NO.	Range in NM_031479.5
AD-1711761.1	CUCAAAGCCAACAAUCCUUGU		1134-1154	ACAAGGAUUGUTGGCUUUGAGCU		1132-1154
AD-1711762.1	UGUGUCCCUACUGCCCGAAGU		1173-1193	ACUUCGGGCAGTAGGGACACACU		1171-1193
AD-1711763.1	GUGUCCCUACUGCCCGAAGGU		1174-1194	ACCUTCGGGCAGUAGGGACACCU		1172-1194
AD-1711764.1	CCUCUACCUGGAUCAUAAUGU		1205-1225	ACAUTATGAUCCAGGUAGAGGCU		1203-1225
AD-1711765.1	CUCUACCUGGAUCAUAAUGGU		1206-1226	ACCATUAUGAUCCAGGUAGAGCU		1204-1226
AD-1711766.1	GGAUCAUAAUGGCAAUGUGGU		1214-1234	ACCACATUGCCAUUAUGAUCCCU		1212-1234
AD-1711767.1	GAUCAUAAUGGCAAUGUGGUU		1215-1235	AACCACAUUGCCAUUAUGAUCCU		1213-1235
AD-1711768.1	AUGGCAAUGUGGUCAAGACGU		1222-1242	ACGUCUTGACCACAUUGCCAUCU		1220-1242
AD-1711769.1	GGCAAUGUGGUCAAGACGGAU		1224-1244	ATCCGUCUUGACCACAUUGCCCU		1222-1244
AD-1711770.1	GCAAUGUGGUCAAGACGGAUU		1225-1245	AAUCCGTCUUGACCACAUUGCCU		1223-1245
AD-1711771.1	UGCCAGAUAUGGUGGUGGAGU		1246-1266	ACUCCACCACCAUAUCUGGCACU		1244-1266
AD-1711772.1	UGGCUGCAGCUAGCAAGAGGU		1271-1291	ACCUCUTGCUAGCUGCAGCCACU		1269-1291
AD-1711773.1	GGAGUGAAGAGACCAAGAUGU		1303-1323	ACAUCUTGGUCTCUUCACUCCCU		1301-1323
AD-1711774.1	AAGAGACCAAGAUGAAGUUUU		1309-1329	AAAACUTCAUCTUGGUCUCUUCU		1307-1329
AD-1711775.1	UUCCAGGUUGGCUGAUGUGUU		1465-1485	AACACATCAGCCAACCUGGAACU		1463-1485
AD-1711776.1	CCAGGUUGGCUGAUGUGUUGU		1467-1487	ACAACACAUCAGCCAACCUGGCU		1465-1487
AD-1711777.1	CAGGUUGGCUGAUGUGUUGGU		1468-1488	ACCAACACAUCAGCCAACCUGCU		1466-1488
AD-1711778.1	GUCCAGCAGGCUUGAAGCAGU		1666-1686	ACUGCUTCAAGCCUGCUGGACCU		1664-1686
AD-1711779.1	GGAGACAAGCAUUUAUACUUU		1862-1882	AAAGTATAAAUGCUUGUCUCCCU		1860-1882

Table 20. Modified Sense and Antisense Strand Sequences of INHBE dsRNA Agents

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO.	Antisense Strand Sequence 5' to 3'	SEQ ID NO.	mRNA target sequence	SEQ ID NO.
AD-1706265.1	gscscagacaUfGfAfgcugugagguL96		asdCscudCadCagcudCaUfgucuggcsusa		UAGCCAGACAUGAGCUGUGAGGG	
AD-1706266.1	cscsagacauGfAfGfcugugaggguL96		asdCsccdTcdAcagcdTcAfugucuggscsu		AGCCAGACAUGAGCUGUGAGGGU	
AD-1706268.1	asgsacaugaGfCfUfgugagggucuL96		asdGsacdCcdTcacadGcUfcaugucusgsg		CCAGACAUGAGCUGUGAGGGUCA	

AD-1706269.1	gsascaugagCfUfGfugagggucauL96		asdTsgadCcdCucacdAgCfucaugucsusg		CAGACAUGAGCUGUGAGGGUCAA	
AD-1706270.1	ascsaugagcUfGfUfgagggucaauL96		asdTsugdAcdCcucadCaGfcucauguscsu		AGACAUGAGCUGUGAGGGUCAAG	
AD-1706271.1	csasugagcuGfUfGfagggucaaguL96		asdCsuudGadCccucdAcAfgcucaugsusc		GACAUGAGCUGUGAGGGUCAAGC	
AD-1706272.1	asusgagcugUfGfAfgggucaagcuL96		asdGscudTgdAcccudCaCfagcucausgsu		ACAUGAGCUGUGAGGGUCAAGCA	
AD-1706273.1	usgsagcuguGfAfGfggucaagcauL96		asdTsgcdTudGacccdTcAfcagcucasusg		CAUGAGCUGUGAGGGUCAAGCAC	
AD-1706274.1	gsasgcugugAfGfGfgucaagcacuL96		asdGsugdCudTgaccdCuCfacagcucsasu		AUGAGCUGUGAGGGUCAAGCACA	
AD-1706275.1	asgscugugaGfGfGfucaagcacauL96		asdTsgudGcdTugacdCcUfcacagcuscsa		UGAGCUGUGAGGGUCAAGCACAG	
AD-1706276.1	gscsugugagGfGfUfcaagcacaguL96		asdCsugdTgdCuugadCcCfucacagcsusc		GAGCUGUGAGGGUCAAGCACAGC	
AD-1706277.1	csusgugaggGfUfCfaagcacagcuL96		asdGscudGudGcuugdAcCfcucacagscsu		AGCUGUGAGGGUCAAGCACAGCU	
AD-1706278.1	usgsugagggUfCfAfagcacagcuuL96		asdAsgcdTgdTgcuudGaCfccucacasgsc		GCUGUGAGGGUCAAGCACAGCUA	
AD-1706279.1	gsusgaggguCfAfAfgcacagcuauL96		asdTsagdCudGugcudTgAfcccucacsasg		CUGUGAGGGUCAAGCACAGCUAU	
AD-1706280.1	usgsagggucAfAfGfcacagcuauuL96		asdAsuadGcdTgugcdTuGfacccucascsa		UGUGAGGGUCAAGCACAGCUAUC	
AD-1706281.1	gsasgggucaAfGfCfacagcuaucuL96		asdGsaudAgdCugugdCuUfgacccucsasc		GUGAGGGUCAAGCACAGCUAUCC	
AD-1706282.1	asgsggucaaGfCfAfcagcuauccuL96		asdGsgadTadGcugudGcUfugacccuscsa		UGAGGGUCAAGCACAGCUAUCCA	
AD-1706283.1	gsgsgucaagCfAfCfagcuauccauL96		asdTsggdAudAgcugdTgCfuugacccsusc		GAGGGUCAAGCACAGCUAUCCAU	
AD-1706287.1	csasagcacaGfCfUfauccaucaguL96		asdCsugdAudGgauadGcUfgugcuugsasc		GUCAAGCACAGCUAUCCAUCAGA	
AD-1706288.1	asasgcacagCfUfAfuccaucagauL96		asdTscudGadTggaudAgCfugugcuusgsa		UCAAGCACAGCUAUCCAUCAGAU	
AD-1706290.1	gscsacagcuAfUfCfcaucagauguL96		asdCsaudCudGauggdAuAfgcugugcsusu		AAGCACAGCUAUCCAUCAGAUGA	
AD-1706291.1	csascagcuaUfCfCfaucagaugauL96		asdTscadTcdTgaugdGaUfagcugugscsu		AGCACAGCUAUCCAUCAGAUGAU	
AD-1706292.1	ascsagcuauCfCfAfucagaugauuL96		asdAsucdAudCugaudGgAfuagcugusgsc		GCACAGCUAUCCAUCAGAUGAUC	
AD-1706293.1	csasgcuaucCfAfUfcagaugaucuL96		asdGsaudCadTcugadTgGfauagcugsusg		CACAGCUAUCCAUCAGAUGAUCU	
AD-1706294.1	asgscuauccAfUfCfagaugaucuuL96		asdAsgadTcdAucugdAuGfgauagcusgsu		ACAGCUAUCCAUCAGAUGAUCUA	
AD-1706295.1	gscsuauccaUfCfAfgaugaucuauL96		asdTsagdAudCaucudGaUfggauagcsusg		CAGCUAUCCAUCAGAUGAUCUAC	
AD-1706296.1	csusauccauCfAfGfaugaucuacuL96		asdGsuadGadTcaucdTgAfuggauagscsu		AGCUAUCCAUCAGAUGAUCUACU	
AD-1706297.1	usasuccaucAfGfAfugaucuacuuL96		asdAsgudAgdAucaudCuGfauggauasgsc		GCUAUCCAUCAGAUGAUCUACUU	
AD-1706298.1	asusccaucaGfAfUfgaucuacuuuL96		asdAsagdTadGaucadTcUfgauggausasg		CUAUCCAUCAGAUGAUCUACUUU	
AD-1706299.1	uscscaucagAfUfGfaucuacuuuuL96		asdAsaadGudAgaucdAuCfugauggasusa		UAUCCAUCAGAUGAUCUACUUUC	

AD-1706300.1	cscsaucagaUfGfAfucuacuuucuL96		asdGsaadAgdTagaudCaUfcugauggsasu		AUCCAUCAGAUGAUCUACUUUCA	
AD-1706301.1	csasucagauGfAfUfcuacuuucauL96		asdTsgadAadGuagadTcAfucugaugsgsa		UCCAUCAGAUGAUCUACUUUCAG	
AD-1706302.1	asuscagaugAfUfCfuacuuucaguL96		asdCsugdAadAguagdAuCfaucugausgsg		CCAUCAGAUGAUCUACUUUCAGC	
AD-1706303.1	uscsagaugaUfCfUfacuuucagcuL96		asdGscudGadAaguadGaUfcaucugasusg		CAUCAGAUGAUCUACUUUCAGCC	
AD-1706304.1	csasgaugauCfUfAfcuuucagccuL96		asdGsgcdTgdAaagudAgAfucaucugsasu		AUCAGAUGAUCUACUUUCAGCCU	
AD-1706305.1	asgsaugaucUfAfCfuuucagccuuL96		asdAsggdCudGaaagdTaGfaucaucusgsa		UCAGAUGAUCUACUUUCAGCCUU	
AD-1706306.1	gsasugaucuAfCfUfuucagccuuuL96		asdAsagdGcdTgaaadGuAfgaucaucsusg		CAGAUGAUCUACUUUCAGCCUUC	
AD-1706307.1	asusgaucuaCfUfUfucagccuucuL96		asdGsaadGgdCugaadAgUfagaucauscsu		AGAUGAUCUACUUUCAGCCUUCC	
AD-1706308.1	usgsaucuacUfUfUfcagccuuccuL96		asdGsgadAgdGcugadAaGfuagaucasusc		GAUGAUCUACUUUCAGCCUUCCU	
AD-1706309.1	gsasucuacuUfUfCfagccuuccuuL96		asdAsggdAadGgcugdAaAfguagaucsasu		AUGAUCUACUUUCAGCCUUCCUG	
AD-1706310.1	asuscuacuuUfCfAfgccuuccuguL96		asdCsagdGadAggcudGaAfaguagauscsa		UGAUCUACUUUCAGCCUUCCUGA	
AD-1706311.1	uscsuacuuuCfAfGfccuuccugauL96		asdTscadGgdAaggcdTgAfaaguagasusc		GAUCUACUUUCAGCCUUCCUGAG	
AD-1706312.1	csusacuuucAfGfCfcuuccugaguL96		asdCsucdAgdGaaggdCuGfaaaguagsasu		AUCUACUUUCAGCCUUCCUGAGU	
AD-1706313.1	usascuuucaGfCfCfuuccugaguuL96		asdAscudCadGgaagdGcUfgaaaguasgsa		UCUACUUUCAGCCUUCCUGAGUC	
AD-1706314.1	ascsuuucagCfCfUfuccugagucuL96		asdGsacdTcdAggaadGgCfugaaagusasg		CUACUUUCAGCCUUCCUGAGUCC	
AD-1706318.1	uscsagccuuCfCfUfgagucccaguL96		asdCsugdGgdAcucadGgAfaggcugasasa		UUUCAGCCUUCCUGAGUCCCAGA	
AD-1706337.1	gsascaauagAfAfGfacagguggcuL96		asdGsccdAcdCugucdTuCfuauugucsusg		CAGACAAUAGAAGACAGGUGGCU	
AD-1706338.1	ascsaauagaAfGfAfcagguggcuuL96		asdAsgcdCadCcugudCuUfcuauugucscsu		AGACAAUAGAAGACAGGUGGCUG	
AD-1706380.1	gsusggcaguGfGfUfgucugcuguuL96		asdAscadGcdAgacadCcAfcugccacsasc		GUGUGGCAGUGGUGUCUGCUGUC	
AD-1706381.1	usgsgcagugGfUfGfucugcugucuL96		asdGsacdAgdCagacdAcCfacugccascsa		UGUGGCAGUGGUGUCUGCUGUCA	
AD-1706382.1	gsgscaguggUfGfUfcugcugucauL96		asdTsgadCadGcagadCaCfcacugccsasc		GUGGCAGUGGUGUCUGCUGUCAC	
AD-1706383.1	gscsagugguGfUfCfugcugucacuL96		asdGsugdAcdAgcagdAcAfccacugcscsa		UGGCAGUGGUGUCUGCUGUCACU	
AD-1706384.1	csasguggugUfCfUfgcugucacuuL96		asdAsgudGadCagcadGaCfaccacugscsc		GGCAGUGGUGUCUGCUGUCACUG	
AD-1706385.1	asgsugguguCfUfGfcugucacuguL96		asdCsagdTgdAcagcdAgAfcaccacusgsc		GCAGUGGUGUCUGCUGUCACUGU	
AD-1706386.1	gsusggugucUfGfCfugucacuguuL96		asdAscadGudGacagdCaGfacaccacsusg		CAGUGGUGUCUGCUGUCACUGUG	
AD-1706387.1	usgsgugucuGfCfUfgucacuguguL96		asdCsacdAgdTgacadGcAfgacaccascsu		AGUGGUGUCUGCUGUCACUGUGC	
AD-1706388.1	gsgsugucugCfUfGfucacugugcuL96		asdGscadCadGugacdAgCfagacaccsasc		GUGGUGUCUGCUGUCACUGUGCC	

AD-1706407.1	csasgacucaAfCfAfgacggagcauL96		asdTsgcdTcdCgucudGuUfgagucugsasu		AUCAGACUCAACAGACGGAGCAA	
AD-1706408.1	asgsacucaaCfAfGfacggagcaauL96		asdTsugdCudCcgucdTgUfugagucusgsa		UCAGACUCAACAGACGGAGCAAC	
AD-1706409.1	gsascucaacAfGfAfcggagcaacuL96		asdGsuudGcdTccgudCuGfuugagucsusg		CAGACUCAACAGACGGAGCAACU	
AD-1706410.1	ascsucaacaGfAfCfggagcaacuuL96		asdAsgudTgdCuccgdTcUfguugaguscsu		AGACUCAACAGACGGAGCAACUG	
AD-1706411.1	csuscaacagAfCfGfgagcaacuguL96		asdCsagdTudGcuccdGuCfuguugagsusc		GACUCAACAGACGGAGCAACUGC	
AD-1706412.1	uscsaacagaCfGfGfagcaacugcuL96		asdGscadGudTgcucdCgUfcuguugasgsu		ACUCAACAGACGGAGCAACUGCC	
AD-1706413.1	csasacagacGfGfAfgcaacugccuL96		asdGsgcdAgdTugcudCcGfucuguugsasg		CUCAACAGACGGAGCAACUGCCA	
AD-1706414.1	asascagacgGfAfGfcaacugccauL96		asdTsggdCadGuugcdTcCfgucuguusgsa		UCAACAGACGGAGCAACUGCCAU	
AD-1706415.1	ascsagacggAfGfCfaacugccauuL96		asdAsugdGcdAguugdCuCfcgucugususg		CAACAGACGGAGCAACUGCCAUC	
AD-1706416.1	csasgacggaGfCfAfacugccaucuL96		asdGsaudGgdCaguudGcUfccgucugsusu		AACAGACGGAGCAACUGCCAUCC	
AD-1706417.1	asgsacggagCfAfAfcugccauccuL96		asdGsgadTgdGcagudTgCfuccgucusgsu		ACAGACGGAGCAACUGCCAUCCG	
AD-1706418.1	gsascggagcAfAfCfugccauccguL96		asdCsggdAudGgcagdTuGfcuccgucsusg		CAGACGGAGCAACUGCCAUCCGA	
AD-1706419.1	ascsggagcaAfCfUfgccauccgauL96		asdTscgdGadTggcadGuUfgcuccguscsu		AGACGGAGCAACUGCCAUCCGAG	
AD-1706420.1	csgsgagcaaCfUfGfccauccgaguL96		asdCsucdGgdAuggcdAgUfugcuccgsusc		GACGGAGCAACUGCCAUCCGAGG	
AD-1706421.1	gsgsagcaacUfGfCfcauccgagguL96		asdCscudCgdGauggdCaGfuugcuccsgsu		ACGGAGCAACUGCCAUCCGAGGC	
AD-1706423.1	asgscaacugCfCfAfuccgaggcuuL96		asdAsgcdCudCggaudGgCfaguugcuscsc		GGAGCAACUGCCAUCCGAGGCUC	
AD-1706424.1	gscsaacugcCfAfUfccgaggcucuL96		asdGsagdCcdTcggadTgGfcaguugcsusc		GAGCAACUGCCAUCCGAGGCUCC	
AD-1706425.1	csasacugccAfUfCfcgaggcuccuL96		asdGsgadGcdCucggdAuGfgcaguugscsu		AGCAACUGCCAUCCGAGGCUCCU	
AD-1706520.1	csasagcagaAfCfGfagcucugguuL96		asdAscdAgdAgcucdGuUfcugcuugsgsg		CCCAAGCAGAACGAGCUCUGGUG	
AD-1706521.1	asasgcagaaCfGfAfgcucugguguL96		asdCsacdCadGagcudCgUfucugcuusgsg		CCAAGCAGAACGAGCUCUGGUGC	
AD-1706522.1	asgscagaacGfAfGfcucuggugcuL96		asdGscadCcdAgagcdTcGfuucugcususg		CAAGCAGAACGAGCUCUGGUGCU	
AD-1706523.1	gscsagaacgAfGfCfucuggugcuuL96		asdAsgcdAcdCagagdCuCfguucugcsusu		AAGCAGAACGAGCUCUGGUGCUG	
AD-1706524.1	csasgaacgaGfCfUfcuggugcuguL96		asdCsagdCadCcagadGcUfcguucugscsu		AGCAGAACGAGCUCUGGUGCUGG	
AD-1706525.1	asgsaacgagCfUfCfuggugcuggUL96		asdCscadGcdAccagdAgCfucguucusgsc		GCAGAACGAGCUCUGGUGCUGGA	
AD-1706526.1	gsasacgagcUfCfUfggugcuggauL96		asdTsccdAgdCaccadGaGfcucguucsusg		CAGAACGAGCUCUGGUGCUGGAG	
AD-1706527.1	asascgagcuCfUfGfgugcuggaguL96		asdCsucdCadGcaccdAgAfgcucguuscsu		AGAACGAGCUCUGGUGCUGGAGC	
AD-1706528.1	ascsgagcucUfGfGfugcuggagcuL96		asdGscudCcdAgcacdCaGfagcucgususc		GAACGAGCUCUGGUGCUGGAGCU	

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AD-1707156.1	asusggcaauGfUfGfgucaagacguL96		asdCsgudCudTgaccdAcAfuugccaususa		UAAUGGCAAUGUGGUCAAGACGG	
AD-1707157.1	usgsgcaaugUfGfGfucaagacgguL96		asdCscgdTcdTugacdCaCfauugccasusu		AAUGGCAAUGUGGUCAAGACGGA	
AD-1707158.1	gsgscaauguGfGfUfcaagacggauL96		asdTsccdGudCuugadCcAfcauugccsasu		AUGGCAAUGUGGUCAAGACGGAU	
AD-1707159.1	gscsaaugugGfUfCfaagacggauuL96		asdAsucdCgdTcuugdAcCfacauugcscsa		UGGCAAUGUGGUCAAGACGGAUG	
AD-1707160.1	csasauguggUfCfAfagacggauguL96		asdCsaudCcdGucuudGaCfcacauugscsc		GGCAAUGUGGUCAAGACGGAUGU	
AD-1707161.1	asasugugguCfAfAfgacggauguuL96		asdAscadTcdCgucudTgAfccacauusgsc		GCAAUGUGGUCAAGACGGAUGUG	
AD-1707162.1	asusguggucAfAfGfacggauguguL96		asdCsacdAudCcgucdTuGfaccacaususg		CAAUGUGGUCAAGACGGAUGUGC	
AD-1707163.1	usgsuggucaAfGfAfcggaugugcuL96		asdGscadCadTccgudCuUfgaccacasusu		AAUGUGGUCAAGACGGAUGUGCC	
AD-1707164.1	gsusggucaaGfAfCfggaugugccuL96		asdGsgcdAcdAuccgdTcUfugaccacsasu		AUGUGGUCAAGACGGAUGUGCCA	
AD-1707165.1	usgsgucaagAfCfGfgaugugccauL96		asdTsggdCadCauccdGuCfuugaccascsa		UGUGGUCAAGACGGAUGUGCCAG	
AD-1707166.1	gsgsucaagaCfGfGfaugugccaguL96		asdCsugdGcdAcaucdCgUfcuugaccsasc		GUGGUCAAGACGGAUGUGCCAGA	
AD-1707167.1	gsuscaagacGfGfAfugugccagauL96		asdTscudGgdCacaudCcGfucuugacscsa		UGGUCAAGACGGAUGUGCCAGAU	
AD-1707168.1	uscsaagacgGfAfUfgugccagauuL96		asdAsucdTgdGcacadTcCfgucuugascsc		GGUCAAGACGGAUGUGCCAGAUA	
AD-1707169.1	csasagacggAfUfGfugccagauauL96		asdTsaudCudGgcacdAuCfcgucuugsasc		GUCAAGACGGAUGUGCCAGAUAU	
AD-1707170.1	asasgacggaUfGfUfgccagauauuL96		asdAsuadTcdTggcadCaUfccgucuusgsa		UCAAGACGGAUGUGCCAGAUAUG	
AD-1707171.1	asgsacggauGfUfGfccagauauguL96		asdCsaudAudCuggcdAcAfuccgucususg		CAAGACGGAUGUGCCAGAUAUGG	

AD-1707172.1	gsascggaugUfGfCfcagauaugguL96		asdCscadTadTcuggdCaCfauccgucsusu		AAGACGGAUGUGCCAGAUAUGGU	
AD-1707173.1	ascsggauguGfCfCfagauaugguuL96		asdAsccdAudAucugdGcAfcauccguscsu		AGACGGAUGUGCCAGAUAUGGUG	
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AD-1707179.1	gsusgccagaUfAfUfggugguggauL96		asdTsccdAcdCaccadTaUfcuggcacsasu		AUGUGCCAGAUAUGGUGGUGGAG	
AD-1707180.1	usgsccagauAfUfGfgugguggaguL96		asdCsucdCadCcaccdAuAfucuggcascsa		UGUGCCAGAUAUGGUGGUGGAGG	
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AD-1707190.1	gsgsugguggAfGfGfccuguggcuuL96		asdAsgcdCadCaggcdCuCfcaccaccsasu		AUGGUGGUGGAGGCCUGUGGCUG	
AD-1707197.1	gsasggccugUfGfGfcugcagcuauL96		asdTsagdCudGcagcdCaCfaggccucscsa		UGGAGGCCUGUGGCUGCAGCUAG	
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AD-1707209.1	usgscagcuaGfCfAfagaggaccuuL96		asdAsggdTcdCucuudGcUfagcugcasgsc		GCUGCAGCUAGCAAGAGGACCUG	
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AD-1707211.1	csasgcuagcAfAfGfaggaccuggUL96		asdCscadGgdTccucdTuGfcuagcugscsa		UGCAGCUAGCAAGAGGACCUGGG	
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AD-1707236.1	gsasaguuucCfCfAfggcacaggguL96		asdCsccdTgdTgccudGgGfaaacuucsasu		AUGAAGUUUCCCAGGCACAGGGC	
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AD-1707308.1	usgsggcacuUfUfCfuugucugaguL96		asdCsucdAgdAcaagdAaAfgugcccasusu		AAUGGGCACUUUCUUGUCUGAGA	
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AD-1707314.1	csusuucuugUfCfUfgagacucuguL96		asdCsagdAgdTcucadGaCfaagaaagsusg		CACUUUCUUGUCUGAGACUCUGG	
AD-1707315.1	ususucuuguCfUfGfagacucugguL96		asdCscadGadGucucdAgAfcaagaaasgsu		ACUUUCUUGUCUGAGACUCUGGC	
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AD-1707482.1	gsasugguccAfGfCfaggcuugaauL96		asdTsucdAadGccugdCuGfgaccaucsusa		UAGAUGGUCCAGCAGGCUUGAAG	
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AD-1707484.1	usgsguccagCfAfGfgcuugaagcuL96		asdGscudTcdAagccdTgCfuggaccasusc		GAUGGUCCAGCAGGCUUGAAGCA	
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AD-1707555.1	gsgsucaagaGfGfGfagaugggcauL96		asdTsgcdCcdAucucdCcUfcuugaccsusu		AAGGUCAAGAGGGAGAUGGGCAA	
AD-1707556.1	gsuscaagagGfGfAfgaugggcaauL96		asdTsugdCcdCaucudCcCfucuugacscsu		AGGUCAAGAGGGAGAUGGGCAAG	
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AD-1707577.1	gscsgcugagGfGfAfggaugcuuauL96		asdTsaadGcdAuccudCcCfucagcgcscsu		AGGCGCUGAGGGAGGAUGCUUAG	
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AD-1707605.1	gscsacuaagCfCfUfaagaaguucuL96		asdGsaadCudTcuuadGgCfuuagugcscsu		AGGCACUAAGCCUAAGAAGUUCC	
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AD-1707623.1	ascsaggaccCfAfCfugggagacauL96		asdTsgudCudCccagdTgGfguccugucscsc		GGACAGGACCCACUGGGAGACAA	
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AD-1707634.1	usgsgggagacAfAfGfcauuuauacuL96		asdGsuadTadAaugcdTuGfucucccasgsu		ACUGGGAGACAAGCAUUUAUACU	
AD-1707636.1	gsgsagacaaGfCfAfuuuauacuuuL96		asdAsagdTadTaaaudGcUfugucuccscsa		UGGGAGACAAGCAUUUAUACUUU	
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AD-1707638.1	asgsacaagcAfUfUfuauacuuucuL96		asdGsaadAgdTauaadAuGfcuugucuscsc		GGAGACAAGCAUUUAUACUUUCU	
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AD-1707640.1	ascsaagcauUfUfAfuacuuucuuuL96		asdAsagdAadAguaudAaAfugcuuguscsu		AGACAAGCAUUUAUACUUUCUUU	
AD-1707641.1	csasagcauuUfAfUfacuuucuuuuL96		asdAsaadGadAaguadTaAfaugcuugsusc		GACAAGCAUUUAUACUUUCUUUC	
AD-1708118.1	cscsagacAfuGfAfGfcugugaggguL96		asCfsccdTc(Agn)cagcucAfuGfucuggscsu		AGCCAGACAUGAGCUGUGAGGGU	
AD-1708120.1	asgsacauGfaGfCfUfgugagggucuL96		asGfsacdCc(Tgn)cacagcUfcAfugucusgsg		CCAGACAUGAGCUGUGAGGGUCA	
AD-1708124.1	asusgagcUfgUfGfAfgggucaagcuL96		asGfscudTg(Agn)cccucaCfaGfcucausgsu		ACAUGAGCUGUGAGGGUCAAGCA	
AD-1708126.1	gsasgcugUfgAfGfGfgucaagcacuL96		asGfsugdCu(Tgn)gacccuCfaCfagcucsasu		AUGAGCUGUGAGGGUCAAGCACA	
AD-1708127.1	asgscuguGfaGfGfGfucaagcacauL96		asUfsgudGc(Tgn)ugacccUfcAfcagcuscsa		UGAGCUGUGAGGGUCAAGCACAG	
AD-1708130.1	usgsugagGfgUfCfAfagcacagcuuL96		asAfsgcdTg(Tgn)gcuugaCfcCfucacasgsc		GCUGUGAGGGUCAAGCACAGCUA	
AD-1708132.1	usgsagggUfcAfAfGfcacagcuauuL96		asAfsuadGc(Tgn)gugcuuGfaCfccucascsa		UGUGAGGGUCAAGCACAGCUAUC	
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AD-1708140.1	asasgcacAfgCfUfAfuccaucagauL96		asUfscudGa(Tgn)ggauagCfuGfugcuusgsa		UCAAGCACAGCUAUCCAUCAGAU	
AD-1708143.1	csascagcUfaUfCfCfaucagaugauL96		asUfscadTc(Tgn)gauggaUfaGfcugugscsu		AGCACAGCUAUCCAUCAGAUGAU	
AD-1708145.1	csasgcuaUfcCfAfUfcagaugaucuL96		asGfsaudCa(Tgn)cugaugGfaUfagcugsusg		CACAGCUAUCCAUCAGAUGAUCU	
AD-1708146.1	asgscuauCfcAfUfCfagaugaucuuL96		asAfsgadTc(Agn)ucugauGfgAfuagcusgsu		ACAGCUAUCCAUCAGAUGAUCUA	
AD-1708148.1	csusauccAfuCfAfGfaugaucuacuL96		asGfsuadGa(Tgn)caucugAfuGfgauagscsu		AGCUAUCCAUCAGAUGAUCUACU	

AD-1708149.1	usasuccaUfcAfGfAfugaucuacuuL96		asAfsgudAg(Agn)ucaucuGfaUfggauasgsc		GCUAUCCAUCAGAUGAUCUACUU	
AD-1708151.1	uscscaucAfgAfUfGfaucuacuuuuL96		asAfsaadGu(Agn)gaucauCfuGfauggasusa		UAUCCAUCAGAUGAUCUACUUUC	
AD-1708152.1	cscsaucaGfaUfGfAfucuacuuucuL96		asGfsaadAg(Tgn)agaucaUfcUfgauggsasu		AUCCAUCAGAUGAUCUACUUUCA	
AD-1708156.1	csasgaugAfuCfUfAfcuuucagccuL96		asGfsgcdTg(Agn)aaguagAfuCfaucugsasu		AUCAGAUGAUCUACUUUCAGCCU	
AD-1708158.1	gsasugauCfuAfCfUfuucagccuuuL96		asAfsagdGc(Tgn)gaaaguAfgAfucaucsusg		CAGAUGAUCUACUUUCAGCCUUC	
AD-1708163.1	uscsuacuUfuCfAfGfccuuccugauL96		asUfscadGg(Agn)aggcugAfaAfguagasusc		GAUCUACUUUCAGCCUUCCUGAG	
AD-1708166.1	ascsuuucAfgCfCfUfuccugagucuL96		asGfsacdTc(Agn)ggaaggCfuGfaaagusasg		CUACUUUCAGCCUUCCUGAGUCC	
AD-1708170.1	uscsagccUfuCfCfUfgagucccaguL96		asCfsugdGg(Agn)cucaggAfaGfgcugasasa		UUUCAGCCUUCCUGAGUCCCAGG	
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AD-1708223.1	gscsagugGfuGfUfCfugcugucacuL96		asGfsugdAc(Agn)gcagacAfcCfacugcscsa		UGGCAGUGGUGUCUGCUGUCACU	
AD-1708225.1	asgsugguGfuCfUfGfcugucacuguL96		asCfsagdTg(Agn)cagcagAfcAfccacusgsc		GCAGUGGUGUCUGCUGUCACUGU	
AD-1708227.1	usgsguguCfuGfCfUfgucacuguguL96		asCfsacdAg(Tgn)gacagcAfgAfcaccascsu		AGUGGUGUCUGCUGUCACUGUGC	
AD-1708245.1	gsascucaAfcAfGfAfcggagcaacuL96		asGfsuudGc(Tgn)ccgucuGfuUfgagucsusg		CAGACUCAACAGACGGAGCAACU	
AD-1708248.1	uscsaacaGfaCfGfGfagcaacugcuL96		asGfscadGu(Tgn)gcuccgUfcUfguugasgsu		ACUCAACAGACGGAGCAACUGCC	
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AD-1708251.1	ascsagacGfgAfGfCfaacugccauuL96		asAfsugdGc(Agn)guugcuCfcGfucugususg		CAACAGACGGAGCAACUGCCAUC	
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AD-1708260.1	gscsaacuGfcCfAfUfccgaggcucuL96		asGfsagdCc(Tgn)cggaugGfcAfguugcsusc		GAGCAACUGCCAUCCGAGGCUCC	
AD-1708342.1	csasagcaGfaAfCfGfagcucugguuL96		asAfscdAg(Agn)gcucguUfcUfgcuugsgsg		CCCAAGCAGAACGAGCUCUGGUG	
AD-1708344.1	asgscagaAfcGfAfGfcucuggugcuL96		asGfscadCc(Agn)gagcucGfuUfcugcususg		CAAGCAGAACGAGCUCUGGUGCU	
AD-1708347.1	asgsaacgAfgCfUfCfuggugcugguL96		asCfscadGc(Agn)ccagagCfuCfguucusgsc		GCAGAACGAGCUCUGGUGCUGGA	
AD-1708350.1	ascsgagcUfcUfGfGfugcuggagcuL96		asGfscudCc(Agn)gcaccaGfaGfcucgususc		GAACGAGCUCUGGUGCUGGAGCU	
AD-1708356.1	uscsugguGfcUfGfGfagcuagccauL96		asUfsggdCu(Agn)gcuccaGfcAfccagasgsc		GCUCUGGUGCUGGAGCUAGCCAA	
AD-1708357.1	csusggugCfuGfGfAfgcuagccaauL96		asUfsugdGc(Tgn)agcuccAfgCfaccagsasg		CUCUGGUGCUGGAGCUAGCCAAG	
AD-1708361.1	usgscuggAfgCfUfAfgccaagcaguL96		asCfsugdCu(Tgn)ggcuagCfuCfcagcascsc		GGUGCUGGAGCUAGCCAAGCAGC	
AD-1708365.1	gsgsagcuAfgCfCfAfagcagcaaauL96		asUfsuudGc(Tgn)gcuuggCfuAfgcuccsasg		CUGGAGCUAGCCAAGCAGCAAAU	
AD-1708368.1	gscsuagcCfaAfGfCfagcaaauccuL96		asGfsgadTu(Tgn)gcugcuUfgGfcuagcsusc		GAGCUAGCCAAGCAGCAAAUCCU	

AD-1708369.1	csusagccAfaGfCfAfgcaaauccuuL96		asAfsggdAu(Tgn)ugcugcUfuGfgcuagscsu		AGCUAGCCAAGCAGCAAAUCCUG	
AD-1708397.1	usgsaccaGfuCfGfUfcccagaauauL96		asUfsaudTc(Tgn)gggacgAfcUfggucasgsg		UCUGACCAGUCGUCCCAGAAUAA	
AD-1708399.1	ascscaguCfgUfCfCfcagaauaacuL96		asGfsuudAu(Tgn)cugggaCfgAfcuggucsa		UGACCAGUCGUCCCAGAAUAACU	
AD-1708401.1	csasgucgUfcCfCfAfgaauaacucuL96		asGfsagdTu(Agn)uucuggGfaCfgacugsgsu		ACCAGUCGUCCCAGAAUAACUCA	
AD-1708402.1	asgsucguCfcCfAfGfaauaacucauL96		asUfsgadGu(Tgn)auucugGfgAfcgacusgsg		CCAGUCGUCCCAGAAUAACUCAU	
AD-1708403.1	gsuscgucCfcAfGfAfauaacucauuL96		asAfsugdAg(Tgn)uauucuGfgGfacgacsusg		CAGUCGUCCCAGAAUAACUCAUC	
AD-1708405.1	csgsucccAfgAfAfUfaacucauccuL96		asGfsgadTg(Agn)guuauuCfuGfggacgsasc		GUCGUCCCAGAAUAACUCAUCCU	
AD-1708407.1	uscsccagAfaUfAfAfcucauccucuL96		asGfsagdGa(Tgn)gaguuaUfuCfugggascsg		CGUCCCAGAAUAACUCAUCCUCC	
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AD-1708454.1	gsasggucAfuCfAfGfcuuugcuacuL96		asGfsuadGc(Agn)aagcugAfuGfaccucscsu		AGGAGGUCAUCAGCUUUGCUACU	
AD-1708457.1	gsuscaucAfgCfUfUfugcuacuguuL96		asAfscadGu(Agn)gcaaagCfuGfaugacscsu		AGGUCAUCAGCUUUGCUACUGUC	
AD-1708458.1	uscsaucaGfcUfUfUfgcuacugucuL96		asGfsacdAg(Tgn)agcaaaGfcUfgaugascsc		GGUCAUCAGCUUUGCUACUGUCA	
AD-1708462.1	csasgcuuUfgCfUfAfcugucacaguL96		asCfsugdTg(Agn)caguagCfaAfagcugsasu		AUCAGCUUUGCUACUGUCACAGA	
AD-1708464.1	gscsuuugCfuAfCfUfgucacagacuL96		asGfsucdTg(Tgn)gacaguAfgCfaaagcsusg		CAGCUUUGCUACUGUCACAGACU	
AD-1708466.1	ususugcuAfcUfGfUfcacagacucuL96		asGfsagdTc(Tgn)gugacaGfuAfgcaaasgsc		GCUUUGCUACUGUCACAGACUCC	
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AD-1708476.1	uscsacagAfcUfCfCfacuucagccuL96		asGfsgcdTg(Agn)aguggaGfuCfugugascsa		UGUCACAGACUCCACUUCAGCCU	
AD-1708478.1	ascsagacUfcCfAfCfuucagccuauL96		asUfsagdGc(Tgn)gaagugGfaGfucugusgsa		UCACAGACUCCACUUCAGCCUAC	
AD-1708482.1	ascsuccaCfuUfCfAfgccuacagcuL96		asGfscudGu(Agn)ggcugaAfgUfggaguscsu		AGACUCCACUUCAGCCUACAGCU	
AD-1708483.1	csusccacUfuCfAfGfccuacagcuuL96		asAfsgcdTg(Tgn)aggcugAfaGfuggagsusc		GACUCCACUUCAGCCUACAGCUC	
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AD-1708561.1	gscsacucUfuUfGfCfuugaggaucuL96		asGfsaudCc(Tgn)caagcaAfaGfagugcscsa		UGGCACUCUUUGCUUGAGGAUCU	
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AD-1708565.1	uscsuuugCfuUfGfAfggaucuuccuL96		asGfsgadAg(Agn)uccucaAfgCfaaagasgsu		ACUCUUUGCUUGAGGAUCUUCCG	

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AD-1708647.1	usgsgcugAfgCfAfCfcacaucaccuL96		asGfsgudGa(Tgn)guggugCfuCfagccasgsg		UUUGGCUGAGCACCACAUCACCA	
AD-1708648.1	gsgscugaGfcAfCfCfacaucaccauL96		asUfsggdTg(Agn)ugugguGfcUfcagccsasg		UUGGCUGAGCACCACAUCACCAA	
AD-1708650.1	csusgagcAfcCfAfCfaucaccaacuL96		asGfsuudGg(Tgn)gaugugGfuGfcucagscsc		GGCUGAGCACCACAUCACCAACC	
AD-1708657.1	cscsacauCfaCfCfAfaccugggcuuL96		asAfsgcdCc(Agn)gguuggUfgAfuguggsusg		CACCACAUCACCAACCUGGGCUG	
AD-1708662.1	uscsaccaAfcCfUfGfggcuggcauuL96		asAfsugdCc(Agn)gcccagGfuUfggugasusg		CAUCACCAACCUGGGCUGGCAUG	
AD-1708680.1	cscsuuaaCfuCfUfGfcccucuaguuL96		asAfscudAg(Agn)gggcagAfgUfuaaggsusa		UACCUUAACUCUGCCCUCUAGUG	
AD-1708683.1	usasacucUfgCfCfCfucuaguggcuL96		asGfsccdAc(Tgn)agagggCfaGfaguuasasg		CUUAACUCUGCCCUCUAGUGGCU	
AD-1708697.1	gsuscuggUfgUfCfCfugaaacugcuL96		asGfscadGu(Tgn)ucaggaCfaCfcagacsusu		AAGUCUGGUGUCCUGAAACUGCA	
AD-1708698.1	uscsugguGfuCfCfUfgaaacugcauL96		asUfsgcdAg(Tgn)uucaggAfcAfccagascsu		AGUCUGGUGUCCUGAAACUGCAA	
AD-1708700.1	usgsguguCfcUfGfAfaacugcaacuL96		asGfsuudGc(Agn)guuucaGfgAfcaccasgsa		UCUGGUGUCCUGAAACUGCAACU	
AD-1708704.1	gsusccugAfaAfCfUfgcaacuagauL96		asUfscudAg(Tgn)ugcaguUfuCfaggacsasc		GUGUCCUGAAACUGCAACUAGAC	
AD-1708706.1	cscsugaaAfcUfGfCfaacuagacuuL96		asAfsgudCu(Agn)guugcaGfuUfucaggsasc		GUCCUGAAACUGCAACUAGACUG	
AD-1708707.1	csusgaaaCfuGfCfAfacuagacuguL96		asCfsagdTc(Tgn)aguugcAfgUfuucagsgsa		UCCUGAAACUGCAACUAGACUGC	
AD-1708709.1	gsasaacuGfcAfAfCfuagacugcauL96		asUfsgcdAg(Tgn)cuaguuGfcAfguuucsasg		CUGAAACUGCAACUAGACUGCAG	
AD-1708711.1	asascugcAfaCfUfAfgacugcagauL96		asUfscudGc(Agn)gucuagUfuGfcaguususc		GAAACUGCAACUAGACUGCAGAC	
AD-1708719.1	gscsaacaGfcAfCfAfguuacuggauL96		asUfsccdAg(Tgn)aacuguGfcUfguugcscsu		AGGCAACAGCACAGUUACUGGAC	
AD-1708721.1	asascagcAfcAfGfUfuacuggacauL96		asUfsgudCc(Agn)guaacuGfuGfcuguusgsc		ACAACAGCACAGUUACUGGACAA	
AD-1708724.1	asgscacaGfuUfAfCfuggacaaccuL96		asGfsgudTg(Tgn)ccaguaAfcUfgugcusgsu		ACAGCACAGUUACUGGACAACCG	
AD-1708746.1	ususggacAfcAfGfCfaggacaccauL96		asUfsggdTg(Tgn)ccugcuGfuGfuccaasgsa		UCUUGGACACAGCAGGACACCAG	
AD-1708748.1	gsgsacacAfgCfAfGfgacaccagcuL96		asGfscudGg(Tgn)guccugCfuGfuguccsasa		CUGGACACAGCAGGACACCAGCA	
AD-1708751.1	csascagcAfgGfAfCfaccagcagcuL96		asGfscudGc(Tgn)ggugucCfuGfcugugsusc		GACACAGCAGGACACCAGCAGCC	
AD-1708759.1	gsascaccAfgCfAfGfcccuuccuauL96		asUfsagdGa(Agn)gggcugCfuGfgugucscsu		AGGACACCAGCAGCCCUUCCUAG	
AD-1708763.1	cscsagcaGfcCfCfUfuccuagagcuL96		asGfscudCu(Agn)ggaaggGfcUfgcuggsusg		CACCAGCAGCCCUUCCUAGAGCU	
AD-1708764.1	csasgcagCfcCfUfUfccuagagcuuL96		asAfsgcdTc(Tgn)aggaagGfgCfugcugsgsu		ACCAGCAGCCCUUCCUAGAGCUU	
AD-1708766.1	gscsagccCfuUfCfCfuagagcuuauL96		asUfsaadGc(Tgn)cuaggaAfgGfgcugcsusg		CAGCAGCCCUUCCUAGAGCUUAA	
AD-1708771.1	cscsuuccUfaGfAfGfcuuaagaucuL96		asGfsaudCu(Tgn)aagcucUfaGfgaaggsgsc		GCCCUUCCUAGAGCUUAAGAUCC	

AD-1708813.1	ususacguAfgAfCfUfuccaggaacuL96		asGfsuudCc(Tgn)ggaaguCfuAfcguaasusg		CAUUACGUAGACUUCCAGGAACU	
AD-1708819.1	asgsacuuCfcAfGfGfaacugggauuL96		asAfsucdCc(Agn)guuccuGfgAfagucusasc		GUAGACUUCCAGGAACUGGGAUG	
AD-1708842.1	gsusaccaGfcUfGfAfauuacugcauL96		asUfsgcdAg(Tgn)aauucaGfcUfgguacscsc		GGGUACCAGCUGAAUUACUGCAG	
AD-1708844.1	ascscagcUfgAfAfUfuacugcaguuL96		asAfscudGc(Agn)guaauuCfaGfcuggusasc		GUACCAGCUGAAUUACUGCAGUG	
AD-1708849.1	csusgaauUfaCfUfGfcagugggcauL96		asUfsgcdCc(Agn)cugcagUfaAfuucagscsu		AGCUGAAUUACUGCAGUGGGCAG	
AD-1708856.1	ascsugcaGfuGfGfGfcagugcccuuL96		asAfsggdGc(Agn)cugcccAfcUfgcagusasa		UUACUGCAGUGGGCAGUGCCCUC	
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AD-1708875.1	csasuugcUfgCfCfUfcuuuccauuuL96		asAfsaudGg(Agn)aagaggCfaGfcaaugscsc		GGCAUUGCUGCCUCUUUCCAUUC	
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AD-1708889.1	uscscauuCfuGfCfCfgucuucagcuL96		asGfscudGa(Agn)gacggcAfgAfauggasasa		UUUCCAUUCUGCCGUCUUCAGCC	
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AD-1708908.1	cscsuccuCfaAfAfGfccaacaaucuL96		asGfsaudTg(Tgn)uggcuuUfgAfggaggscsu		AGCCUCCUCAAAGCCAACAAUCC	
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AD-1708921.1	asascaauCfcUfUfGfgccugccaguL96		asCfsugdGc(Agn)ggccaaGfgAfuuguusgsg		CCAACAAUCCUUGGCCUGCCAGU	
AD-1708956.1	uscsuccuCfuAfCfCfcuggaucauauL96		asUfsaudGa(Tgn)ccagguAfgAfggagasgsa		UCUCUCCUCUACCUGGAUCAUAA	
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AD-1708971.1	uscsauaaUfgGfCfAfauguggucauL96		asUfsgadCc(Agn)cauugcCfaUfuaugasusc		GAUCAUAAUGGCAAUGUGGUCAA	
AD-1708974.1	usasauggCfaAfUfGfuggucaagauL96		asUfscudTg(Agn)ccacauUfgCfcauuasusg		CAUAAUGGCAAUGUGGUCAAGAC	
AD-1708976.1	asusggcaAfuGfUfGfgucaagacguL96		asCfsgudCu(Tgn)gaccacAfuUfgccaususa		UAAUGGCAAUGUGGUCAAGACGG	
AD-1708977.1	usgsgcaaUfgUfGfGfucaagacgguL96		asCfscgdTc(Tgn)ugaccaCfaUfugccasusu		AAUGGCAAUGUGGUCAAGACGGA	

AD-1708984.1	gsusggucAfaGfAfCfggaugugccuL96		asGfsgcdAc(Agn)uccgucUfuGfaccacsasu		AUGUGGUCAAGACGGAUGUGCCA	
AD-1708986.1	gsgsucaaGfaCfGfGfaugugccaguL96		asCfsugdGc(Agn)cauccgUfcUfugaccsasc		GUGGUCAAGACGGAUGUGCCAGA	
AD-1708990.1	asasgacgGfaUfGfUfgccagauauuL96		asAfsuadTc(Tgn)ggcacaUfcCfgucuusgsa		UCAAGACGGAUGUGCCAGAUAUG	
AD-1709009.1	usgsguggUfgGfAfGfgccuguggcuL96		asGfsccdAc(Agn)ggccucCfaCfcaccasusa		UAUGGUGGUGGAGGCCUGUGGCU	
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AD-1709022.1	csusguggCfuGfCfAfgcuagcaaguL96		asCfsuudGc(Tgn)agcugcAfgCfcacagsgsc		GCCUGUGGCUGCAGCUAGCAAGA	
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AD-1709044.1	asgsagacCfaAfGfAfugaaguuucuL96		asGfsaadAc(Tgn)ucaucuUfgGfucucususc		GAAGAGACCAAGAUGAAGUUUCC	
AD-1709052.1	asgsaugaAfgUfUfUfcccaggcacuL96		asGfsugdCc(Tgn)gggaaaCfuUfcaucususg		CAAGAUGAAGUUUCCCAGGCACA	
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AD-1709090.1	ascsccaaCfaAfCfCfaccuggcaauL96		asUfsugdCc(Agn)ggugguUfgUfugggususg		CAACCCAACAACCACCUGGCAAU	
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AD-1709098.1	ascscaccUfgGfCfAfauaugacucuL96		asGfsagdTc(Agn)uauugcCfaGfguggususg		CAACCACCUGGCAAUAUGACUCA	
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AD-1709106.1	gscsaauaUfgAfCfUfcacuugaccuL96		asGfsgudCa(Agn)gugaguCfaUfauugcscsa		UGGCAAUAUGACUCACUUGACCC	
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AD-1709124.1	csascuuuCfuUfGfUfcugagacucuL96		asGfsagdTc(Tgn)cagacaAfgAfaagugcsc		GGCACUUUCUUGUCUGAGACUCU	

AD-1709126.1	csusuucuUfgUfCfUfgagacucuguL96		asCfsagdAg(Tgn)cucagaCfaAfgaaagsusg		CACUUUCUUGUCUGAGACUCUGG	
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AD-1709148.1	usasuuccAfgGfUfUfggcugauguuL96		asAfscadTc(Agn)gccaacCfuGfgaauasasg		CUUAUUCCAGGUUGGCUGAUGUG	
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AD-1709201.1	csuscucuCfcUfCfUfaccuggaucuL96		asGfsaudCc(Agn)gguagaGfgAfgagagsasg		CUCUCUCUCCUCUACCUGGAUCA	
AD-1709237.1	gsasuuucCfuGfCfCfcuaaguccuuL96		asAfsggdAc(Tgn)uagggcAfgGfaaaucsasu		AUGAUUUCCUGCCCUAAGUCCUG	
AD-1709239.1	ususuccuGfcCfCfUfaaguccuguuL96		asAfscadGg(Agn)cuuaggGfcAfggaaasusc		GAUUUCCUGCCCUAAGUCCUGUG	
AD-1709253.1	asgsaagaUfgUfCfAfgggacuagguL96		asCfscudAg(Tgn)cccugaCfaUfcuucuscsa		UGAGAAGAUGUCAGGGACUAGGG	
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AD-1709298.1	asgsgaggAfaGfCfAfgauagaugguL96		asCfscadTc(Tgn)aucugcUfuCfcuccuscsc		GGAGGAGGAAGCAGAUAGAUGGU	
AD-1709300.1	gsasggaaGfcAfGfAfuagauggucuL96		asGfsacdCa(Tgn)cuaucuGfcUfuccucscsu		AGGAGGAAGCAGAUAGAUGGUCC	
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AD-1709304.1	asasgcagAfuAfGfAfugguccagcuL96		asGfscudGg(Agn)ccaucuAfuCfugcuuscsc		GGAAGCAGAUAGAUGGUCCAGCA	
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AD-1709314.1	asusggucCfaGfCfAfggcuugaaguL96		asCfsuudCa(Agn)gccugcUfgGfaccauscsu		AGAUGGUCCAGCAGGCUUGAAGC	
AD-1709315.1	usgsguccAfgCfAfGfgcuugaagcuL96		asGfscudTc(Agn)agccugCfuGfgaccasusc		GAUGGUCCAGCAGGCUUGAAGCA	
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AD-1709372.1	gsgsucaaGfaGfGfGfagaugggcauL96		asUfsgcdCc(Agn)ucucccUfcUfugaccsusu		AGGGUCAAGAGGGAGAUGGGCAA	
AD-1709390.1	gscsgcugAfgGfGfAfggaugcuuauL96		asUfsaadGc(Agn)uccuccCfuCfagcgcscsu		AGGCGCUGAGGGAGGAUGCUUAG	
AD-1709410.1	gscsacuaAfgCfCfUfaagaaguucuL96		asGfsaadCu(Tgn)cuuaggCfuUfagugcscsu		AGGCACUAAGCCUAAGAAGUUCC	
AD-1709411.1	csascuaaGfcCfUfAfagaaguuccuL96		asGfsgadAc(Tgn)ucuuagGfcUfuagugscsc		GGCACUAAGCCUAAGAAGUUCCC	
AD-1709429.1	csasggacCfcAfCfUfgggagacaauL96		asUfsugdTc(Tgn)cccaguGfgGfuccugsusc		GACAGGACCCACUGGGAGACAAG	
AD-1709431.1	gsgsacccAfcUfGfGfgagacaagcuL96		asGfscudTg(Tgn)cucccaGfuGfgguccsusg		CAGGACCCACUGGGAGACAAGCA	
AD-1709433.1	ascsccacUfgGfGfAfgacaagcauuL96		asAfsugdCu(Tgn)gucuccCfaGfuggguscsc		GGACCCACUGGGAGACAAGCAUU	
AD-1709434.1	cscscacuGfgGfAfGfacaagcauuuL96		asAfsaudGc(Tgn)ugucucCfcAfgugggsusc		GACCCACUGGGAGACAAGCAUUU	

AD-1709442.1	gsasgacaAfgCfAfUfuuauacuuuuL96		asAfsaadGu(Agn)uaaaugCfuUfgucucscsc		GGGAGACAAGCAUUUAUACUUUC	
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AD-1711741.1	csasagcacaGfCfUfauccaucaguL96		asdCsugdAudGgauadGcUfgugcuugscsu		GUCAAGCACAGCUAUCCAUCAGA	
AD-1711742.1	asuscuacuuUfCfAfgccuuccuguL96		asdCsagdGadAggcudGaAfaguagauscsu		UGAUCUACUUUCAGCCUUCCUGA	
AD-1711743.1	asgsccaagcAfGfCfaaauccugguL96		asdCscadGgdAuuugdCuGfcuuggcuscsu		CUAGCCAAGCAGCAAAUCCUGGA	
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AD-1711747.1	csusuugcuuGfAfGfgaucuuccguL96		asdCsggdAadGauccdTcAfagcaaagscsu		CUCUUUGCUUGAGGAUCUUCCGA	
AD-1711748.1	ususugcuugAfGfGfaucuuccgauL96		asdTscgdGadAgaucdCuCfaagcaaascsu		UCUUUGCUUGAGGAUCUUCCGAU	
AD-1711749.1	ususgcuugaGfGfAfucuuccgauuL96		asdAsucdGgdAagaudCcUfcaagcaascsu		CUUUGCUUGAGGAUCUUCCGAUG	
AD-1711750.1	usgscuugagGfAfUfcuuccgauguL96		asdCsaudCgdGaagadTcCfucaagcascsu		UUUGCUUGAGGAUCUUCCGAUGG	
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AD-1711752.1	asgscaccacAfUfCfaccaaccuguL96		asdCsagdGudTggugdAuGfuggugcuscsu		UGAGCACCACAUCACCAACCUGG	
AD-1711753.1	ascsguagacUfUfCfcaggaacuguL96		asdCsagdTudCcuggdAaGfucuacguscsu		UUACGUAGACUUCCAGGAACUGG	
AD-1711754.1	csgsuagacuUfCfCfaggaacuggUL96		asdCscadGudTccugdGaAfgucuacgscsu		UACGUAGACUUCCAGGAACUGGG	
AD-1711755.1	gsascuuccaGfGfAfacugggauguL96		asdCsaudCcdCaguudCcUfggaagucscsu		UAGACUUCCAGGAACUGGGAUGG	
AD-1711756.1	usgscugccuCfUfUfuccauucuguL96		asdCsagdAadTggaadAgAfggcagcascsu		AUUGCUGCCUCUUUCCAUUCUGC	
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AD-1711759.1	ususccauucUfGfCfcgucuucaguL96		asdCsugdAadGacggdCaGfaauggaascsu		CUUUCCAUUCUGCCGUCUUCAGC	
AD-1711760.1	cscsucaaagCfCfAfacaauccuuuL96		asdAsagdGadTuguudGgCfuuugaggscsu		CUCCUCAAAGCCAACAAUCCUUG	
AD-1711761.1	csuscaaagcCfAfAfcaauccuuguL96		asdCsaadGgdAuugudTgGfcuuugagscsu		UCCUCAAAGCCAACAAUCCUUGG	
AD-1711762.1	usgsugucccUfAfCfugcccgaaguL96		asdCsuudCgdGgcagdTaGfggacacascsu		GUUGUGUCCCUACUGCCCGAAGG	
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AD-1711767.1	gsasucauaaUfGfGfcaaugugguuL96	asdAsccdAcdAuugcdCaUfuaugaucscsu		UGGAUCAUAAUGGCAAUGUGGUC	
AD-1711768.1	asusggcaauGfUfGfgucaagacguL96	asdCsgudCudTgaccdAcAfuugccauscsu		UAAUGGCAAUGUGGUCAAGACGG	
AD-1711769.1	gsgscaauguGfGfUfcaagacggauL96	asdTsccdGudCuugadCcAfcauugccscsu		AUGGCAAUGUGGUCAAGACGGAU	
AD-1711770.1	gscsaauguGfUfCfaagacggauuL96	asdAsucdCgdTcuugdAcCfacauugcscsu		UGGCAAUGUGGUCAAGACGGAUG	
AD-1711771.1	usgsccaguAfUfGfgugguggaguL96	asdCsucdCadCcaccdAuAfucuggcascsu		UGUGCCAGAUAUGGUGGUGGAGG	
AD-1711772.1	usgsgcugcaGfCfUfagcaagagguL96	asdCscudCudTgcuadGcUfgcagccascsu		UGUGGCUGCAGCUAGCAAGAGGA	
AD-1711773.1	gsgsagugaaGfAfGfaccaagauguL96	asdCsaudCudTggucdTcUfucacucccscsu		UUGGAGUGAAGAGACCAAGAUGA	
AD-1711774.1	asasgagaccAfAfGfaugaaguuuuuL96	asdAsaadCudTcaucdTuGfgucucuuscsu		UGAAGAGACCAAGAUGAAGUUUC	
AD-1711775.1	ususccagguUfGfGfcugaugugguuL96	asdAscadCadTcagcdCaAfccuggaascsu		UAUUCCAGGUUGGCUGAUGUGUU	
AD-1711776.1	cscsagguugGfCfUfgaugugguguL96	asdCsaadCadCaucadGcCfaaccuggscsu		UUCCAGGUUGGCUGAUGUGUUGG	
AD-1711777.1	csasgguuggCfUfGfaugugguugguL96	asdCscadAcdAcaucdAgCfcaaccugscsu		UCCAGGUUGGCUGAUGUGUUGGG	
AD-1711778.1	gsusccagcaGfGfCfuugaagcaguL96	asdCsugdCudTcaagdCcUfgcuggacscsu		UGGUCCAGCAGGCUUGAAGCAGG	
AD-1711779.1	gsgsagacaaGfCfAfuuuauacuuuL96	asdAsagdTadTaaaudGcUfugucuccscsu		UGGGAGACAAGCAUUUAUACUUU	

Table 21A. Single dose screen for dsRNA agents targeting INHBE in Hep3b cells

	10 nM		1 nM		0.1 nM	
Duplex Name	% Avg message remaining	STDEV	% Avg message remaining	STDEV	% Avg message remaining	STDEV
AD-1708158.1	34.54	8.05	71.33	9.23	107.64	15.41
AD-1706305.1	35.48	5.41	73.21	3.56	104.59	20.16
AD-1706299.1	36.87	8.53	79.64	15.65	114.93	19.80
AD-1706300.1	37.80	4.13	73.84	6.08	114.88	21.29
AD-1706297.1	39.37	5.42	70.23	10.61	86.59	21.82
AD-1706306.1	39.71	4.79	72.04	14.92	130.55	3.74
AD-1706410.1	40.85	1.71	62.77	3.66	109.95	30.95
AD-1706298.1	40.98	10.04	64.11	16.28	101.43	28.55
AD-1706304.1	44.69	8.85	92.06	13.52	109.73	9.34
AD-1706302.1	50.26	9.48	84.61	11.73	122.60	29.73
AD-1706292.1	52.60	17.55	75.07	12.50	124.87	12.45
AD-1706296.1	52.71	5.68	75.22	5.52	131.62	16.26
AD-1708152.1	53.50	0.47	87.86	10.25	136.07	12.18
AD-1706307.1	54.31	26.05	89.68	30.45	110.24	8.38
AD-1706301.1	54.75	12.47	84.13	5.13	124.19	16.94
AD-1706287.1	55.23	11.82	83.57	17.26	115.00	21.38
AD-1706411.1	55.84	10.32	89.82	7.68	103.89	21.25
AD-1706295.1	56.58	15.21	71.06	10.26	113.27	21.71
AD-1706294.1	56.72	15.26	76.70	11.02	129.67	23.61
AD-1706409.1	56.75	9.70	86.44	11.10	119.28	17.80
AD-1706293.1	61.24	25.25	76.63	12.52	130.80	28.10
AD-1706290.1	62.56	11.16	95.20	16.61	116.52	11.90
AD-1706383.1	64.06	16.13	86.94	9.74	112.75	11.83
AD-1706291.1	64.59	12.17	108.70	24.87	106.57	31.50
AD-1706280.1	65.32	6.57	91.46	16.24	108.01	13.13
AD-1708140.1	65.34	2.95	87.20	9.24	106.96	6.65
AD-1708146.1	65.43	11.72	84.84	10.88	112.01	18.37
AD-1706313.1	66.71	16.10	94.16	19.83	100.38	27.90
AD-1706408.1	67.80	19.49	71.97	16.90	125.25	16.19
AD-1708120.1	68.00	23.76	81.05	8.12	121.03	26.25
AD-1711741.1	68.04	23.87	87.67	14.56	132.56	17.04
AD-1708151.1	69.02	16.00	89.83	4.84	118.89	22.05
AD-1706309.1	69.77	8.67	84.02	11.60	138.93	37.04
AD-1706318.1	70.20	18.67	91.66	23.35	114.12	16.35
AD-1706273.1	70.34	15.43	134.72	59.02	106.63	19.73
AD-1708156.1	70.85	5.13	94.15	10.42	122.14	12.71
AD-1706310.1	70.85	8.64	92.35	8.01	109.09	13.66
AD-1708143.1	72.22	46.65	74.07	2.75	99.36	33.10
AD-1706270.1	73.33	11.55	107.41	33.72	104.81	18.07
AD-1708245.1	74.06	11.02	91.64	18.81	115.07	18.23

	10 nM		1 nM		0.1 nM	
Duplex Name	% Avg message remaining	STDEV	% Avg message remaining	STDEV	% Avg message remaining	STDEV
AD-1708148.1	75.43	10.51	110.24	42.78	127.20	18.92
AD-1706288.1	78.50	9.54	106.30	33.79	112.08	17.34
AD-1706269.1	78.75	9.19	97.34	9.54	94.15	26.99
AD-1706387.1	79.56	16.72	90.68	20.17	99.57	33.24
AD-1708126.1	81.86	10.41	89.72	13.80	110.36	19.57
AD-1706268.1	82.69	6.38	87.59	10.70	91.80	35.13
AD-1708149.1	83.56	16.19	87.38	11.09	116.42	10.39
AD-1706283.1	83.95	15.44	114.55	19.46	110.69	12.30
AD-1708118.1	83.97	11.32	78.18	3.60	92.20	9.25
AD-1708166.1	84.10	9.90	120.20	18.18	104.28	12.44
AD-1711742.1	84.46	23.20	96.26	12.03	105.58	8.27
AD-1708145.1	84.74	24.20	97.39	17.29	113.55	20.45
AD-1706282.1	85.07	19.02	95.14	23.04	120.96	13.71
AD-1708135.1	87.22	17.87	100.41	17.38	108.11	12.87
AD-1706314.1	87.98	27.86	94.95	10.60	118.63	19.08
AD-1706381.1	90.73	25.96	112.16	35.12	117.51	25.58
AD-1706311.1	92.14	18.67	116.08	9.92	129.88	24.01
AD-1706384.1	93.18	20.64	101.34	25.11	104.37	25.79
AD-1706385.1	93.50	27.94	105.31	39.58	104.75	6.41
AD-1706308.1	94.84	25.04	103.73	23.79	113.80	17.87
AD-1706338.1	95.49	12.86	98.18	6.39	136.37	13.09
AD-1708132.1	96.59	16.59	110.68	23.93	127.48	24.20
AD-1706380.1	96.60	21.61	90.75	13.70	111.95	26.19
AD-1706407.1	97.98	15.10	117.50	33.82	125.93	8.66
AD-1708170.1	98.46	11.64	116.36	41.97	132.15	17.12
AD-1706337.1	98.84	10.33	101.92	12.86	124.77	20.13
AD-1706272.1	99.84	23.62	102.80	15.05	118.13	8.50
AD-1706386.1	100.40	14.63	96.49	11.10	119.90	15.42
AD-1706271.1	101.04	6.69	99.68	8.67	133.49	59.61
AD-1708223.1	101.44	30.82	98.53	16.39	117.67	7.67
AD-1706276.1	101.53	28.71	96.11	25.46	115.66	33.58
AD-1708124.1	102.72	19.13	102.79	8.17	120.68	21.81
AD-1706277.1	103.69	22.61	112.76	19.13	90.36	25.09
AD-1706303.1	103.98	5.20	97.67	13.09	113.42	28.98
AD-1706279.1	104.53	24.13	99.52	8.70	122.09	25.99
AD-1708225.1	104.78	20.86	105.12	19.62	108.70	16.14
AD-1708127.1	106.25	18.25	114.08	21.32	118.31	11.91
AD-1708227.1	106.53	19.55	107.67	15.93	120.02	29.17
AD-1706388.1	106.60	11.81	110.39	11.58	121.56	34.41
AD-1706281.1	107.68	6.05	98.05	9.70	127.45	22.05
AD-1706266.1	107.82	**19.26**	98.57	12.19	110.48	5.27

	10 nM		1 nM		0.1 nM	
Duplex Name	% Avg message remaining	STDEV	% Avg message remaining	STDEV	% Avg message remaining	STDEV
AD-1706312.1	108.02	20.50	107.33	27.61	118.30	21.42
AD-1708163.1	109.49	8.50	95.21	3.04	100.00	28.35
AD-1708130.1	112.07	20.84	114.29	5.99	135.90	28.66
AD-1708220.1	114.56	17.32	93.03	8.40	127.48	21.09
AD-1706274.1	117.23	47.42	95.56	7.23	95.48	3.56
AD-1706275.1	117.99	17.97	122.96	24.59	102.24	29.51
AD-1706265.1	119.46	15.25	106.15	16.69	130.11	27.52
AD-1706278.1	122.93	41.94	93.47	14.43	116.53	8.92
AD-1706382.1	130.38	29.68	115.88	31.75	114.07	27.35
AD-1706642.1	9.07	1.33	33.95	3.33	73.03	9.20
AD-1706584.1	11.10	1.36	39.89	8.90	62.11	12.60
AD-1711744.1	14.39	2.21	50.24	8.89	79.57	19.84
AD-1706588.1	14.86	1.91	40.60	4.38	72.24	12.92
AD-1706583.1	16.40	0.91	54.91	8.04	90.07	11.50
AD-1706591.1	16.85	2.64	45.21	8.78	75.32	9.41
AD-1706593.1	16.97	1.82	62.83	22.14	82.42	26.66
AD-1706587.1	17.58	1.56	58.63	25.19	80.99	11.23
AD-1706547.1	17.83	3.49	53.09	6.40	81.19	10.29
AD-1708399.1	17.89	2.66	59.18	20.24	81.63	18.75
AD-1706548.1	17.90	0.67	52.53	5.08	96.83	14.58
AD-1708368.1	21.79	3.78	74.77	6.39	117.69	7.52
AD-1706640.1	23.16	2.61	60.43	5.36	91.90	28.74
AD-1706641.1	23.47	7.60	61.82	8.03	86.84	9.06
AD-1708357.1	24.90	5.49	64.54	8.39	99.70	20.16
AD-1706524.1	25.32	5.84	71.07	11.04	105.11	25.09
AD-1706585.1	26.06	3.02	64.13	14.21	104.94	17.17
AD-1706590.1	27.08	6.74	90.13	35.33	97.84	35.28
AD-1708407.1	27.22	9.42	61.08	8.83	82.76	13.93
AD-1706594.1	28.01	3.55	68.81	7.80	93.18	9.04
AD-1706414.1	28.37	4.53	58.04	13.63	87.06	19.77
AD-1706538.1	28.83	3.95	87.81	10.78	103.20	18.94
AD-1708251.1	29.62	3.42	61.88	15.03	91.39	20.22
AD-1706546.1	30.40	3.43	74.52	6.92	108.55	16.73
AD-1706543.1	32.12	2.74	73.00	8.20	108.30	25.23
AD-1706536.1	32.84	7.47	64.01	14.33	92.38	12.26
AD-1706545.1	34.25	3.85	62.46	5.73	98.45	9.25
AD-1706520.1	35.55	5.51	81.69	15.12	110.53	13.75
AD-1706582.1	35.83	6.13	61.53	16.96	94.95	16.97
AD-1706525.1	36.55	4.29	94.16	23.25	91.09	12.66
AD-1708369.1	38.82	21.75	70.72	3.62	97.58	17.63
AD-1708255.1	39.07	5.04	67.52	11.96	90.89	8.17

	10 nM		1 nM		0.1 nM	
Duplex Name	% Avg message remaining	STDEV	% Avg message remaining	STDEV	% Avg message remaining	STDEV
AD-1706535.1	39.19	8.70	104.28	31.11	97.46	6.66
AD-1706415.1	39.83	5.22	55.55	6.77	80.55	9.38
AD-1706544.1	39.98	3.88	60.76	7.29	80.11	18.18
AD-1706639.1	42.73	3.36	79.43	15.67	101.15	20.49
AD-1706550.1	42.82	15.97	94.02	43.73	107.95	26.18
AD-1708248.1	43.04	3.60	68.74	8.58	93.13	19.62
AD-1708365.1	43.52	8.08	106.40	35.35	101.61	17.99
AD-1706589.1	43.66	11.75	73.57	3.09	103.81	11.11
AD-1706523.1	43.71	6.67	91.11	14.54	116.01	5.91
AD-1706586.1	44.05	8.35	99.17	34.89	102.65	24.81
AD-1706412.1	44.67	9.33	82.62	12.75	95.04	15.60
AD-1706420.1	45.19	4.57	71.65	14.31	101.49	40.85
AD-1708401.1	46.32	4.32	109.46	36.49	137.97	46.10
AD-1706537.1	47.21	3.01	83.85	7.81	113.39	14.02
AD-1708397.1	47.56	4.70	82.21	16.77	103.46	14.37
AD-1706592.1	49.61	12.76	74.80	17.42	103.97	30.99
AD-1706539.1	50.47	7.14	64.47	6.46	81.84	2.50
AD-1706532.1	51.25	5.15	79.01	18.04	96.02	7.54
AD-1706580.1	51.56	13.09	58.56	10.84	100.76	23.90
AD-1706413.1	51.63	5.56	67.89	6.33	81.80	12.55
AD-1706419.1	54.23	19.04	93.19	30.98	121.41	34.52
AD-1706581.1	54.84	7.00	71.33	14.93	84.09	14.17
AD-1708447.1	54.87	13.52	104.94	21.63	118.08	18.05
AD-1706579.1	54.95	7.90	70.62	4.25	104.36	27.78
AD-1708408.1	56.12	12.89	90.61	8.36	99.13	20.61
AD-1706549.1	56.65	9.42	81.71	9.47	97.16	9.63
AD-1708342.1	56.93	7.61	80.26	12.73	106.80	25.07
AD-1706636.1	57.82	5.41	85.94	12.63	99.00	13.47
AD-1706425.1	58.29	2.96	76.30	14.61	95.32	14.22
AD-1706578.1	60.60	13.60	87.09	12.39	109.98	28.08
AD-1706418.1	63.28	10.61	96.91	13.82	111.41	24.53
AD-1708356.1	64.77	12.61	78.57	18.09	99.15	15.61
AD-1708347.1	65.00	17.57	82.04	19.82	95.21	15.90
AD-1706424.1	65.38	7.09	85.09	16.40	105.96	30.35
AD-1706417.1	66.98	12.66	85.33	20.21	111.43	27.23
AD-1706521.1	68.72	12.27	90.93	12.68	119.35	25.53
AD-1706530.1	70.98	12.28	86.64	9.70	94.88	14.24
AD-1706522.1	71.46	9.68	106.53	20.33	92.61	7.37
AD-1706527.1	71.63	5.56	97.88	24.77	112.26	31.32
AD-1706416.1	72.34	8.83	80.67	4.08	98.15	20.87
AD-1706534.1	76.28	8.47	81.77	15.66	99.83	24.74

	10 nM		1 nM		0.1 nM	
Duplex Name	% Avg message remaining	STDEV	% Avg message remaining	STDEV	% Avg message remaining	STDEV
AD-1706421.1	79.32	6.14	93.79	19.12	122.72	30.72
AD-1711743.1	80.13	9.62	88.65	8.30	93.61	12.47
AD-1706635.1	80.53	12.44	85.68	19.07	105.70	21.04
AD-1706528.1	81.09	5.66	73.66	5.18	122.46	19.28
AD-1706637.1	82.19	27.49	90.88	12.79	111.05	20.25
AD-1708403.1	83.00	19.04	92.02	7.56	116.05	23.70
AD-1708405.1	85.44	23.49	103.54	43.41	116.29	44.00
AD-1706533.1	85.51	14.92	115.23	27.84	101.95	17.97
AD-1708344.1	85.73	11.66	97.48	5.76	110.94	21.22
AD-1708361.1	86.28	9.76	88.85	15.65	109.24	31.96
AD-1706423.1	88.17	11.15	84.06	8.73	122.58	38.31
AD-1708260.1	88.99	5.12	94.37	17.05	114.30	29.22
AD-1708350.1	90.61	12.13	85.27	9.24	100.73	9.67
AD-1706638.1	95.90	12.95	85.50	18.85	110.68	17.30
AD-1708402.1	99.66	13.44	91.37	13.19	111.56	29.33
AD-1706526.1	101.27	3.70	93.41	11.90	113.66	19.87
AD-1708249.1	102.18	16.36	97.35	19.73	116.55	34.10
AD-1706661.1	6.60	0.84	74.72	4.36	110.66	17.49
AD-1708473.1	6.62	1.40	69.52	3.82	108.89	15.87
AD-1706665.1	6.77	0.79	67.01	13.10	103.64	16.11
AD-1706650.1	7.00	1.13	70.73	11.82	108.62	8.15
AD-1706645.1	7.25	3.64	74.87	8.06	107.77	11.83
AD-1706653.1	7.74	1.35	76.42	7.69	113.74	17.40
AD-1711749.1	8.54	1.25	68.74	2.15	106.66	11.71
AD-1706763.1	8.70	2.21	72.90	15.62	107.52	10.92
AD-1708478.1	9.57	1.33	78.24	7.40	107.29	10.61
AD-1706749.1	10.07	1.20	74.95	9.09	99.46	4.18
AD-1706643.1	10.53	1.64	73.09	9.66	90.78	10.00
AD-1706666.1	13.18	2.44	80.01	9.39	106.83	5.84
AD-1706796.1	15.63	3.43	89.88	10.35	103.93	11.87
AD-1706667.1	17.36	4.27	101.51	16.36	111.65	19.15
AD-1706671.1	17.42	2.37	90.42	16.21	103.59	6.63
AD-1706662.1	18.09	2.45	95.05	11.73	105.69	13.23
AD-1706660.1	18.70	4.24	91.56	4.98	105.45	10.46
AD-1706668.1	19.20	2.47	80.70	4.94	104.90	16.86
AD-1706678.1	19.89	4.19	95.24	9.95	106.34	7.14
AD-1706761.1	20.09	5.94	103.36	8.72	110.93	4.49
AD-1706729.1	20.69	1.20	82.71	9.83	98.57	7.22
AD-1706758.1	20.84	2.84	97.40	12.07	111.12	8.71
AD-1706802.1	21.81	2.61	87.99	12.58	104.85	6.50
AD-1706762.1	21.86	1.22	87.78	3.24	106.95	10.71

	10 nM		1 nM		0.1 nM	
Duplex Name	% Avg message remaining	STDEV	% Avg message remaining	STDEV	% Avg message remaining	STDEV
AD-1706673.1	22.52	4.61	95.13	17.07	106.48	11.75
AD-1706656.1	24.59	2.05	83.54	7.22	100.64	2.81
AD-1706654.1	24.83	1.15	109.60	22.66	105.15	8.80
AD-1706651.1	25.30	2.94	93.94	14.27	112.44	11.34
AD-1708561.1	25.60	3.99	104.77	12.81	102.89	6.87
AD-1706644.1	26.90	0.85	84.09	3.99	101.42	5.45
AD-1706674.1	28.45	3.09	88.45	9.49	104.73	2.90
AD-1706759.1	29.16	20.00	85.18	8.32	110.91	17.22
AD-1711747.1	29.23	3.34	92.97	13.24	109.77	11.44
AD-1706655.1	29.64	16.36	94.04	14.12	106.67	15.84
AD-1706755.1	29.74	4.96	90.27	13.45	89.74	8.63
AD-1706750.1	29.94	9.26	87.13	8.39	109.44	12.06
AD-1706756.1	29.99	0.59	92.61	17.60	106.44	15.86
AD-1706799.1	30.02	5.93	97.59	14.48	111.47	11.09
AD-1708485.1	30.12	11.59	89.97	7.46	105.61	12.03
AD-1706652.1	31.17	4.31	94.61	4.74	105.02	6.14
AD-1706649.1	32.31	8.03	95.79	12.11	97.70	9.45
AD-1706764.1	32.90	0.57	96.72	28.52	109.38	11.25
AD-1706760.1	33.00	4.03	89.53	11.65	101.22	11.01
AD-1706748.1	35.18	4.35	96.77	10.82	110.03	9.91
AD-1711750.1	37.69	7.93	98.35	9.29	106.27	9.06
AD-1708457.1	38.56	5.40	93.19	5.67	107.79	12.22
AD-1706751.1	39.44	19.99	94.73	9.40	109.19	8.46
AD-1708454.1	40.71	3.27	89.75	12.18	107.44	15.74
AD-1706753.1	40.99	9.16	100.89	28.03	110.69	15.45
AD-1708564.1	41.34	4.73	88.93	5.25	95.35	1.26
AD-1706746.1	42.57	6.65	88.82	8.77	107.73	13.47
AD-1708464.1	42.62	3.80	95.60	4.87	104.61	11.22
AD-1706672.1	43.78	10.25	95.27	10.60	98.19	9.52
AD-1711746.1	45.65	2.07	112.78	25.92	102.47	13.57
AD-1708483.1	48.04	7.38	101.48	24.43	102.75	7.74
AD-1708565.1	48.61	10.48	99.08	14.13	99.70	5.83
AD-1706797.1	48.74	5.96	90.55	14.02	100.91	9.04
AD-1711748.1	50.55	10.58	104.32	12.32	105.92	11.82
AD-1706646.1	50.78	11.75	105.91	14.08	101.10	6.21
AD-1708468.1	50.98	6.40	99.67	13.25	111.96	9.91
AD-1706664.1	51.96	13.92	90.04	8.66	108.53	15.23
AD-1706747.1	52.03	8.41	103.06	21.38	114.38	11.30
AD-1706765.1	53.56	7.63	93.88	18.00	95.27	4.65
AD-1706800.1	53.95	8.49	95.50	8.96	107.45	9.95
AD-1708462.1	54.04	6.29	92.64	7.40	118.65	14.56

	10 nM		1 nM		0.1 nM	
Duplex Name	% Avg message remaining	STDEV	% Avg message remaining	STDEV	% Avg message remaining	STDEV
AD-1706752.1	55.51	8.14	88.82	6.13	97.91	7.54
AD-1706745.1	57.43	9.49	93.02	5.38	97.74	7.60
AD-1706669.1	63.72	7.32	90.06	8.80	102.31	8.84
AD-1708466.1	64.64	14.05	95.96	16.75	100.99	12.25
AD-1706675.1	64.77	2.67	100.96	6.87	108.17	9.63
AD-1711751.1	65.52	14.01	99.40	20.89	95.72	19.18
AD-1711745.1	68.13	7.56	101.21	11.15	100.69	4.58
AD-1706803.1	73.64	8.01	92.32	11.60	104.35	10.44
AD-1706754.1	73.79	5.20	88.05	10.42	101.75	12.74
AD-1708482.1	75.95	14.79	99.22	6.65	99.58	19.78
AD-1706801.1	78.50	13.33	93.60	9.95	100.32	4.13
AD-1708458.1	78.70	7.33	87.84	4.93	103.98	9.93
AD-1711752.1	79.38	12.59	82.60	8.23	97.25	4.37
AD-1708567.1	80.84	18.53	93.23	9.30	100.82	7.56
AD-1706804.1	81.90	4.96	97.61	18.31	104.98	5.27
AD-1706670.1	83.22	11.36	101.97	12.99	99.92	6.96
AD-1706732.1	85.31	21.66	96.44	10.50	104.05	12.80
AD-1708647.1	85.35	15.28	119.04	41.38	108.04	20.54
AD-1706798.1	85.62	7.06	103.36	13.05	100.71	15.44
AD-1708476.1	88.09	5.36	99.39	9.61	107.56	11.68
AD-1708650.1	89.03	12.02	113.51	14.13	106.25	8.75
AD-1706735.1	92.62	7.77	111.07	11.08	108.42	10.58
AD-1706731.1	94.79	6.67	97.21	9.56	99.62	3.81
AD-1708559.1	95.00	7.62	100.14	12.07	102.77	7.98
AD-1708648.1	108.92	28.51	99.75	9.85	106.66	6.01
AD-1706854.1	25.37	3.01	103.72	47.41	103.23	9.61
AD-1708766.1	26.83	6.17	96.07	18.36	102.24	7.86
AD-1706929.1	27.18	8.06	75.76	7.80	97.46	18.20
AD-1706934.1	27.89	6.08	92.28	12.84	98.05	12.81
AD-1706879.1	35.05	3.81	88.34	13.15	104.53	21.27
AD-1706833.1	35.80	6.70	95.10	10.15	105.49	8.37
AD-1706856.1	36.63	4.23	110.20	26.30	107.65	12.80
AD-1706858.1	37.72	6.21	81.87	12.77	92.77	14.43
AD-1706930.1	40.50	1.61	108.05	35.35	86.82	30.20
AD-1706875.1	40.60	4.27	118.37	25.42	98.68	15.75
AD-1706855.1	41.18	11.54	131.44	55.87	98.30	19.73
AD-1706863.1	43.26	4.15	100.28	15.63	92.69	21.34
AD-1706933.1	43.61	9.36	102.54	30.69	104.09	5.81
AD-1706849.1	47.30	6.81	102.81	19.95	84.13	29.87
AD-1708707.1	50.03	11.97	108.24	34.23	104.48	11.54
AD-1706831.1	52.48	7.54	115.05	20.86	102.75	17.63

	10 nM		1 nM		0.1 nM	
Duplex Name	% Avg message remaining	STDEV	% Avg message remaining	STDEV	% Avg message remaining	STDEV
AD-1706861.1	52.54	16.14	101.45	26.45	108.92	30.66
AD-1706878.1	53.45	9.24	104.31	24.53	108.89	11.75
AD-1706860.1	54.13	8.56	93.86	12.56	107.75	22.52
AD-1706876.1	54.16	11.40	102.97	37.17	100.98	9.73
AD-1706922.1	54.52	11.46	116.79	22.40	97.89	10.04
AD-1706877.1	54.71	8.75	124.94	31.32	111.27	15.98
AD-1706910.1	56.13	5.44	100.89	10.10	99.37	24.39
AD-1708724.1	56.38	11.75	113.47	33.12	96.26	14.65
AD-1706851.1	56.88	8.13	99.19	16.09	100.04	9.14
AD-1706848.1	57.59	19.63	88.30	19.11	108.41	23.17
AD-1706862.1	57.90	17.76	100.76	21.18	98.92	19.89
AD-1706873.1	60.54	4.01	77.98	11.86	83.33	21.11
AD-1706925.1	61.27	5.41	141.22	45.16	112.13	14.93
AD-1706807.1	63.36	6.27	119.59	35.44	106.38	16.29
AD-1706808.1	63.79	6.32	81.18	2.15	83.79	14.66
AD-1706913.1	64.51	5.44	86.83	10.13	102.68	11.81
AD-1708771.1	65.72	13.62	73.79	9.06	99.46	12.36
AD-1708657.1	66.55	5.60	90.80	25.74	100.19	11.20
AD-1706852.1	66.74	13.45	110.13	42.60	109.17	10.74
AD-1706908.1	68.07	13.31	114.93	23.24	97.36	4.38
AD-1706927.1	69.35	9.74	96.16	18.41	110.08	10.62
AD-1706932.1	69.69	5.02	104.45	21.71	97.67	11.10
AD-1706834.1	70.38	6.62	84.04	8.43	99.35	17.43
AD-1706918.1	71.54	17.49	113.13	10.29	114.70	17.65
AD-1706866.1	71.83	14.46	88.92	33.22	106.35	14.58
AD-1706983.1	73.76	8.01	112.98	24.54	86.85	26.78
AD-1706859.1	74.92	24.74	90.87	21.71	100.06	13.80
AD-1706982.1	76.10	19.78	106.63	36.38	98.22	13.19
AD-1706835.1	77.42	15.50	104.09	23.87	101.43	22.46
AD-1706921.1	77.52	19.03	100.22	19.85	98.95	16.37
AD-1706989.1	78.00	22.52	93.63	12.00	92.94	19.53
AD-1708746.1	79.02	19.60	114.66	35.50	100.74	15.01
AD-1706850.1	79.32	13.85	91.59	5.45	94.78	15.55
AD-1706985.1	80.89	13.10	88.36	16.54	108.60	10.83
AD-1706923.1	81.37	21.19	106.79	11.31	103.06	13.83
AD-1706909.1	81.73	14.01	116.11	47.50	105.49	14.70
AD-1706811.1	81.88	17.25	92.52	16.10	101.66	13.54
AD-1708813.1	85.76	27.33	115.49	21.38	109.30	9.84
AD-1708748.1	87.90	14.15	86.02	8.62	100.81	2.57
AD-1706984.1	88.94	16.25	113.85	25.66	108.56	14.03
AD-1708697.1	89.52	10.09	120.53	38.28	113.90	9.54

	10 nM		1 nM		0.1 nM	
Duplex Name	% Avg message remaining	STDEV	% Avg message remaining	STDEV	% Avg message remaining	STDEV
AD-1706911.1	89.91	17.73	101.81	15.95	95.76	15.10
AD-1708709.1	90.74	14.16	100.10	17.53	107.72	14.67
AD-1706853.1	91.75	13.32	113.59	26.59	113.95	29.85
AD-1706926.1	96.63	6.03	95.17	15.95	103.87	30.98
AD-1706832.1	97.54	16.47	104.10	33.68	107.00	11.63
AD-1706987.1	98.29	12.34	95.69	20.12	98.30	10.47
AD-1706809.1	98.67	26.38	99.13	15.24	82.43	14.61
AD-1708700.1	99.27	21.13	106.72	9.99	96.03	19.58
AD-1706988.1	101.65	24.29	106.78	29.53	106.48	20.25
AD-1706914.1	101.79	11.21	90.48	4.14	100.55	13.62
AD-1706931.1	103.40	66.16	107.78	26.76	101.02	24.37
AD-1708683.1	104.06	8.55	125.73	42.10	107.19	5.34
AD-1711754.1	104.34	15.76	114.12	40.53	105.06	9.88
AD-1706836.1	106.36	12.55	100.96	22.23	103.19	32.20
AD-1708662.1	107.32	8.18	88.67	10.59	96.58	9.88
AD-1708759.1	107.49	28.12	89.51	14.33	101.64	19.99
AD-1708680.1	108.20	15.23	97.77	24.39	102.61	12.78
AD-1706874.1	109.21	20.84	100.69	38.85	100.93	14.52
AD-1706864.1	110.63	16.57	101.39	23.00	101.73	22.95
AD-1711753.1	111.19	14.58	93.59	17.39	110.58	13.90
AD-1706912.1	111.75	15.92	105.01	18.67	108.43	10.78
AD-1708751.1	112.97	12.72	116.26	23.93	104.25	11.26
AD-1708721.1	114.27	20.90	100.77	14.87	104.56	12.44
AD-1708819.1	116.07	29.98	91.50	9.56	112.22	10.56
AD-1708698.1	117.55	77.59	94.05	14.37	72.00	40.57
AD-1706857.1	118.83	19.85	117.65	40.36	108.84	4.65
AD-1708704.1	119.12	34.40	128.50	32.16	109.76	22.57
AD-1706812.1	119.69	43.53	122.34	33.51	87.62	24.43
AD-1708719.1	122.89	21.25	107.22	23.83	99.76	9.98
AD-1708706.1	127.72	37.05	95.70	14.61	99.73	16.92
AD-1708764.1	131.45	28.75	107.92	18.70	105.12	19.46
AD-1708763.1	137.95	34.65	119.14	40.49	113.97	7.55
AD-1708711.1	175.32	14.43	126.75	39.55	116.98	7.84
AD-1707061.1	8.33	1.86	88.81	10.65	90.67	24.02
AD-1707058.1	9.98	1.11	94.75	9.86	101.20	14.48
AD-1707063.1	12.85	3.24	99.95	14.44	104.17	16.47
AD-1707050.1	13.92	2.38	93.91	11.33	98.57	8.81
AD-1707060.1	13.97	2.53	92.54	10.48	120.97	7.47
AD-1707075.1	16.10	2.42	99.13	4.47	111.23	16.36
AD-1707017.1	17.50	2.11	99.33	5.23	109.99	17.00
AD-1708882.1	18.85	3.63	101.54	16.25	108.57	19.96

	10 nM		1 nM		0.1 nM	
Duplex Name	% Avg message remaining	STDEV	% Avg message remaining	STDEV	% Avg message remaining	STDEV
AD-1707086.1	19.02	2.90	101.81	13.51	110.60	8.16
AD-1707088.1	19.02	1.40	105.64	12.93	111.73	30.08
AD-1707087.1	19.19	2.03	105.11	7.90	115.78	14.42
AD-1707053.1	19.50	3.76	94.83	13.66	109.87	21.89
AD-1711760.1	20.00	1.81	88.73	4.33	110.48	5.26
AD-1711761.1	21.94	3.63	97.37	7.10	120.53	32.80
AD-1707051.1	22.12	1.59	105.96	10.05	112.06	12.44
AD-1707084.1	22.54	7.73	105.12	14.83	112.28	15.31
AD-1707085.1	22.65	1.28	97.83	9.25	123.86	10.32
AD-1707054.1	23.29	2.06	99.81	8.18	109.43	12.98
AD-1707052.1	23.59	2.74	94.34	13.80	111.93	13.23
AD-1707095.1	25.27	3.63	104.94	27.94	110.90	14.62
AD-1707092.1	25.31	6.58	92.76	19.70	101.56	14.57
AD-1711756.1	25.49	5.39	96.10	8.16	104.56	9.24
AD-1707062.1	25.58	5.66	92.16	4.07	117.28	15.75
AD-1707047.1	25.77	8.14	99.31	12.88	114.18	9.49
AD-1707070.1	27.17	2.34	94.16	12.13	119.42	12.78
AD-1708899.1	27.37	5.49	100.65	3.32	111.69	14.24
AD-1708902.1	27.66	3.25	92.63	7.26	106.35	19.13
AD-1707098.1	28.90	9.71	92.87	12.33	96.92	27.94
AD-1707066.1	32.02	8.19	94.37	9.02	107.58	12.73
AD-1707083.1	34.19	13.45	97.84	13.54	126.24	32.35
AD-1707057.1	34.23	5.87	100.62	7.09	121.36	13.17
AD-1707059.1	34.79	4.28	108.93	6.94	125.08	3.39
AD-1707018.1	36.61	3.49	112.84	18.20	103.78	12.48
AD-1707067.1	37.21	9.85	101.33	2.41	109.01	6.56
AD-1711758.1	37.55	1.79	95.70	13.53	101.50	11.23
AD-1707082.1	39.65	9.15	98.31	8.81	107.83	11.35
AD-1707076.1	40.68	4.39	100.27	1.83	120.22	15.13
AD-1707048.1	41.96	8.19	104.43	20.77	100.43	17.11
AD-1707019.1	42.99	5.23	99.22	6.55	107.64	17.16
AD-1708890.1	43.91	18.14	100.48	14.09	98.26	19.93
AD-1707093.1	44.02	1.40	105.14	8.37	117.58	5.28
AD-1708911.1	44.15	7.91	95.63	15.64	108.40	21.86
AD-1707105.1	44.17	8.08	110.35	11.53	115.89	15.69
AD-1707064.1	44.50	3.66	102.70	9.58	110.63	13.42
AD-1707074.1	44.84	9.51	101.54	7.85	104.90	13.69
AD-1707056.1	46.78	10.10	102.19	11.68	113.06	22.60
AD-1711762.1	49.02	6.03	97.20	2.29	107.59	3.47
AD-1707078.1	52.73	5.48	107.20	15.35	115.13	11.87
AD-1707030.1	53.66	6.53	111.11	14.02	113.90	15.90

	10 nM		1 nM		0.1 nM	
Duplex Name	% Avg message remaining	STDEV	% Avg message remaining	STDEV	% Avg message remaining	STDEV
AD-1707077.1	53.70	8.63	101.57	13.11	111.56	8.32
AD-1707065.1	53.74	1.99	108.29	8.35	122.33	12.73
AD-1707127.1	54.77	8.44	105.15	8.40	108.70	12.81
AD-1707094.1	57.47	8.53	108.23	12.77	105.37	10.86
AD-1707020.1	58.01	13.48	101.09	15.13	110.62	22.22
AD-1707021.1	58.79	18.20	124.68	43.20	100.48	22.35
AD-1707080.1	58.94	7.31	104.10	9.25	116.61	6.61
AD-1707126.1	59.59	9.32	96.42	13.31	109.61	12.60
AD-1708908.1	59.96	11.47	105.79	7.21	205.27	163.17
AD-1707125.1	60.35	4.53	103.79	11.65	116.67	11.23
AD-1708901.1	60.42	16.23	92.03	15.94	119.73	19.06
AD-1711755.1	60.73	5.54	97.60	4.64	113.80	6.04
AD-1707055.1	61.12	9.30	96.50	10.89	102.20	22.76
AD-1707014.1	61.49	4.18	99.29	8.04	109.12	13.68
AD-1707023.1	62.68	15.83	97.52	15.74	104.31	8.10
AD-1706991.1	64.23	11.46	88.71	9.37	95.92	12.46
AD-1707081.1	64.73	13.16	107.14	11.08	112.73	29.65
AD-1708872.1	66.53	19.46	88.90	9.68	112.87	12.88
AD-1707097.1	67.80	12.95	105.41	12.10	108.88	12.85
AD-1708907.1	69.34	5.34	111.02	6.94	103.77	12.88
AD-1707013.1	70.83	20.94	107.47	7.74	94.44	11.05
AD-1707015.1	71.33	23.32	105.50	8.59	106.57	16.42
AD-1708887.1	71.55	15.47	106.33	10.29	110.30	17.14
AD-1707129.1	71.65	20.96	103.58	6.43	91.33	26.27
AD-1708844.1	72.88	12.10	116.14	37.29	110.62	3.95
AD-1708856.1	73.95	18.67	103.53	5.03	80.24	39.02
AD-1708875.1	76.60	11.35	99.59	15.59	135.66	18.88
AD-1708889.1	79.17	11.66	110.70	17.57	120.98	7.68
AD-1707049.1	80.31	5.85	108.76	7.19	119.03	5.82
AD-1711763.1	84.78	21.20	99.75	14.69	113.14	14.33
AD-1707024.1	87.28	6.38	93.68	12.29	108.98	14.26
AD-1707022.1	87.29	14.92	98.16	14.55	102.07	11.52
AD-1707128.1	87.44	2.93	94.65	5.66	109.94	20.88
AD-1711759.1	88.12	18.24	106.57	14.25	111.09	6.10
AD-1707016.1	88.23	17.94	94.55	2.56	104.53	16.40
AD-1711757.1	88.63	12.42	95.80	12.28	122.43	7.14
AD-1708842.1	89.93	21.36	125.99	41.26	125.37	9.77
AD-1708849.1	91.50	19.06	116.08	31.45	79.83	13.17
AD-1706990.1	91.94	11.09	125.77	47.09	109.78	6.85
AD-1708921.1	112.06	22.19	112.08	21.18	113.33	20.65
AD-1707025.1	122.67	6.40	108.76	12.64	120.07	12.98

	10 nM		1 nM		0.1 nM	
Duplex Name	% Avg message remaining	STDEV	% Avg message remaining	STDEV	% Avg message remaining	STDEV
AD-1707152.1	13.98	2.96	115.15	23.84	101.84	9.78
AD-1708956.1	16.83	1.85	87.80	11.44	100.21	20.00
AD-1707143.1	17.33	4.80	104.40	35.77	110.39	5.62
AD-1707136.1	17.36	2.50	98.63	18.72	82.73	17.99
AD-1707146.1	20.98	3.84	108.41	18.98	107.36	8.80
AD-1707132.1	22.58	2.33	97.25	9.13	105.94	17.38
AD-1707161.1	22.68	5.03	89.57	15.63	96.67	20.00
AD-1707170.1	23.62	2.34	95.73	12.86	95.31	5.70
AD-1707154.1	25.29	4.40	86.51	3.91	105.27	17.71
AD-1707144.1	26.58	6.16	94.66	17.37	101.45	9.43
AD-1707134.1	28.54	6.01	99.26	11.19	89.22	17.73
AD-1707159.1	28.79	5.65	107.12	15.73	105.46	10.57
AD-1707149.1	29.32	2.79	155.91	29.51	94.83	22.67
AD-1707137.1	29.64	2.96	105.39	14.31	104.18	20.24
AD-1708957.1	30.15	5.52	88.33	6.86	98.55	13.20
AD-1707160.1	32.76	3.02	88.95	7.30	116.76	17.01
AD-1711769.1	32.88	5.54	83.54	10.19	93.62	9.98
AD-1711767.1	33.68	3.93	92.83	21.12	106.68	6.50
AD-1711770.1	34.57	6.07	99.82	17.88	93.32	18.62
AD-1707169.1	36.98	4.18	110.99	33.26	105.09	14.13
AD-1707210.1	37.13	8.07	95.18	12.01	100.39	16.02
AD-1711765.1	37.53	15.27	100.34	14.43	100.63	30.48
AD-1707173.1	37.95	3.50	96.79	15.17	101.14	6.92
AD-1707162.1	38.24	3.82	116.22	44.16	107.92	20.94
AD-1708974.1	38.68	2.37	109.51	33.43	100.84	3.83
AD-1707140.1	38.77	6.98	87.96	19.28	102.71	19.68
AD-1707145.1	38.82	7.25	82.00	14.95	112.74	34.49
AD-1708971.1	38.93	6.26	104.04	20.22	94.40	15.26
AD-1707166.1	39.32	7.06	101.96	7.66	98.75	7.43
AD-1707151.1	40.38	6.23	97.29	17.49	106.17	15.07
AD-1708963.1	40.88	2.50	118.93	18.80	108.47	11.31
AD-1707153.1	40.91	6.24	92.88	15.02	97.58	7.63
AD-1707157.1	44.06	14.33	97.51	12.37	98.71	6.68
AD-1707158.1	44.79	7.72	99.01	16.41	111.74	9.29
AD-1708990.1	46.04	5.68	96.56	15.31	110.10	7.50
AD-1707197.1	46.35	4.78	99.28	9.06	103.29	2.99
AD-1707168.1	46.52	7.25	114.85	40.01	121.67	21.33
AD-1707164.1	46.52	4.87	107.61	4.25	105.06	9.80
AD-1707142.1	48.03	9.69	88.73	20.26	97.14	19.70
AD-1707147.1	48.39	9.65	102.36	10.85	106.88	15.92
AD-1707133.1	48.55	7.85	90.89	12.15	94.27	15.48

	10 nM		1 nM		0.1 nM	
Duplex Name	% Avg message remaining	STDEV	% Avg message remaining	STDEV	% Avg message remaining	STDEV
AD-1707156.1	50.21	9.50	87.48	10.24	100.76	13.47
AD-1707150.1	50.56	5.47	128.77	29.09	106.27	11.80
AD-1711768.1	51.31	6.81	94.55	5.18	86.83	16.67
AD-1707177.1	52.17	7.40	97.31	19.25	93.24	6.70
AD-1707176.1	52.38	5.97	103.31	15.62	123.43	31.50
AD-1707209.1	54.24	10.92	90.52	15.49	93.77	7.34
AD-1707135.1	55.06	6.19	97.90	12.98	95.86	18.67
AD-1707201.1	56.43	9.50	141.33	27.95	111.61	7.09
AD-1707141.1	56.83	21.84	106.75	16.22	96.91	17.42
AD-1707139.1	56.98	2.61	108.61	19.57	96.36	9.51
AD-1707163.1	57.43	9.97	102.98	6.88	110.92	8.77
AD-1707211.1	58.08	16.77	100.46	12.93	89.06	15.85
AD-1707171.1	59.68	7.29	88.87	10.18	96.17	14.09
AD-1711764.1	61.91	4.80	88.61	13.52	94.06	7.03
AD-1709201.1	62.48	5.31	83.62	13.75	89.35	9.59
AD-1707167.1	64.49	6.21	88.47	6.99	93.88	9.17
AD-1707155.1	64.64	13.86	107.37	28.96	106.86	12.33
AD-1707202.1	65.35	7.10	95.62	18.04	98.52	13.35
AD-1707203.1	66.47	8.06	105.42	26.74	102.48	8.85
AD-1708977.1	67.97	6.89	111.17	12.98	112.14	9.94
AD-1707178.1	68.77	23.43	115.97	35.56	85.13	14.23
AD-1707200.1	69.32	10.45	105.72	23.83	104.89	7.43
AD-1707138.1	74.31	12.00	107.37	12.17	108.82	8.30
AD-1707207.1	76.91	13.93	119.04	36.69	105.00	9.19
AD-1707190.1	77.90	11.71	92.83	14.82	93.57	9.45
AD-1708984.1	78.01	8.72	95.54	14.71	103.87	15.45
AD-1707148.1	78.60	9.21	105.45	9.27	106.10	20.83
AD-1707172.1	79.74	8.47	106.69	11.16	99.53	16.18
AD-1708986.1	80.65	10.97	121.14	24.43	108.29	8.71
AD-1707165.1	82.20	12.26	128.70	34.94	101.82	15.99
AD-1708962.1	84.11	7.41	91.81	13.52	81.71	30.08
AD-1707204.1	84.21	9.53	104.10	25.70	98.83	16.90
AD-1711772.1	84.59	8.95	91.65	21.63	102.48	22.65
AD-1711766.1	87.33	12.72	93.37	15.24	109.16	2.18
AD-1709022.1	87.35	12.09	89.48	15.28	102.93	16.68
AD-1709028.1	88.42	9.93	93.89	24.08	104.19	7.73
AD-1707179.1	89.17	13.08	100.09	8.41	105.13	8.34
AD-1707205.1	92.52	12.36	108.95	4.96	112.68	11.95
AD-1707180.1	93.48	21.70	98.26	9.31	105.78	14.35
AD-1707174.1	93.87	10.14	95.00	16.23	109.95	15.51
AD-1707208.1	94.27	14.12	117.41	38.11	110.38	9.20

	10 nM		1 nM		0.1 nM	
Duplex Name	% Avg message remaining	STDEV	% Avg message remaining	STDEV	% Avg message remaining	STDEV
AD-1708976.1	94.71	18.83	101.36	7.68	107.96	12.07
AD-1709021.1	97.52	17.75	92.57	13.43	99.20	6.38
AD-1707189.1	99.48	6.62	96.95	9.64	97.68	11.39
AD-1707206.1	100.82	16.60	96.42	11.21	106.77	24.93
AD-1711771.1	104.52	3.03	88.98	15.82	102.81	12.47
AD-1709026.1	116.40	6.19	101.82	20.63	112.17	12.49
AD-1707182.1	118.95	22.62	116.54	37.28	114.08	5.65
AD-1709009.1	119.75	15.80	122.88	22.76	108.96	16.73
AD-1709032.1	10.65	1.46	72.91	9.78	87.30	6.27
AD-1709044.1	10.97	0.72	93.48	14.31	112.97	13.33
AD-1707224.1	12.74	2.75	71.54	13.48	91.74	19.65
AD-1707306.1	13.25	1.84	78.47	12.33	103.70	13.65
AD-1707225.1	13.42	2.08	75.80	6.57	107.46	18.05
AD-1707223.1	13.58	4.79	79.36	12.93	108.17	24.63
AD-1707305.1	13.79	0.84	97.69	13.40	103.89	16.61
AD-1711773.1	13.84	1.32	90.16	16.57	134.96	30.18
AD-1707214.1	14.01	4.99	80.78	9.25	102.66	21.99
AD-1709038.1	14.03	1.38	100.99	17.22	138.67	38.28
AD-1707317.1	14.12	1.62	84.03	15.86	107.44	6.76
AD-1707216.1	14.52	2.86	86.31	10.19	85.93	0.00
AD-1707318.1	14.74	1.94	69.40	5.08	127.81	35.42
AD-1707304.1	15.23	2.90	97.01	7.85	152.32	32.19
AD-1707313.1	15.77	3.15	80.19	14.57	98.62	21.63
AD-1707221.1	16.00	2.73	83.56	12.11	104.63	25.69
AD-1707213.1	17.50	1.12	91.79	13.61	110.12	14.97
AD-1707218.1	18.01	2.72	95.39	8.58	137.53	31.38
AD-1709130.1	18.28	2.33	73.33	9.92	95.68	6.54
AD-1711774.1	18.77	16.50	98.28	26.33	146.32	49.75
AD-1707303.1	18.77	2.61	86.31	8.27	118.33	22.15
AD-1707290.1	19.51	2.26	97.82	7.63	114.46	14.53
AD-1709034.1	19.87	8.67	95.49	13.97	134.79	30.19
AD-1707289.1	21.00	5.23	94.06	5.36	111.31	11.21
AD-1707280.1	21.21	2.95	86.67	9.47	96.46	8.51
AD-1707212.1	22.71	3.39	94.41	5.67	120.86	31.47
AD-1707288.1	22.72	4.43	93.00	14.56	113.10	14.44
AD-1707291.1	22.84	3.29	105.07	22.57	105.16	16.77
AD-1707314.1	23.13	3.99	98.59	23.48	106.37	23.07
AD-1707308.1	23.74	4.68	95.43	13.97	113.65	28.74
AD-1707217.1	25.94	18.18	80.34	11.48	105.73	13.57
AD-1707287.1	25.99	6.84	92.78	9.70	108.94	18.00
AD-1707299.1	26.27	3.08	97.87	5.04	123.11	10.32

	10 nM		1 nM		0.1 nM	
Duplex Name	% Avg message remaining	STDEV	% Avg message remaining	STDEV	% Avg message remaining	STDEV
AD-1707292.1	27.32	2.25	99.62	13.65	103.35	36.19
AD-1709124.1	27.62	2.53	93.80	21.22	117.31	37.59
AD-1707312.1	28.79	3.24	101.19	13.56	125.78	26.36
AD-1707311.1	29.58	5.31	102.79	19.49	108.80	18.25
AD-1707231.1	29.70	3.41	110.87	12.10	122.78	6.80
AD-1707315.1	29.82	4.37	94.22	15.09	117.40	27.65
AD-1709041.1	30.64	5.89	112.79	34.30	123.67	39.64
AD-1709090.1	30.91	4.76	96.67	16.65	106.46	17.17
AD-1707337.1	31.57	5.82	93.58	16.80	108.70	17.59
AD-1707281.1	33.35	3.66	101.45	3.78	107.40	22.02
AD-1707284.1	33.41	3.61	98.04	21.19	117.03	25.08
AD-1707310.1	35.62	1.48	118.56	40.26	107.58	17.75
AD-1709102.1	35.85	4.29	107.66	21.90	124.11	45.38
AD-1707307.1	35.88	8.73	96.17	12.20	109.75	10.94
AD-1707226.1	36.27	4.27	107.71	10.16	111.11	11.64
AD-1707302.1	36.97	7.05	91.71	19.52	113.79	16.00
AD-1709126.1	37.18	7.60	101.43	19.25	124.72	16.78
AD-1707228.1	38.56	18.34	98.73	17.99	112.83	33.73
AD-1707278.1	41.71	3.76	106.79	12.12	120.88	13.90
AD-1709104.1	42.57	6.08	98.63	15.39	107.51	18.98
AD-1707227.1	43.56	5.85	105.34	7.24	106.96	21.11
AD-1707279.1	43.64	6.62	95.09	24.45	98.32	22.69
AD-1709122.1	45.93	9.47	121.35	21.87	110.30	15.15
AD-1709052.1	48.00	6.56	104.18	17.40	141.43	55.52
AD-1707286.1	49.25	9.69	96.94	11.77	107.88	8.01
AD-1707232.1	49.71	4.79	103.13	6.35	101.42	20.85
AD-1707239.1	51.17	9.25	94.08	19.53	111.03	12.43
AD-1709100.1	51.61	16.14	106.55	9.21	138.74	28.67
AD-1707293.1	52.59	13.82	118.95	30.71	102.52	20.23
AD-1707338.1	52.76	8.61	101.81	10.45	115.79	26.48
AD-1707283.1	53.75	5.20	120.04	14.87	136.81	54.63
AD-1707285.1	54.11	6.28	108.86	7.48	113.13	12.98
AD-1707301.1	55.03	8.84	90.63	17.10	107.24	27.55
AD-1707309.1	56.19	6.30	97.08	9.15	105.76	21.42
AD-1707240.1	58.92	8.28	96.05	10.01	93.42	16.45
AD-1707316.1	59.31	17.56	109.46	32.98	157.17	69.02
AD-1707277.1	60.63	17.08	100.69	11.68	115.49	9.64
AD-1709106.1	61.42	6.05	98.37	14.84	129.70	28.96
AD-1709120.1	62.12	11.73	96.87	22.29	120.52	32.78
AD-1707276.1	62.36	7.14	101.51	20.17	100.78	19.23
AD-1709148.1	62.57	15.47	94.00	3.55	95.21	2.66

	10 nM		1 nM		0.1 nM	
Duplex Name	% Avg message remaining	STDEV	% Avg message remaining	STDEV	% Avg message remaining	STDEV
AD-1707275.1	62.62	6.51	93.58	14.35	99.46	19.67
AD-1709111.1	63.90	15.14	95.56	9.44	120.37	39.53
AD-1709097.1	69.40	7.55	103.39	27.37	128.13	10.58
AD-1707282.1	69.63	7.45	99.24	17.79	124.74	38.28
AD-1707234.1	70.71	9.87	114.33	37.40	110.04	19.59
AD-1707230.1	74.46	12.47	95.56	8.67	115.51	17.32
AD-1709098.1	79.18	4.31	104.27	10.48	116.87	26.13
AD-1707241.1	79.49	9.37	111.57	20.66	120.03	23.30
AD-1707236.1	85.92	13.55	109.82	23.40	131.32	45.71
AD-1709128.1	86.19	11.09	117.37	14.30	114.43	20.56
AD-1707242.1	87.51	6.96	97.20	14.18	110.78	22.01
AD-1707233.1	91.33	10.63	105.56	19.90	95.12	23.29
AD-1707237.1	91.92	10.46	106.06	19.52	113.76	36.13
AD-1707229.1	92.04	4.24	101.96	21.38	130.00	26.36
AD-1709056.1	94.72	20.30	109.17	32.34	119.96	16.65
AD-1709031.1	107.23	18.65	105.11	9.56	115.47	29.46
AD-1707636.1	10.58	3.09	73.37	13.26	101.03	16.01
AD-1711779.1	12.37	2.63	71.60	15.39	110.73	23.21
AD-1707639.1	14.43	3.04	76.92	14.30	99.84	12.54
AD-1707641.1	14.56	1.31	72.69	13.14	87.79	19.99
AD-1707640.1	15.36	5.50	73.67	8.05	84.94	24.69
AD-1707638.1	15.84	2.03	74.50	10.42	102.75	14.50
AD-1707637.1	16.00	1.31	84.11	20.33	120.69	21.72
AD-1707340.1	18.02	4.57	71.49	7.53	86.85	11.99
AD-1707632.1	19.56	3.37	101.07	23.16	99.62	10.24
AD-1711775.1	20.20	2.65	91.97	18.77	103.33	4.55
AD-1707339.1	21.62	5.49	91.29	16.30	107.99	14.63
AD-1707634.1	23.26	5.19	94.39	10.58	110.43	6.43
AD-1709151.1	24.09	2.26	95.46	13.85	85.84	17.45
AD-1709442.1	24.19	1.70	99.99	21.91	106.91	7.38
AD-1707630.1	24.82	2.27	82.71	18.99	100.07	9.51
AD-1709310.1	25.64	4.25	113.85	44.32	117.47	5.21
AD-1707605.1	25.97	3.89	94.46	16.93	109.86	6.59
AD-1709372.1	27.94	2.72	115.20	28.81	94.89	9.83
AD-1707631.1	28.93	4.48	100.66	29.44	98.29	12.45
AD-1711776.1	29.75	7.50	96.97	16.01	79.21	26.10
AD-1707633.1	30.49	6.28	103.63	27.18	99.15	10.39
AD-1709301.1	31.17	2.49	100.61	18.34	106.10	9.33
AD-1707466.1	33.17	3.58	80.17	10.16	91.78	17.83
AD-1709410.1	33.26	11.51	109.37	45.97	89.98	28.25
AD-1707629.1	34.41	10.14	100.46	13.51	108.44	26.17

	10 nM		1 nM		0.1 nM	
Duplex Name	% Avg message remaining	STDEV	% Avg message remaining	STDEV	% Avg message remaining	STDEV
AD-1707388.1	34.54	7.23	95.22	14.50	102.57	10.06
AD-1707341.1	35.41	11.95	89.30	5.48	100.63	9.92
AD-1707472.1	36.07	7.86	79.99	12.62	97.28	14.58
AD-1707470.1	37.22	3.26	80.96	13.21	106.70	7.03
AD-1709300.1	37.80	2.04	133.54	24.47	107.60	9.91
AD-1707606.1	37.97	8.54	103.68	30.81	99.47	10.48
AD-1709434.1	38.13	5.93	93.06	10.01	92.27	6.32
AD-1707479.1	38.62	3.53	100.45	19.44	104.42	10.85
AD-1707474.1	40.76	12.33	91.91	7.21	92.10	6.30
AD-1707478.1	40.81	7.35	92.42	19.60	92.52	18.25
AD-1709433.1	40.81	2.17	93.17	12.95	107.44	15.95
AD-1707342.1	41.92	3.25	95.88	23.23	99.12	7.85
AD-1707481.1	43.58	6.80	82.30	6.97	84.65	18.42
AD-1707577.1	43.88	4.91	85.72	6.14	95.04	14.26
AD-1707556.1	44.01	5.20	101.93	28.43	101.74	10.99
AD-1711777.1	45.14	11.21	114.45	10.62	96.73	20.52
AD-1709443.1	45.22	0.83	100.07	11.26	97.92	7.67
AD-1707486.1	45.51	9.49	100.63	5.39	100.14	11.85
AD-1707628.1	46.62	6.73	113.39	21.12	93.74	13.75
AD-1707480.1	46.88	6.69	102.09	18.77	110.14	13.44
AD-1709411.1	47.31	13.14	87.52	8.56	91.88	24.45
AD-1711778.1	48.28	11.80	111.20	13.56	94.81	18.75
AD-1709237.1	48.28	6.38	94.22	8.15	96.80	12.70
AD-1707483.1	48.39	4.85	99.57	17.10	94.96	21.55
AD-1709304.1	50.75	12.20	99.78	16.16	92.66	11.59
AD-1707578.1	51.22	9.70	105.42	11.28	98.33	5.94
AD-1707626.1	51.23	8.00	93.89	16.64	107.20	11.75
AD-1707553.1	51.76	10.35	97.28	9.61	95.98	19.82
AD-1709317.1	53.03	12.07	95.68	17.98	106.76	17.19
AD-1707627.1	53.41	17.00	90.59	17.84	98.25	18.90
AD-1709429.1	53.84	4.92	98.91	15.37	103.18	17.21
AD-1707469.1	54.22	8.62	96.86	15.86	105.03	6.45
AD-1707555.1	54.36	14.24	95.46	9.45	101.46	22.99
AD-1709502.1	54.67	11.47	97.24	11.50	96.65	11.03
AD-1707467.1	55.71	8.17	105.11	18.31	108.78	10.76
AD-1707473.1	57.10	9.09	85.76	12.49	101.37	17.12
AD-1707557.1	58.60	9.88	96.92	24.28	97.24	15.17
AD-1707625.1	59.10	4.85	107.25	29.88	114.62	8.75
AD-1707482.1	59.61	7.43	105.12	9.08	107.28	12.66
AD-1707471.1	60.25	8.69	115.63	30.61	110.02	25.57
AD-1707468.1	60.62	11.06	98.79	8.96	98.07	21.08

	10 nM		1 nM		0.1 nM	
Duplex Name	% Avg message remaining	STDEV	% Avg message remaining	STDEV	% Avg message remaining	STDEV
AD-1709307.1	60.77	11.96	104.13	18.31	99.16	16.21
AD-1707416.1	62.39	10.60	106.20	29.09	108.74	6.92
AD-1707476.1	62.69	6.78	98.18	21.33	114.57	25.32
AD-1707477.1	63.06	14.52	106.74	20.36	106.68	14.21
AD-1707475.1	65.11	5.23	98.37	14.42	105.46	7.86
AD-1709254.1	66.79	23.87	101.35	11.41	89.71	18.70
AD-1707390.1	67.23	7.60	100.09	13.09	95.79	8.38
AD-1709298.1	68.03	10.97	96.34	17.17	108.50	15.76
AD-1709390.1	68.34	8.57	105.65	25.15	99.82	10.51
AD-1707484.1	69.92	9.74	97.85	20.58	99.48	13.58
AD-1709314.1	72.02	3.76	122.26	28.02	109.58	16.56
AD-1709431.1	73.69	13.99	115.10	20.10	103.94	18.67
AD-1707554.1	74.14	16.74	103.41	15.16	99.75	11.58
AD-1707412.1	78.12	15.95	135.10	34.55	107.09	20.15
AD-1707624.1	81.73	10.74	121.46	18.90	111.10	15.87
AD-1707623.1	84.10	14.14	117.90	34.70	101.07	11.24
AD-1707485.1	85.82	5.18	96.24	6.20	108.58	7.26
AD-1707418.1	89.78	16.64	90.19	15.94	96.15	12.68
AD-1709315.1	92.79	10.37	93.51	7.08	103.41	13.56
AD-1707411.1	95.22	14.65	90.23	10.17	99.59	20.10
AD-1709239.1	95.51	10.13	94.42	8.85	94.47	10.55
AD-1707415.1	96.35	27.83	87.14	14.90	101.20	19.14
AD-1709253.1	99.77	27.82	101.30	20.97	100.35	31.79
AD-1707417.1	104.79	17.20	115.55	22.60	107.73	8.99

Table 21B. Single Dose Screen for dsRNA agents targeting INHBE in PHH cells (% average mRNA remaining).

	Primary Human Hepatocytes Transfection						Primary Human Hepatocytes Free Uptake							
Duplex Name	10 nM	StDev	1 nM	StDev	0.1 nM	StDev	250 nM	StDev	100 nM	StDev	10 nM	StDev	1 nM	StDev
AD-1708473	3.84	1.35	4.83	0.78	11.90	5.80	9.05	2.26	7.91	2.05	20.30	4.14	26.88	9.48
AD-1707061	4.14	0.80	7.73	1.54	10.01	4.27	5.05	2.70	9.15	1.74	19.29	6.44	22.54	5.46
AD-1708478	4.21	0.86	8.74	1.95	12.12	2.57	15.32	3.35	15.49	4.78	32.44	12.86	47.21	3.08
AD-1706584	6.01	1.00	12.11	2.32	20.47	1.86	15.62	6.96	12.92	3.51	31.81	9.56	39.52	13.24
AD-1707306	5.41	0.99	8.64	1.68	15.40	3.91	14.67	4.08	12.03	5.26	31.22	4.85	29.94	12.32
AD-1711744	7.34	0.93	22.17	1.93	24.84	6.82	16.09	6.18	18.31	7.16	46.93	10.77	21.15	6.60
AD-1707639	7.39	0.40	15.74	1.72	25.11	1.15	20.36	7.67	22.33	6.58	33.27	5.33	35.71	13.43
AD-1707641	6.30	1.05	11.48	0.98	13.72	2.64	14.35	5.72	16.48	6.07	27.41	4.58	37.17	12.82
AD-1707640	14.25	5.27	9.89	2.61	11.62	2.53	19.98	9.23	9.86	1.84	29.19	8.23	46.42	16.24
AD-1706583	9.59	2.03	11.01	2.55	33.23	7.79	32.08	9.27	34.18	1.07	44.93	7.59	47.65	14.84
AD-1708956	8.29	1.74	7.69	1.78	20.17	2.12	27.77	10.81	21.34	8.65	51.13	12.95	62.63	10.70
AD-1706591	17.87	2.33	21.38	2.89	33.74	2.09	35.01	8.34	43.04	5.73	55.08	8.42	49.40	1.88
AD-1706593	16.39	2.72	21.56	5.13	38.39	4.68	38.38	2.01	40.78	12.66	67.80	3.57	57.75	2.38
AD-1707136	9.73	2.61	12.76	1.74	18.58	4.48	21.70	6.52	26.72	8.13	49.51	9.16	62.04	21.31
AD-1706587	19.27	2.95	29.03	3.31	42.92	2.35	37.95	9.76	48.29	7.11	63.48	11.56	91.09	9.80
AD-1706547	9.05	1.63	19.91	2.05	26.11	6.44	44.96	7.86	39.42	6.77	60.57	6.79	51.76	15.33
AD-1708399	16.90	6.46	26.04	3.67	32.84	8.56	27.69	8.64	31.00	7.18	40.88	11.44	65.34	24.97
AD-1707340	12.13	0.79	18.29	2.31	35.44	5.97	51.01	14.05	57.39	11.96	66.47	11.16	81.96	6.06
AD-1706662	10.58	2.12	14.50	1.46	21.49	2.39	38.97	3.56	46.03	9.20	51.78	16.38	75.97	5.93
AD-1709130	20.00	2.26	22.86	3.41	35.13	5.88	33.52	8.58	31.04	5.07	48.54	15.67	85.19	20.45
AD-1708882	14.97	1.54	17.39	3.37	41.21	1.66	33.36	6.74	51.38	5.73	43.23	14.27	93.31	10.28
AD-1707087	10.79	2.18	20.93	4.44	27.23	4.01	33.09	7.91	45.27	4.15	61.83	8.84	92.73	15.04
AD-1707632	14.96	3.95	27.48	2.83	34.46	5.77	60.90	17.76	45.59	14.85	62.59	2.82	83.12	21.68
AD-1709034	14.35	3.38	23.39	2.66	32.18	8.41	42.08	9.32	44.37	7.57	72.83	4.37	92.28	2.99
AD-1706761	9.18	3.40	17.68	4.49	23.93	4.88	34.19	6.86	41.28	7.96	54.90	3.62	86.71	21.91

Duplex Name	Primary Human Hepatocytes Transfection						Primary Human Hepatocytes Free Uptake							
	10 nM	StDev	1 nM	StDev	0.1 nM	StDev	250 nM	StDev	100 nM	StDev	10 nM	StDev	1 nM	StDev
AD-1711775	29.82	4.53	38.15	3.94	51.68	4.29	76.87	14.21	89.53	9.82	94.63	6.00	124.76	12.67
AD-1706758	29.57	6.34	33.96	2.09	53.10	9.12	59.66	3.42	65.91	9.15	65.69	12.66	105.66	22.32
AD-1707339	28.32	2.83	31.07	1.55	52.58	4.24	59.15	8.31	73.87	2.72	86.02	5.27	100.65	6.19
AD-1708368	24.61	5.44	37.31	3.95	60.77	6.60	79.25	15.90	67.90	12.41	90.06	6.70	131.88	7.90
AD-1706762	11.26	2.98	25.09	2.72	35.72	3.49	46.85	13.20	50.92	17.34	84.37	11.82	94.03	4.93
AD-1707291	8.89	0.54	16.30	2.83	28.25	7.47	42.60	7.79	37.31	5.08	68.87	7.93	72.32	15.94
AD-1707314	20.85	2.68	25.87	2.99	42.31	12.16	56.47	12.93	42.72	5.67	66.58	13.04	88.09	1.99
AD-1706640	16.91	3.11	36.66	3.88	40.86	10.18	28.39	6.96	46.43	6.76	78.03	17.64	133.63	32.82
AD-1707054	14.13	2.53	22.61	2.39	34.17	3.97	55.10	7.84	59.59	7.96	87.74	3.87	119.92	16.53
AD-1706641	24.33	3.32	32.23	5.92	45.48	8.35	61.06	5.81	66.77	17.98	83.39	19.40	107.19	7.61
AD-1707308	15.25	2.92	27.67	2.72	36.27	7.33	51.25	8.34	43.23	11.57	88.07	18.70	103.21	9.29
AD-1709151	32.08	6.47	44.97	9.45	50.34	12.76	90.75	8.27	82.92	14.60	115.33	3.62	122.19	13.92
AD-1706656	8.91	1.04	21.35	4.03	31.89	3.90	43.20	8.76	58.20	16.02	89.89	23.74	118.47	20.90
AD-1706651	17.38	2.79	24.64	1.52	39.31	3.47	37.87	6.88	49.12	7.91	96.91	9.76	93.62	13.63
AD-1711756	20.57	4.05	23.96	2.75	36.33	11.33	72.94	13.08	54.99	8.99	85.20	23.87	99.26	9.01
AD-1707605	35.03	2.49	46.37	9.61	55.57	13.31	83.69	7.72	96.68	15.17	95.74	27.12	110.00	19.41
AD-1707287	27.61	1.70	32.48	1.14	47.24	9.39	73.48	6.92	70.18	9.33	93.02	11.38	110.85	27.51
AD-1708766	19.22	3.37	24.71	4.87	34.20	7.62	60.19	7.39	69.81	13.98	92.36	11.05	125.22	12.99
AD-1706644	18.94	2.78	25.14	3.46	49.00	1.82	68.06	11.84	83.45	4.42	87.08	12.23	127.39	7.76
AD-1706590	24.14	4.90	34.95	3.80	53.60	6.42	78.09	12.28	113.12	26.95	114.41	16.33	135.34	15.94
AD-1708407	24.10	7.20	30.72	4.39	43.60	6.30	74.49	11.38	70.25	8.69	90.22	13.32	105.77	8.20
AD-1707292	24.48	4.27	34.78	2.52	45.46	9.22	72.04	12.03	58.89	13.58	86.65	5.87	86.26	19.87
AD-1708899	17.77	2.91	21.87	1.95	26.43	7.65	68.65	14.69	99.52	14.24	94.06	11.30	111.70	15.07
AD-1706674	20.19	2.23	26.54	1.38	47.96	2.84	70.03	6.72	69.05	8.66	102.69	11.08	104.89	21.93
AD-1707631	20.66	2.86	19.79	4.30	32.43	5.70	61.81	11.29	71.35	13.55	93.00	11.79	126.82	9.10
AD-1706759	18.55	2.17	26.28	2.28	40.19	5.23	63.77	4.79	77.91	12.04	97.13	8.57	111.16	27.11

Duplex Name	Primary Human Hepatocytes Transfection						Primary Human Hepatocytes Free Uptake							
	10 nM	StDev	1 nM	StDev	0.1 nM	StDev	250 nM	StDev	100 nM	StDev	10 nM	StDev	1 nM	StDev
AD-1711747	11.52	4.71	17.00	2.82	33.59	6.89	55.08	11.20	85.92	27.07	98.80	9.94	133.36	9.56
AD-1707149	15.95	3.01	28.26	5.99	40.68	5.31	57.51	12.07	83.78	12.31	102.28	8.63	121.17	7.59
AD-1708251	31.99	5.46	30.05	3.30	44.02	7.05	65.77	7.52	59.12	18.47	100.89	12.16	103.22	24.69
AD-1711776	38.30	15.35	48.19	5.85	63.98	12.66	90.37	9.23	85.76	14.78	97.44	13.61	110.66	12.48
AD-1707315	22.73	2.34	24.01	5.64	46.41	5.45	84.80	11.81	72.86	8.03	102.13	20.54	110.56	7.38
AD-1706750	18.16	1.56	20.63	4.42	29.43	10.64	40.85	4.80	55.55	5.48	105.85	15.64	117.08	19.52
AD-1706799	31.99	6.20	33.80	5.58	46.45	8.79	90.17	12.69	101.66	26.60	111.12	20.30	133.05	18.74
AD-1708485	13.61	3.64	23.72	2.33	52.65	11.16	73.70	2.25	77.15	6.87	103.41	11.13	127.34	12.36
AD-1707633	23.63	5.15	28.24	4.65	36.48	6.12	75.57	11.01	110.02	45.47	112.62	17.17	128.91	16.41
AD-1709090	20.30	2.87	24.48	3.75	37.02	8.76	77.61	7.95	99.11	14.22	114.49	22.90	117.89	14.16
AD-1707466	63.36	14.56	61.06	10.24	79.45	2.15	92.63	22.18	85.04	23.68	98.11	26.25	92.94	9.69
AD-1711767	24.16	3.71	28.27	4.36	42.24	10.42	60.63	4.45	72.25	7.49	96.33	15.95	122.97	18.33
AD-1707388	61.29	14.42	59.32	8.57	69.95	15.09	95.33	7.44	105.65	6.00	113.84	11.51	128.35	23.12
AD-1711770	18.87	3.61	20.46	5.47	32.18	8.80	57.75	16.97	61.76	7.82	104.71	7.77	122.13	13.61
AD-1706748	24.20	6.04	35.62	6.64	50.19	11.08	78.53	12.43	88.65	8.77	105.57	16.18	128.56	25.42
AD-1707307	26.97	4.34	35.22	4.99	63.75	9.28	59.79	4.39	75.85	8.88	101.29	7.21	120.76	17.30
AD-1707302	20.32	7.78	29.18	5.74	45.72	7.23	63.84	7.84	76.67	4.98	112.01	4.31	136.13	16.48
AD-1709126	27.45	10.18	32.34	4.21	57.05	10.57	53.83	6.16	49.10	5.95	88.09	16.28	112.27	11.26
AD-1711765	17.66	4.49	22.90	2.22	28.06	8.93	40.32	5.52	60.56	12.85	94.87	19.12	99.62	14.72
AD-1707140	14.92	5.79	15.70	5.48	29.72	5.60	45.36	2.81	60.43	8.25	51.92	22.84	106.75	10.76
AD-1706751	19.74	4.12	19.51	8.94	51.31	13.73	31.89	5.76	61.33	16.59	86.50	16.71	119.06	17.21
AD-1706930	18.10	6.15	17.27	4.50	29.73	6.81	44.91	14.50	53.16	2.39	92.88	11.31	94.54	12.43
AD-1708564	33.34	10.11	34.73	8.99	65.01	8.10	68.81	10.42	82.59	24.87	107.17	6.26	105.04	13.30
AD-1706746	28.39	9.86	38.43	9.94	65.72	12.30	56.28	12.49	81.09	8.55	106.87	14.96	91.27	18.95
AD-1706863	21.83	8.44	29.55	2.92	39.21	8.12	64.73	12.20	61.97	17.33	61.21	5.92	91.41	19.42
AD-1706933	19.52	6.57	24.12	4.64	36.58	13.09	52.18	9.14	60.25	8.05	76.05	5.15	89.07	34.13

	Primary Human Hepatocytes Transfection						Primary Human Hepatocytes Free Uptake							
Duplex Name	10 nM	StDev	1 nM	StDev	0.1 nM	StDev	250 nM	StDev	100 nM	StDev	10 nM	StDev	1 nM	StDev
AD-1706650	8.22	2.78	9.86	1.53	18.29	4.10	18.41	2.70	31.54	9.06	47.21	2.59	82.80	6.30
AD-1706645	9.54	2.94	13.04	1.86	19.68	5.15	23.19	1.25	31.74	9.21	58.68	3.98	75.47	14.03
AD-1706763	8.78	2.73	10.89	2.20	18.03	2.25	24.39	5.06	32.66	2.25	57.89	9.13	83.09	3.30
AD-1706642	10.21	2.41	14.73	4.43	29.08	10.15	26.47	6.44	44.93	12.38	65.76	1.34	80.97	14.28
AD-1706749	10.78	3.21	18.58	2.61	29.08	1.90	40.07	4.58	45.28	6.05	78.38	3.11	70.35	25.84
AD-1709044	12.38	3.44	19.35	3.08	27.49	7.29	39.88	7.52	48.75	6.09	70.84	5.85	82.43	6.36
AD-1707063	6.22	2.57	4.60	1.96	11.68	3.24	12.46	0.47	15.19	1.73	42.37	9.63	53.30	26.27
AD-1706666	11.63	2.89	10.71	2.18	16.80	4.52	21.12	6.46	28.56	5.28	45.18	3.28	27.94	3.80
AD-1707305	10.26	4.05	7.94	3.22	10.70	3.10	15.00	2.72	19.14	2.01	52.56	17.22	58.51	0.00
AD-1707060	8.16	3.68	9.02	2.54	18.61	4.71	29.10	5.61	37.29	2.54	51.66	11.49	43.46	16.10
AD-1707318	8.67	3.65	8.96	1.42	16.04	5.89	25.62	2.76	29.27	3.58	47.38	12.44	57.54	2.19
AD-1707290	18.38	5.04	17.99	3.06	32.26	7.70	46.85	2.48	56.51	9.06	67.51	11.70	82.20	11.04
AD-1711760	10.18	3.91	15.74	2.67	25.12	9.22	40.81	3.41	42.21	6.96	65.57	7.30	50.87	7.17

Table 21C. Single Dose Screen for dsRNA agents targeting INHBE in PCH cells (% average mRNA remaining).

	Primary Cyno Hepatocytes Transfection						Primary Cyno Hepatocytes Free Uptake							
Duplex Name	10 nM	StDev	1 nM	StDev	0.1 nM	StDev	250 nM	StDev	100 nM	StDev	10 nM	StDev	1 nM	StDev
AD-1708473	7.47	2.74	32.98	4.49	38.46	5.22	5.83	1.24	7.90	0.68	13.73	3.81	36.44	9.10
AD-1707061	5.91	1.59	25.97	2.80	37.95	4.74	4.93	1.33	6.19	1.17	12.75	1.19	24.67	3.29
AD-1708478	10.87	1.82	34.31	4.82	44.21	8.99	8.33	1.99	9.75	1.98	12.20	3.03	22.11	6.43
AD-1706584	13.05	2.93	32.59	4.71	35.84	5.03	8.45	2.09	11.65	2.82	17.02	1.74	33.73	6.39
AD-1707306	9.51	0.94	34.07	4.86	43.92	7.44	11.65	1.92	8.48	1.71	14.04	3.13	39.14	5.62
AD-1711744	18.10	4.00	42.42	4.03	53.93	8.59	8.55	2.85	10.68	2.12	13.50	4.06	38.67	0.25
AD-1707639	18.01	2.14	45.23	3.14	57.21	6.84	16.87	2.63	13.75	2.87	20.90	6.68	37.20	1.37
AD-1707641	14.45	1.14	36.97	4.67	53.00	3.54	11.06	1.98	12.53	1.52	24.21	4.94	41.21	5.67

	Primary Cyno Hepatocytes Transfection						Primary Cyno Hepatocytes Free Uptake					
Duplex Name	10 nM	StDev	1 nM	StDev	0.1 nM	StDev	250 nM	StDev	100 nM	StDev	10 nM	StDev	1 nM	StDev
AD-1707640	20.53	3.28	37.16	9.19	62.35	9.81	15.05	3.30	20.19	1.59	24.58	4.89	25.42	2.79
AD-1706583	14.48	3.67	47.86	4.86	61.48	8.01	10.32	3.93	15.82	6.07	18.61	4.66	48.58	11.62
AD-1708956	11.09	2.08	35.23	5.58	50.07	7.79	9.32	0.27	11.90	2.85	24.94	5.33	45.15	8.24
AD-1706591	19.64	2.79	56.40	7.78	62.31	6.78	9.18	1.92	15.12	0.82	25.21	7.00	62.16	9.52
AD-1706593	18.22	3.15	50.39	3.94	50.47	8.38	9.42	2.42	11.27	2.59	23.69	6.94	50.88	10.01
AD-1707136	10.23	2.58	27.34	6.99	46.91	8.54	9.04	1.81	8.49	1.70	21.51	2.16	42.87	4.46
AD-1706587	23.87	3.81	46.95	8.49	62.57	11.27	14.48	2.31	15.69	2.72	25.82	4.63	47.27	5.35
AD-1706547	29.86	3.63	53.87	10.28	66.80	3.64	23.99	4.15	26.80	8.35	46.70	7.85	64.97	16.25
AD-1708399	24.39	4.14	56.93	4.99	62.91	13.62	12.07	3.35	13.83	4.69	26.04	4.79	66.91	13.04
AD-1707340	39.28	4.82	64.21	4.81	79.59	4.44	29.23	6.08	32.92	12.21	38.14	5.42	71.22	22.52
AD-1706662	14.59	0.79	39.23	10.93	58.74	14.45	16.76	3.53	14.74	1.00	30.41	4.29	60.37	3.75
AD-1709130	16.24	2.78	52.70	10.74	65.15	10.76	17.57	3.03	18.14	2.88	27.68	4.76	65.67	7.63
AD-1708882	16.97	1.09	45.63	12.78	77.02	4.42	11.89	0.90	12.60	2.44	27.58	2.96	58.25	5.90
AD-1707087	18.19	1.93	38.32	10.98	74.09	4.20	17.93	3.41	18.11	2.79	37.96	5.53	69.05	2.24
AD-1707632	25.08	3.09	40.42	13.55	58.16	4.73	18.92	0.75	17.82	6.37	27.71	7.00	53.11	5.97
AD-1709034	26.18	2.74	62.45	7.84	69.43	9.15	14.25	1.45	13.43	4.36	22.01	7.95	42.74	7.41
AD-1706761	14.04	2.46	48.49	12.33	57.31	7.84	11.03	0.09	9.71	1.51	22.26	3.89	83.78	32.45
AD-1711775	43.13	4.73	79.00	6.98	88.54	8.11	44.74	6.00	49.54	8.66	54.24	14.15	104.57	8.08
AD-1706758	32.06	5.59	68.22	14.20	82.73	11.67	22.92	5.17	22.67	2.26	40.00	0.42	73.16	9.75
AD-1707339	39.24	2.12	74.96	0.78	68.46	12.48	33.30	3.28	34.74	9.08	54.47	10.26	74.36	15.15
AD-1708368	40.73	3.67	67.92	16.66	91.79	9.70	23.02	3.99	26.31	3.29	39.13	4.09	76.42	15.36
AD-1706762	28.37	6.96	62.89	6.26	77.63	9.41	14.52	1.86	14.28	1.73	35.29	4.03	60.12	9.31
AD-1707291	23.69	2.29	43.10	5.34	63.68	14.11	20.65	2.71	15.40	3.39	31.37	3.02	62.75	15.07
AD-1707314	29.79	6.31	65.15	5.49	83.38	12.47	21.26	5.85	25.31	2.95	28.72	3.30	80.36	4.21
AD-1706640	35.22	5.23	62.17	10.30	72.73	4.13	12.56	2.49	13.90	2.35	31.22	3.54	67.25	0.70
AD-1707054	19.36	3.19	54.28	2.70	68.42	3.25	15.34	2.10	19.26	3.32	36.61	5.50	73.41	6.83
AD-1706641	38.81	2.77	83.23	5.90	81.54	10.41	26.69	3.72	24.16	7.74	49.31	6.53	98.76	9.65

	Primary Cyno Hepatocytes Transfection						Primary Cyno Hepatocytes Free Uptake							
Duplex Name	10 nM	StDev	1 nM	StDev	0.1 nM	StDev	250 nM	StDev	100 nM	StDev	10 nM	StDev	1 nM	StDev
AD-1707308	31.18	3.14	67.03	11.46	72.91	13.64	17.47	5.59	25.13	0.65	29.27	3.23	81.25	8.44
AD-1709151	58.99	7.07	99.08	24.13	82.51	23.90	49.15	8.11	35.96	12.08	52.50	11.94	106.94	11.16
AD-1706656	22.28	2.36	52.59	5.56	69.36	9.76	11.40	2.25	12.08	3.81	29.92	2.75	46.55	4.66
AD-1706651	31.17	5.34	55.09	7.98	50.19	9.10	12.74	1.10	12.86	2.14	28.96	2.78	58.95	12.54
AD-1711756	22.78	4.88	51.83	14.00	73.32	15.55	18.21	2.09	20.58	2.82	35.07	2.15	65.70	19.08
AD-1707605	51.27	4.38	77.10	19.46	83.78	3.65	48.36	10.82	47.85	10.00	49.56	7.16	93.66	26.70
AD-1707287	17.93	2.05	48.59	9.40	63.94	7.11	19.30	2.43	21.57	2.40	32.78	6.36	57.70	4.49
AD-1708766	18.81	3.17	55.43	5.57	70.17	4.47	15.34	2.89	17.95	2.34	25.44	3.89	64.23	13.01
AD-1706644	28.89	6.40	51.39	16.56	79.04	6.62	26.48	2.52	32.64	2.30	49.95	1.49	81.75	8.97
AD-1706590	38.15	1.61	80.31	6.44	92.30	6.41	26.35	3.32	25.15	5.92	40.61	6.35	78.62	8.57
AD-1708407	35.96	4.47	67.88	12.42	94.43	8.89	17.03	2.89	19.27	4.04	42.22	5.00	64.72	15.64
AD-1707292	39.27	5.95	72.26	26.50	73.87	16.12	21.97	3.63	28.47	3.81	42.02	6.40	83.02	16.74
AD-1708899	37.10	1.50	74.69	9.73	88.87	10.06	19.00	6.82	25.47	3.31	50.32	9.44	81.40	2.23
AD-1706674	32.84	9.12	64.73	4.42	83.67	6.57	23.52	5.70	28.16	5.66	35.56	3.67	79.83	4.59
AD-1707631	17.72	3.24	32.29	8.79	73.51	6.20	19.06	3.32	21.57	2.84	30.74	2.52	57.82	7.61
AD-1706759	22.82	5.97	59.65	15.92	81.70	12.26	15.52	1.03	15.75	2.69	31.88	3.25	64.72	9.61
AD-1711747	16.88	1.38	51.75	5.39	77.38	9.80	7.61	1.11	10.05	2.18	18.90	2.56	45.02	6.23
AD-1707149	30.43	7.20	68.03	10.50	95.47	10.74	12.97	2.94	15.39	4.97	31.35	3.87	51.94	2.96
AD-1708251	67.20	2.14	75.30	12.49	80.77	12.76	28.28	6.61	37.65	10.05	51.75	12.05	78.36	9.89
AD-1711776	42.99	0.86	80.17	9.26	89.90	2.55	33.31	3.56	39.81	7.57	61.94	4.12	88.88	14.71
AD-1707315	31.05	8.92	70.52	5.55	98.15	8.08	36.35	6.21	33.91	4.76	46.61	2.99	86.97	17.28
AD-1706750	20.76	2.52	61.32	8.84	71.39	12.47	16.65	1.24	15.84	3.69	29.05	2.00	65.00	9.30
AD-1706799	27.06	4.43	65.37	6.49	84.62	11.72	36.11	8.14	36.55	9.82	46.21	10.11	87.85	10.61
AD-1708485	21.96	3.70	48.80	10.16	86.49	16.04	18.55	5.12	24.80	4.25	28.45	4.00	72.48	20.64
AD-1707633	21.02	2.82	47.90	7.29	60.86	3.25	17.84	4.49	22.25	9.40	25.12	5.14	58.59	13.07
AD-1709090	21.63	1.82	53.58	8.28	75.93	13.41	25.00	6.30	24.74	12.69	36.00	2.38	65.83	23.02
AD-1707466	72.22	20.46	96.23	13.67	89.94	17.07	62.02	9.68	63.83	11.34	82.95	20.07	89.09	5.98

	Primary Cyno Hepatocytes Transfection						Primary Cyno Hepatocytes Free Uptake					
Duplex Name	10 nM	StDev	1 nM	StDev	0.1 nM	StDev	250 nM	StDev	100 nM	StDev	10 nM	StDev	1 nM	StDev
AD-1711767	30.18	5.67	66.05	9.01	71.99	9.45	12.82	1.91	18.77	4.64	31.68	1.25	63.00	4.37
AD-1707388	78.28	3.85	81.05	21.06	92.40	9.78	56.73	14.94	59.70	18.76	70.84	9.94	117.00	32.65
AD-1711770	24.22	4.30	50.53	10.17	60.23	15.99	13.64	4.56	18.17	4.10	29.29	5.60	63.32	20.42
AD-1706748	27.88	7.45	58.08	8.17	85.22	9.26	19.35	7.28	23.70	10.45	35.92	2.11	82.43	29.42
AD-1707307	38.24	4.51	69.58	18.90	81.80	12.11	22.77	1.58	24.06	5.50	34.26	5.34	72.51	11.65
AD-1707302	22.90	3.30	56.34	5.01	77.35	8.51	14.86	4.07	16.11	7.60	37.43	6.16	65.34	12.89
AD-1709126	37.24	1.81	67.53	14.34	74.35	12.21	25.21	2.16	25.01	0.88	40.35	2.47	78.75	5.06
AD-1711765	26.06	4.01	54.94	4.24	85.81	12.69	12.51	3.92	12.54	2.33	27.24	4.60	58.54	9.15
AD-1707140	20.69	2.95	41.27	7.55	65.60	2.37	10.68	1.92	13.99	2.40	28.57	4.11	48.20	7.92
AD-1706751	19.01	0.80	51.90	10.38	93.47	7.11	17.08	4.62	16.12	5.22	25.48	3.88	68.13	17.00
AD-1706930	13.61	2.50	33.64	4.46	54.73	9.10	15.41	3.46	19.00	6.91	30.56	6.18	74.72	7.50
AD-1708564	33.12	3.93	64.85	7.58	77.16	9.05	23.64	4.07	36.07	9.13	38.87	5.58	79.09	9.95
AD-1706746	36.26	6.43	72.34	12.42	100.13	3.81	23.12	8.26	28.72	10.09	45.63	4.80	72.75	8.12
AD-1706863	26.84	5.99	64.11	16.03	75.02	16.52	28.71	5.45	30.51	4.57	53.96	7.78	75.02	6.39
AD-1706933	24.84	2.39	53.63	19.88	61.71	13.32	16.45	2.89	21.72	2.52	33.18	7.42	67.85	12.54
AD-1706650	7.75	1.33	28.02	3.29	52.07	12.66	6.10	2.27	7.05	1.70	16.05	4.29	37.57	4.81
AD-1706645	10.74	0.62	29.43	8.71	52.47	2.06	7.63	1.56	9.23	1.42	17.05	1.33	42.18	7.55
AD-1706763	7.28	0.69	31.38	8.79	53.36	11.31	6.52	0.85	8.04	2.06	14.76	2.55	36.65	8.26
AD-1706642	8.66	3.81	30.56	5.40	54.72	4.19	8.78	3.63	11.66	6.36	16.43	3.88	36.47	4.72
AD-1706749	10.66	1.62	37.02	7.09	59.79	5.94	10.16	0.80	9.50	2.34	20.32	2.72	48.14	5.76
AD-1709044	17.47	3.75	34.89	11.05	65.44	14.86	17.68	6.18	13.10	2.45	29.34	3.15	50.29	6.25
AD-1707063	8.70	1.45	29.38	5.78	47.59	2.97	7.93	1.13	8.36	1.64	21.41	1.43	32.97	9.60
AD-1706666	16.48	2.20	40.53	4.15	60.54	0.68	15.42	6.42	15.54	5.16	40.29	3.51	35.82	2.33
AD-1707305	9.42	1.49	32.49	3.03	58.24	8.28	6.79	2.33	8.64	2.70	18.06	4.38	29.85	7.65
AD-1707060	17.25	1.90	46.73	5.87	61.56	4.71	9.86	4.04	10.63	3.23	25.87	2.46	44.20	13.53
AD-1707318	13.61	2.20	42.86	9.79	54.22	9.49	10.33	3.55	11.95	3.18	23.43	2.08	36.27	12.76
AD-1707290	17.86	5.21	49.67	8.59	62.49	5.49	14.25	3.65	13.86	4.57	36.67	7.08	43.04	4.48

	Primary Cyno Hepatocytes Transfection						Primary Cyno Hepatocytes Free Uptake					
Duplex Name	10 nM	StDev	1 nM	StDev	0.1 nM	StDev	250 nM	StDev	100 nM	StDev	10 nM	StDev	1 nM	StDev
AD-1711760	18.10	3.22	45.83	12.27	61.36	9.28	10.80	1.65	11.13	3.37	34.34	3.50	43.15	11.26

Example 5: *In Vitro* Single Dose Screening of dsRNA Duplexes targeting PDE3B

Using methods as described above, the dsRNA agents targeting PDE3B listed in Tables 14 and 15 were screened *in vitro* in Hep3B cells. The results of the single dose screen are shown in Table 22.

Table 22. Single dose screen for dsRNA agents targeting PDE3B in Hep3b cells

Duplex Name	PDE3B/GAPDH	
	10 nM	
	% Avg message remaining (n=4)	SD
AD-1735860.1	23.709	2.696
AD-1735859.1	20.551	5.347
AD-1735858.1	14.679	1.474
AD-1735857.1	16.078	1.257
AD-1735856.1	64.047	7.135
AD-1735855.1	18.703	1.706
AD-1735854.1	91.214	2.665
AD-1735853.1	61.829	7.675
AD-1735852.1	24.913	1.561
AD-1735851.1	24.650	1.255
AD-1735850.1	51.046	2.446
AD-1735849.1	40.548	3.364
AD-1735848.1	71.080	3.478
AD-1735847.1	28.692	1.123
AD-1735846.1	19.800	1.135
AD-1735845.1	22.788	1.056
AD-1735844.1	44.102	0.526
AD-1735843.1	52.791	8.362
AD-1735842.1	35.622	1.690
AD-1735841.1	18.613	2.422
AD-1735840.1	57.636	0.785
AD-1735839.1	97.956	4.340
AD-1735838.1	40.270	2.411
AD-1735837.1	30.805	1.988
AD-1735836.1	35.379	6.026
AD-1735835.1	26.142	3.567
AD-1735834.1	35.490	3.096
AD-1735833.1	64.925	1.880
AD-1735832.1	21.201	2.311
AD-1735831.1	37.417	4.395
AD-1735830.1	23.780	2.967
AD-1735829.1	40.465	2.494
AD-1735828.1	53.338	1.805
AD-1735827.1	23.074	6.126

Duplex Name	PDE3B/GAPDH	
	10 nM	
	% Avg message remaining (n=4)	SD
AD-1735826.1	61.743	0.745
AD-1735825.1	42.766	14.280
AD-1735824.1	19.157	0.711
AD-1735823.1	38.720	1.905
AD-1735822.1	71.730	3.742
AD-1735821.1	37.215	0.923
AD-1735820.1	24.961	0.995
AD-1735819.1	16.917	0.728
AD-1735818.1	46.222	0.902
AD-1735817.1	61.037	0.700
AD-1735816.1	35.774	2.507
AD-1735815.1	43.474	2.475
AD-1735814.1	45.076	0.985
AD-1735813.1	28.507	1.743
AD-1735812.1	70.709	1.627
AD-1735811.1	22.367	0.715
AD-1735810.1	32.837	1.316
AD-1735809.1	19.024	1.358
AD-1735808.1	37.406	3.104
AD-1735807.1	39.498	3.599
AD-1735806.1	32.960	1.566
AD-1735805.1	76.711	1.049
AD-1735804.1	30.205	1.234
AD-1735803.1	29.615	0.884
AD-1735802.1	89.553	2.905
AD-1735801.1	35.954	0.721
AD-1735800.1	22.730	2.119
AD-1735799.1	38.084	2.611
AD-1735798.1	21.808	1.760
AD-1735797.1	39.127	5.754
AD-1735796.1	24.799	3.324
AD-1735795.1	29.095	2.968
AD-1735794.1	74.630	2.670
AD-1735793.1	50.655	2.625
AD-1735792.1	21.774	1.922
AD-1735791.1	29.879	1.379
AD-1735790.1	45.278	3.178
AD-1735789.1	53.799	3.522
AD-1735788.1	24.525	2.272
AD-1735787.1	41.825	5.048
AD-1735786.1	47.854	2.516

Duplex Name	PDE3B/GAPDH	
	10 nM	
	% Avg message remaining (n=4)	SD
AD-1735785.1	24.928	5.836
AD-1735784.1	26.802	2.165
AD-1735783.1	22.593	2.437
AD-1735782.1	51.096	3.906
AD-1735781.1	25.026	1.459
AD-1735780.1	17.158	1.252
AD-1735779.1	93.272	6.172
AD-1735778.1	24.207	1.738
AD-1735777.1	21.304	0.659
AD-1735776.1	23.915	5.465
AD-1735775.1	21.095	1.525
AD-1735774.1	51.845	2.742
AD-1735773.1	28.834	5.357
AD-1735772.1	22.993	2.710
AD-1735771.1	21.214	1.330
AD-1735770.1	29.426	7.369
AD-1735769.1	50.021	9.727
AD-1735768.1	51.776	2.906
AD-1735767.1	66.112	13.788
AD-1735766.1	48.132	2.745
AD-1735765.1	78.926	8.535
AD-1735764.1	31.425	6.159
AD-1735763.1	39.086	4.992
AD-1735762.1	28.522	1.684
AD-1735761.1	24.999	1.443
AD-1735760.1	100.922	13.187
AD-1735759.1	44.830	2.225
AD-1735758.1	24.656	3.386
AD-1735757.1	39.249	2.608
AD-1735756.1	25.038	2.266
AD-1735755.1	59.725	1.902
AD-1735754.1	58.172	3.336
AD-1735753.1	19.504	1.090
AD-1735752.1	39.414	3.022
AD-1735751.1	99.329	6.328
AD-1735750.1	20.627	0.706
AD-1735749.1	46.816	1.166
AD-1735748.1	28.579	1.052
AD-1735747.1	79.882	6.062
AD-1735746.1	22.412	1.094
AD-1735745.1	35.269	1.846

Duplex Name	PDE3B/GAPDH	
	10 nM	
	% Avg message remaining (n=4)	SD
AD-1735744.1	80.796	4.208
AD-1735743.1	16.948	0.992
AD-1735742.1	33.029	1.186
AD-1735741.1	20.754	1.851
AD-1735740.1	65.848	4.934
AD-1735739.1	29.858	0.742
AD-1735738.1	15.106	1.527
AD-1735737.1	18.822	0.946
AD-1735736.1	21.250	2.499
AD-1735735.1	29.588	2.812
AD-1735734.1	40.456	4.030
AD-1735733.1	32.308	6.658
AD-1735732.1	84.880	4.774
AD-1735731.1	92.758	5.134
AD-1735730.1	30.568	2.601
AD-1735729.1	25.859	6.962
AD-1735728.1	14.793	0.736
AD-1735727.1	24.247	2.191
AD-1735726.1	19.711	2.888
AD-1735725.1	26.066	0.946
AD-1735724.1	21.329	0.845
AD-1735723.1	41.212	5.232
AD-1735722.1	19.123	1.479
AD-1735721.1	32.446	2.942
AD-1735720.1	27.006	6.384
AD-1735719.1	24.997	8.940
AD-1735718.1	19.553	2.845
AD-1735717.1	47.688	16.341
AD-1735716.1	20.980	2.028
AD-1735715.1	41.194	6.384
AD-1735714.1	25.154	4.575
AD-1735713.1	17.184	2.579
AD-1735712.1	17.501	1.079
AD-1735711.1	30.023	3.460
AD-1735710.1	25.387	5.162
AD-1735709.1	62.222	7.071
AD-1735708.1	85.988	22.851
AD-1735707.1	20.219	2.756
AD-1735706.1	18.664	3.260
AD-1735705.1	25.208	2.956
AD-1735704.1	20.478	1.354

Duplex Name	PDE3B/GAPDH	
	10 nM	
	% Avg message remaining (n=4)	SD
AD-1735703.1	22.386	4.605
AD-1735702.1	65.465	18.354
AD-1735701.1	58.432	21.264
AD-1735700.1	29.458	1.405
AD-1735699.1	26.141	2.115
AD-1735698.1	25.475	1.590
AD-1735697.1	110.116	4.516
AD-1735696.1	21.957	2.061
AD-1735695.1	38.524	7.895
AD-1735694.1	16.352	2.076
AD-1735693.1	13.906	2.757
AD-1735692.1	87.266	12.920
AD-1735691.1	57.983	4.032
AD-1735690.1	62.142	3.477
AD-1735689.1	84.924	5.580
AD-1735688.1	17.170	1.339
AD-1735687.1	19.041	1.800
AD-1735686.1	37.229	1.697
AD-1735685.1	63.412	8.597
AD-1735684.1	82.100	4.966
AD-1735683.1	19.608	4.567
AD-1735682.1	39.393	5.573
AD-1735681.1	28.252	3.787
AD-1735680.1	20.977	1.302
AD-1735679.1	26.540	1.005
AD-1735678.1	75.941	10.521
AD-1735677.1	71.242	12.310
AD-1735676.1	14.192	4.284
AD-1735675.1	25.581	2.905
AD-1735674.1	18.237	1.270
AD-1735673.1	49.950	4.698
AD-1735672.1	45.190	4.895
AD-1735671.1	48.600	14.146
AD-1735670.1	27.972	1.043
AD-1735669.1	37.706	4.548
AD-1735668.1	21.295	2.205
AD-1735667.1	20.943	1.604
AD-1735666.1	22.679	0.591
AD-1735665.1	23.466	3.781
AD-1735664.1	21.604	7.639
AD-1735663.1	18.338	4.288

Duplex Name	PDE3B/GAPDH	
	10 nM	
	% Avg message remaining (n=4)	SD
AD-1735662.1	58.417	7.253
AD-1735661.1	21.512	1.617
AD-1735660.1	17.670	1.798
AD-1735659.1	28.972	5.188
AD-1735658.1	27.689	0.477
AD-1735657.1	75.794	6.235
AD-1735656.1	21.802	5.378
AD-1735655.1	19.501	1.729
AD-1735654.1	23.484	2.101
AD-1735653.1	63.740	33.435
AD-1735652.1	27.984	3.477
AD-1735651.1	39.385	1.397
AD-1735650.1	15.347	0.813
AD-1735649.1	25.165	2.325
AD-1735648.1	33.073	2.315
AD-1735647.1	16.820	1.985
AD-1735646.1	55.994	5.828
AD-1735645.1	12.154	1.921
AD-1735644.1	17.745	1.643
AD-1735643.1	13.923	3.189
AD-1735642.1	55.255	2.792
AD-1735641.1	48.249	6.537
AD-1735640.1	18.494	0.962
AD-1735639.1	27.638	2.892
AD-1735638.1	47.689	6.093
AD-1735637.1	38.073	5.322
AD-1735636.1	19.722	3.753
AD-1735635.1	32.670	1.578
AD-1735634.1	18.063	1.428
AD-1735633.1	16.891	2.258
AD-1735632.1	95.524	0.685
AD-1735631.1	40.879	4.633
AD-1735630.1	26.068	3.356
AD-1735629.1	19.330	2.600
AD-1735628.1	17.470	1.514
AD-1735627.1	45.620	5.372
AD-1735626.1	30.086	2.595
AD-1735625.1	47.252	6.513
AD-1735624.1	83.854	10.000
AD-1735623.1	22.800	1.603
AD-1735622.1	16.870	1.728

Duplex Name	PDE3B/GAPDH	
	10 nM	
	% Avg message remaining (n=4)	SD
AD-1735621.1	32.332	9.786
AD-1735620.1	42.507	1.603
AD-1735619.1	89.434	2.676
AD-1735618.1	25.773	2.560
AD-1735617.1	35.284	4.815
AD-1735616.1	13.217	1.679
AD-1735615.1	35.212	5.461
AD-1735614.1	13.061	1.196
AD-1735613.1	21.191	1.016
AD-1735612.1	62.200	9.169
AD-1735611.1	17.737	2.166
AD-1735610.1	46.749	2.389
AD-1735609.1	20.890	1.371
AD-1735608.1	16.779	2.166
AD-1735607.1	10.409	0.676
AD-1735606.1	34.953	10.155
AD-1735605.1	81.087	8.632
AD-1735604.1	53.898	11.426
AD-1735603.1	34.331	3.868
AD-1735602.1	35.125	3.978
AD-1735601.1	17.106	0.910
AD-1735600.1	38.242	3.303
AD-1735599.1	10.192	2.638
AD-1735598.1	67.145	9.671
AD-1735597.1	25.931	3.096
AD-1735596.1	70.287	11.476
AD-1735595.1	70.859	20.399
AD-1735594.1	14.430	0.732
AD-1735593.1	20.530	2.301
AD-1735592.1	45.267	10.242
AD-1735591.1	14.976	0.539

Example 6: *In Vitro* Single Dose Screening of dsRNA Duplexes targeting INHBC

The dsRNA agents targeting INHBC listed in Tables 16 and 17 were screened in Hepa1-6 cells by an *in vitro* dual-Luciferase assay.

Briefly, Hepa1-6 cells were transfected by adding 50 µL of siRNA duplexes and 100 ng of a V180 plasmid, comprising human INHBC target sequence, nucleotides 1425 – 3202 of NM_005538.4, or 75 ng of a V179 plasmid, comprising human INHBC target sequence, nucleotides 1 – 1485 of NM_005538.4, per well along with 100 µL of Opti-MEM plus 0.5 µL of Lipofectamine 2000 per well (Invitrogen, Carlsbad CA. cat # 13778-150) and then incubated at room temperature for

15 minutes. The mixture was then added to the cells which were re-suspended in 35 µL of fresh complete media. The transfected cells were incubated at 37°C in an atmosphere of 5% CO2. Single-dose experiments were performed at 10 nM.

Twenty-four hours after the siRNAs and plasmid were transfected, Firefly (transfection control) and Renilla (fused to INHBC target sequence comprising nucleotides 1425-3202 or nucleotides 1-1485 of NM_005538.4) luciferase were measured. First, media was removed from the cells. Then, Firefly luciferase activity was measured by adding 75 µL of Dual-Glo® Luciferase Reagent equal to the culture medium volume to each well and mix. The mixture was incubated at room temperature for 30 minutes before luminescense (500nm) was measured on a Spectramax (Molecular Devices) to detect the Firefly luciferase signal. Renilla luciferase activity was measured by adding 75 µL of room temperature of Dual-Glo® Stop & Glo® Reagent to each well and the plates were incubated for 10-15 minutes before luminescence was again measured to determine the Renilla luciferase signal. The Dual-Glo® Stop & Glo® Reagent quenches the firefly luciferase signal and sustained luminescence for the Renilla luciferase reaction. siRNA activity was determined by normalizing the Renilla (INHBC) signal to the Firefly (control) signal within each well. The magnitude of siRNA activity was then assessed relative to cells that were transfected with the same vector but were not treated with siRNA or were treated with a non-targeting siRNA. All transfections were done with n=4.

The results of the dual-luciferase assays of the agents are provided in Table 23.

Table 23. Dual-Luciferase Screen for dsRNA agents targeting INHBC in Hepa1-6 Cells

Reporter Plasmid	Duplex ID	RLuc/FLuc	
		10 nM	
		% Avg message remaining (n=4)	SD
V180	AD-1732940.1	14.150	0.629
	AD-1732908.1	7.967	0.476
	AD-1732890.1	10.260	0.453
	AD-1732885.1	8.392	0.401
	AD-1732881.1	61.954	0.878
	AD-1732865.1	16.807	0.670
	AD-1732849.1	41.476	2.680
	AD-1732827.1	14.425	0.743
	AD-1732807.1	19.622	0.725
	AD-1732786.1	17.152	0.302
	AD-1732757.1	18.612	1.287
	AD-1732744.1	16.097	1.579
	AD-1732728.1	29.876	2.334
	AD-1732708.1	68.958	7.072

Reporter Plasmid	Duplex ID	RLuc/FLuc	
		10 nM	
		% Avg message remaining (n=4)	SD
	AD-1732696.1	11.309	1.048
	AD-1732677.1	10.846	0.810
	AD-1732661.1	12.693	0.648
	AD-1732644.1	21.739	2.433
	AD-1732625.1	20.810	0.984
	AD-1732604.1	34.719	1.881
	AD-1732584.1	25.478	0.950
	AD-1732565.1	23.217	1.123
	AD-1732549.1	77.904	2.566
	AD-1732533.1	55.404	2.637
	AD-1732520.1	75.941	4.976
	AD-1732500.1	60.074	4.736
	AD-1732479.1	76.945	3.845
	AD-1732469.1	28.398	4.223
	AD-1732440.1	69.737	3.729
	AD-1732415.1	79.748	4.738
	AD-1732389.1	19.244	0.749
	AD-1732372.1	12.871	1.092
	AD-1732353.1	14.060	0.517
	AD-1732335.1	16.929	0.643
	AD-1732308.1	7.798	0.528
	AD-1732291.1	16.073	0.324
	AD-1732269.1	15.369	0.454
	AD-1732253.1	11.966	0.396
	AD-1732235.1	15.662	0.455
	AD-1732217.1	11.891	0.307
	AD-1732195.1	22.664	2.324
	AD-1732176.1	40.545	3.354
	AD-1732173.1	36.333	4.051
	AD-1732157.1	12.425	0.688
	AD-1732110.1	8.878	0.368
	AD-1732094.1	16.277	0.992
	AD-1732078.1	12.292	0.574
	AD-1732062.1	13.286	1.417
	AD-1732048.1	25.400	0.737
	AD-1732031.1	12.699	1.522
	AD-1732013.1	13.228	0.746
	AD-1731997.1	14.695	2.144

Reporter Plasmid	Duplex ID	RLuc/FLuc	
		10 nM	
		% Avg message remaining (n=4)	SD
	AD-1731978.1	22.496	3.865
	AD-1731958.1	20.145	0.926
	AD-1731932.1	66.101	5.314
	AD-1731923.1	74.139	8.370
	AD-1731906.1	45.134	4.197
	AD-1731890.1	33.397	2.478
	AD-1731874.1	41.801	1.190
	AD-1731858.1	4.851	0.510
	AD-1731842.1	6.224	0.565
	AD-1731819.1	11.143	0.815
	AD-1731813.1	8.497	0.331
	AD-1731782.1	4.415	0.145
	AD-1731753.1	11.691	1.185
	AD-1731750.1	5.301	0.362
	AD-1731745.1	10.404	0.658
	AD-1731728.1	22.012	2.859
	AD-1731720.1	12.432	0.820
	AD-1731704.1	5.547	0.321
	AD-1731687.1	3.065	0.161
	AD-1731671.1	19.915	2.526
V179	AD-1731704.1	15.257	0.906
	AD-1731687.1	11.014	0.767
	AD-1731671.1	34.407	2.796
	AD-1731646.1	50.018	5.438
	AD-1731618.1	15.753	1.031
	AD-1731600.1	12.780	0.848
	AD-1731584.1	8.732	0.637
	AD-1731564.1	13.821	1.071
	AD-1731562.1	9.409	0.428
	AD-1731545.1	66.529	4.870
	AD-1731527.1	92.440	1.602
	AD-1731511.1	75.267	3.429
	AD-1731492.1	9.940	0.588
	AD-1731484.1	27.855	1.905
	AD-1731457.1	18.170	2.945
	AD-1731431.1	42.677	4.621
	AD-1731415.1	12.748	1.092
	AD-1731398.1	28.945	3.717

Reporter Plasmid	Duplex ID	RLuc/FLuc	
		10 nM	
		% Avg message remaining (n=4)	SD
	AD-1731380.1	48.750	4.591
	AD-1731371.1	72.563	2.686
	AD-1731358.1	65.200	3.035
	AD-1731340.1	8.662	0.132
	AD-1731323.1	43.722	2.197
	AD-1731307.1	67.294	4.521
	AD-1731289.1	52.881	4.906
	AD-1731264.1	22.594	2.101
	AD-1731234.1	55.843	3.247
	AD-1731205.1	10.827	0.702
	AD-1731189.1	18.905	0.211
	AD-1731173.1	58.483	2.870
	AD-1731156.1	82.335	3.005
	AD-1731137.1	20.307	1.198
	AD-1731134.1	80.176	2.738
	AD-1731117.1	65.192	2.858
	AD-1731088.1	68.296	3.034
	AD-1731064.1	44.769	2.606
	AD-1731042.1	50.015	2.644
	AD-1731035.1	57.224	3.625
	AD-1731019.1	98.342	5.416
	AD-1731003.1	30.570	3.760
	AD-1730982.1	20.454	3.248
	AD-1730958.1	25.954	0.786
	AD-1730942.1	19.353	1.173
	AD-1730926.1	36.218	0.945
	AD-1730910.1	9.242	0.575
	AD-1730873.1	17.439	1.317
	AD-1730857.1	7.533	0.374
	AD-1730841.1	15.620	1.085
	AD-1730825.1	35.996	1.675
	AD-1730807.1	13.721	0.994
	AD-1730790.1	8.641	0.196
	AD-1730769.1	37.556	1.872
	AD-1730765.1	32.573	2.368
	AD-1730749.1	41.768	1.107
	AD-1730726.1	37.291	1.641
	AD-1730691.1	20.187	1.873

Reporter Plasmid	Duplex ID	RLuc/FLuc	
		10 nM	
		% Avg message remaining (n=4)	SD
	AD-1730667.1	36.466	4.387
	AD-1730643.1	35.649	2.632
	AD-1730636.1	90.291	3.709
	AD-1730606.1	35.942	0.833
	AD-1730588.1	34.769	1.603
	AD-1730570.1	46.879	2.310
	AD-1730554.1	10.475	0.681
	AD-1730529.1	42.962	3.284
	AD-1730512.1	25.624	1.247
	AD-1730493.1	72.772	4.634
	Positive control	0.663	0.053

Example 7: *In Vitro* Single Dose Screening of dsRNA Duplexes targeting PLIN1

Using methods as described above, the dsRNA agents targeting PLIN1 listed in Tables 10 and 11 were screened *in vitro* in Hepa1-6 cells by the dual-Luciferase assay. The results of the single dose screen are shown in Table 24.

Table 24. Dual-Luciferase Screen for dsRNA agents targeting PLIN1 in Hepa1-6 Cells

Duplex ID	RLuc/FLuc	
	10 nM	
	% Avg message remaining	SD
AD-1735320.1	53.561	4.672
AD-1735319.1	33.212	3.061
AD-1735318.1	87.299	11.406
AD-1735317.1	72.995	9.626
AD-1735316.1	80.346	7.389
AD-1735315.1	34.013	3.602
AD-1735314.1	77.100	9.948
AD-1735313.1	61.678	7.363
AD-1735312.1	47.388	4.892
AD-1735311.1	57.067	4.870
AD-1735310.1	69.433	2.837
AD-1735309.1	87.563	6.359
AD-1735308.1	54.214	6.804
AD-1735307.1	77.536	7.971
AD-1735306.1	44.999	0.952
AD-1735305.1	20.312	0.690

Duplex ID	RLuc/FLuc	
	10 nM	
	% Avg message remaining	SD
AD-1735304.1	37.885	1.346
AD-1735303.1	89.423	1.906
AD-1735302.1	71.173	4.238
AD-1735301.1	70.170	3.690
AD-1735300.1	62.217	7.128
AD-1735299.1	45.332	4.595
AD-1735298.1	75.846	7.520
AD-1735297.1	69.820	5.033
AD-1735296.1	64.227	7.301
AD-1735295.1	90.389	7.070
AD-1735294.1	73.067	7.141
AD-1735293.1	26.508	3.863
AD-1735292.1	91.596	11.766
AD-1735291.1	84.530	11.202
AD-1735290.1	80.139	6.540
AD-1735289.1	40.946	2.761
AD-1735288.1	33.302	3.704
AD-1735287.1	37.684	3.007
AD-1735286.1	47.467	3.016
AD-1735285.1	28.454	1.209
AD-1735284.1	30.826	3.351
AD-1735283.1	35.399	1.914
AD-1735282.1	39.620	3.772
AD-1735281.1	65.860	1.354
AD-1735280.1	21.944	2.006
AD-1735279.1	52.047	4.181
AD-1735278.1	36.993	3.597
AD-1735277.1	43.703	0.939
AD-1735276.1	24.075	1.681
AD-1735275.1	41.179	1.720
AD-1735274.1	30.228	2.242
AD-1735273.1	37.603	3.724
AD-1735272.1	27.325	2.573
AD-1735271.1	54.654	4.358
AD-1735270.1	30.214	2.322
AD-1735269.1	47.580	1.497
AD-1735268.1	29.621	2.529
AD-1735267.1	38.804	3.763
AD-1735266.1	29.659	0.328

Duplex ID	RLuc/FLuc	
	10 nM	
	% Avg message remaining	SD
AD-1735265.1	34.545	2.741
AD-1735264.1	80.144	6.568
AD-1735263.1	26.159	1.851
AD-1735262.1	37.861	1.332
AD-1735261.1	43.807	5.808
AD-1735260.1	30.677	2.583
AD-1735259.1	43.570	4.475
AD-1735258.1	40.682	3.274
AD-1735257.1	43.057	2.824
AD-1735256.1	38.041	2.568
AD-1735255.1	21.650	0.909
AD-1735254.1	27.873	3.744
AD-1735253.1	77.253	3.270
AD-1735252.1	39.960	2.697
AD-1735251.1	41.732	2.546
AD-1735250.1	27.088	1.383
AD-1735249.1	29.574	1.839
AD-1735248.1	45.794	3.063
AD-1735247.1	68.096	8.378
AD-1735246.1	40.621	2.231
AD-1735245.1	59.324	3.637
AD-1735244.1	22.847	1.836
AD-1735243.1	85.325	3.497
AD-1735242.1	35.687	3.410
AD-1735241.1	23.433	0.870
AD-1735240.1	31.517	1.780
AD-1735239.1	36.244	2.725
AD-1735238.1	32.611	1.443
AD-1735237.1	14.047	0.939
AD-1735236.1	16.631	0.772
AD-1735235.1	31.488	3.435
AD-1735234.1	39.842	2.222
AD-1735233.1	13.998	0.629
AD-1735232.1	47.840	5.226
AD-1735231.1	31.494	1.469
AD-1735230.1	23.989	1.990
AD-1735229.1	19.072	2.237
AD-1735228.1	16.810	1.007
AD-1735227.1	27.650	2.449

Duplex ID	RLuc/FLuc	
	10 nM	
	% Avg message remaining	SD
AD-1735226.1	24.667	1.786
AD-1735225.1	23.622	2.500
AD-1735224.1	24.205	1.728
AD-1735223.1	13.924	1.257
AD-1735222.1	16.961	1.476
AD-1735221.1	26.245	1.531
AD-1735220.1	28.657	1.159
AD-1735219.1	16.124	1.387
AD-1735218.1	23.929	1.107
AD-1735217.1	71.822	3.235
AD-1735216.1	22.636	1.631
AD-1735215.1	10.556	1.255
AD-1735214.1	92.571	5.143
AD-1735213.1	25.487	2.249
AD-1735212.1	12.128	0.655
AD-1735211.1	29.064	2.614
AD-1735210.1	19.343	2.334
AD-1735209.1	17.586	1.040
AD-1735208.1	13.678	0.528
AD-1735207.1	25.561	1.744
AD-1735206.1	21.848	2.252
AD-1735205.1	17.025	1.043
AD-1735204.1	15.538	0.982
AD-1735203.1	16.080	1.928
AD-1735202.1	16.432	0.718
AD-1735201.1	34.346	1.470
AD-1735200.1	24.511	1.673
AD-1735199.1	7.066	0.486
AD-1735198.1	14.709	1.084
AD-1735197.1	16.627	1.417
AD-1735196.1	13.687	0.708
AD-1735195.1	22.964	1.902
AD-1735194.1	39.620	0.928
AD-1735193.1	27.843	1.143
AD-1735192.1	17.138	0.504
AD-1735191.1	20.200	1.123
AD-1735190.1	18.874	0.788
AD-1735189.1	21.167	0.415
AD-1735188.1	25.098	3.920

Duplex ID	RLuc/FLuc	
	10 nM	
	% Avg message remaining	SD
AD-1735187.1	33.725	1.983
AD-1735186.1	17.016	0.284
positive control	0.759	0.092

Example 8. *In vivo* Assessment of RNAi Agents in Non-Human Primates (NHP)

The pharmacodynamic activity of duplexes targeting INHBE was also assessed *in vivo* in non-human primates (NHP).

As depicted in Figure 1, on Day 0 female non-human primates (n=3) were subcutaneously administered a single 3 mg/kg dose of AD-1707306, AD-1711744, AD-1708473, AD-1707640, AD-1707639, AD-1706583, AD-1706593, AD-1706761, or AD-1706662, or PBS control. Post-dose, plasma samples were collected biweekly, serum samples were collected weekly, and liver biopsy samples were collected at Days 28 and 57 post-dose to determine the effect of the agents on INHBE and INHBC mRNA expression, as described above, and clinical chemistry and hematological read-outs. Animals were sacrificed at Day 90 post-dose, tissue samples were collected and the levels of INHBE and INHBC mRNA were quantified as described above.

As depicted in Figures 2A and 2B, at Day 28 post-dose, a single 3 mg/kg subcutaneous dose of the agents potently inhibited INHBE expression *in vivo* (Figure 2A) but not INHBC (Figure 2B) expression.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments and methods described herein. Such equivalents are intended to be encompassed by the scope of the following claims.

Informal Sequence Listing

SEQ ID NO: 1

>NM_031479.5 Homo sapiens inhibin subunit beta E (INHBE), mRNA

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SEQ ID NO: 2 REVERSE COMPLEMENT OF SEQ ID NO: 1

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SEQ ID NO: 3

>NM_008382.3 Mus musculus inhibin beta-E (Inhbe), mRNA
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SEQ ID NO: 4 REVERSE COMPLEMENT OF SEQ ID NO: 3

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SEQ ID NO: 5

>NM_031815.2 Rattus norvegicus inhibin subunit beta E (Inhbe), mRNA

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SEQ ID NO: 6 REVERSE COMPLEMENT OF SEQ ID NO: 5

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SEQ ID NO: 7

>XM_001115958.3 PREDICTED: Macaca mulatta inhibin subunit beta E (INHBE), mRNA

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SEQ ID NO: 8 REVERSE COMPLEMENT OF SEQ ID NO: 7

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SEQ ID NO:9
>NM_145259.3 Homo sapiens activin A receptor type 1C (ACVR1C), transcript variant 1, mRNA

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SEQ ID NO:21

>NM_139090.2 Rattus norvegicus activin A receptor type 1C (Acvr1c), mRNA

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SEQ ID NO:22 Reverse complement of SEQ ID NO:21

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SEQ ID NO:23

>NM_001266690.1 Macaca mulatta activin A receptor type 1C (ACVR1C), mRNA

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SEQ ID NO:24 Reverse complement of SEQ ID NO:23

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SEQ ID NO:25
>NM_002666.5 Homo sapiens perilipin 1 (PLIN1), transcript variant 1, mRNA
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SEQ ID NO:28 Reverse complement of SEQ ID NO:27

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SEQ ID NO:29
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SEQ ID NO:33
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SEQ ID NO:36 Reverse complement of SEQ ID NO:35

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SEQ ID NO:44 Reverse complement of SEQ ID NO:43

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SEQ ID NO:45
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SEQ ID NO:46 Reverse complement of SEQ ID NO:45

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SEQ ID NO:47
>XM_015114810.2 PREDICTED: Macaca mulatta phosphodiesterase 3B (PDE3B), transcript variant X1, mRNA

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SEQ ID NO:48 Reverse complement of SEQ ID NO:47

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SEQ ID NO:49

>NM_005538.4 Homo sapiens inhibin subunit beta C (INHBC), mRNA

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SEQ ID NO:50 Reverse complement of SEQ ID NO:49

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SEQ ID NO:51
>NM_010565.4 Mus musculus inhibin beta-C (Inhbc), mRNA
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SEQ ID NO:52 Reverse complement of SEQ ID NO:51
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SEQ ID NO:53
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SEQ ID NO:56 Reverse complement of SEQ ID NO:55
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GCCCTGGAAGAAGTGTGTGTCCAGCTGGCATGGCTCCTTGTTGCAGGGGACAGAGCAGCAGCCAAACATCTG
ACTTGAAAATGAAGCCAGTTACAGGTAGAACTTGGCAGAATCTGCCAACGCATAGTCAGTGAAAGTACAGAG
TGGGGGACGTGAGGAGAGGTTGGTTTGTTTAGGGAAAGACATGTCCCTGGGCCAATGTTGGGAGACAGTTGT
TATCCATGTGAGCTGCCAAGCCTGGGGACAAAGGTGA

We claim:

1. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of a metabolic disorder-associated target gene selected from the group consisting of inhibin subunit beta E (INHBE), activin A receptor type 1C (ACVR1C), perilipin-1 (PLIN1), phosphodiesterase 3B (PDE3B), and inhibin subunit beta C (INHBC) in a cell, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of any one of SEQ ID NOs:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, or 55, and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the corresponding portion of the nucleotide sequence of any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, or 56.

2. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of a metabolic disorder-associated target gene selected from the group consisting of inhibin subunit beta E (INHBE), activin A receptor type 1C (ACVR1C), perilipin-1 (PLIN1), phosphodiesterase 3B (PDE3B), and inhibin subunit beta C (INHBC) in a cell, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a region of complementarity to an mRNA encoding the target gene, and wherein the region of complementarity comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense nucleotide sequences in any one of Tables 2-17, 19 and 20.

3. The dsRNA agent of claim 1, wherein the dsRNA agent comprises a sense strand comprising at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequences of the sense strands in any one of Tables 2-17, 19 and 20 and an antisense strand comprising at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequences of the antisense strands in any one of Tables 2-17, 19 and 20.

4. The dsRNA agent of claim 1, wherein the dsRNA agent comprises a sense strand comprising at least 15 contiguous nucleotides differing by no more than two nucleotides from any one of the nucleotide sequences of the sense strands in any one of Tables 2-17, 19 and 20 and an antisense strand comprising at least 15 contiguous nucleotides differing by no more than two nucleotides from any one of the nucleotide sequences of the antisense strands in any one of Tables 2-17, 19 and 20.

5. The dsRNA agent of claim 1, wherein the dsRNA agent comprises a sense strand comprising at least 15 contiguous nucleotides differing by no more than one nucleotide from any one of the nucleotide sequences of the sense strands in any one of Tables 2-17, 19 and 20 and an antisense strand

comprising at least 15 contiguous nucleotides differing by no more than one nucleotide from any one of the nucleotide sequences of the antisense strands in any one of Tables 2-17, 19 and 20.

6. The dsRNA agent of claim 1, wherein the dsRNA agent comprises a sense strand comprising a nucleotide sequence selected from the group consisting of any one of the nucleotide sequences of the sense strands in any one of Tables 2-17, 19 and 20 and an antisense strand comprising a nucleotide sequence selected from the group consisting of any one of the nucleotide sequences of the antisense strands in any one of Tables 2-17, 19 and 20.

7. The dsRNA agent of any one of claims 1-6, wherein the target gene is INHBE.

8. The dsRNA agent of any one of claims 1-6, wherein the target gene is ACVR1C.

9. The dsRNA agent of any one of claims 1-6, wherein the target gene is PLIN1.

10. The dsRNA agent of any one of claims 1-6, wherein the target gene is PDE3B.

11. The dsRNA agent of any one of claims 1-6, wherein the target gene is INHBC.

12. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of inhibin subunit beta E (INHBE) in a cell, wherein said dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 400-422, 410-432, 518-540, 519-541, 640-662, 1430-1452, 1863-1885, or 1864-1886 of SEQ ID NO: 1, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2.

13. The dsRNA agent of any one of claims 1-7 and 12, wherein the antisense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the antisense strand nucleotide sequences of an agent selected from the group consisting of AD-1706583, AD-1711744, AD-1706593, AD-1708473, AD-1706662, AD-1706761, AD-1707306, AD-1707639, and AD-1707640.

14. The dsRNA agent of any one of claims 1-7 and 12, wherein the antisense strand comprises at least 15 contiguous nucleotides differing by no more than two nucleotides from any one of the antisense strand nucleotide sequences of an agent selected from the group consisting of AD-

1706583, AD-1711744, AD-1706593, AD-1708473, AD-1706662, AD-1706761, AD-1707306, AD-1707639, and AD-1707640.

15. The dsRNA agent of any one of claims 1-7 and 12, wherein the antisense strand comprises at least 15 contiguous nucleotides differing by no more than one nucleotide from any one of the antisense strand nucleotide sequences of an agent selected from the group consisting of AD-1706583, AD-1711744, AD-1706593, AD-1708473, AD-1706662, AD-1706761, AD-1707306, AD-1707639, and AD-1707640.

16. The dsRNA agent of any one of claims 1-7 and 12, wherein the sense and the antisense strand comprise at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the sense and the antisense strand nucleotide sequences of an agent selected from the group consisting of AD-1706583, AD-1711744, AD-1706593, AD-1708473, AD-1706662, AD-1706761, AD-1707306, AD-1707639, and AD-1707640.

17. The dsRNA agent of any one of claims 1-7 and 12, wherein the sense and the antisense strand comprise at least 15 contiguous nucleotides differing by no more than two nucleotides from any one of the sense and the antisense strand nucleotide sequences of an agent selected from the group consisting of AD-1706583, AD-1711744, AD-1706593, AD-1708473, AD-1706662, AD-1706761, AD-1707306, AD-1707639, and AD-1707640.

18. The dsRNA agent of any one of claims 1-7 and 12, wherein the sense and the antisense strand comprise at least 15 contiguous nucleotides differing by no more than one nucleotide from any one of the sense and the antisense strand nucleotide sequences of an agent selected from the group consisting of AD-1706583, AD-1711744, AD-1706593, AD-1708473, AD-1706662, AD-1706761, AD-1707306, AD-1707639, and AD-1707640.

19. The dsRNA agent of any one of claims 1-7 and 12, wherein the sense and the antisense strand comprise the sense and the antisense strand nucleotide sequences of an agent selected from the group consisting of AD-1706583, AD-1711744, AD-1706593, AD-1708473, AD-1706662, AD-1706761, AD-1707306, AD-1707639, and AD-1707640.

20. The dsRNA agent of any one of claims 1-7 and 12, wherein the sense and the antisense strand consist of the sense and the antisense strand nucleotide sequences of an agent selected from the group consisting of AD-1706583, AD-1711744, AD-1706593, AD-1708473, AD-1706662, AD-1706761, AD-1707306, AD-1707639, and AD-1707640.

21. The dsRNA agent of any one of claims 1-7 and 12-20, wherein the antisense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the antisense strand nucleotide sequences selected from the group consisting of

(a) 5'- AGUUAUTCUGGGACGACUGGUCA -3';
(b) 5'- AGUUAUTCUGGGACGACUGGUCU -3';
(c) 5'- ATGGAGGAUGAGUUAUUCUGGGA -3';
(d) 5'- AUGAAGTGGAGUCUGUGACAGUA -3';
(e) 5'- ACUGAAGUGGAGUCUGUGACAGU -3';
(f) 5'- ACGGAAGAUCCTCAAGCAAAGAG -3';
(g) 5'- ACAGACAAGAAAGUGCCCAUUUG -3';
(h) 5'- AAGAAAGUAUAAAUGCUUGUCUC -3'; and
(i) 5'- AAAGAAAGUAUAAAUGCUUGUCU -3'.

22. The dsRNA agent of any one of claims 1-7 and 12-21, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the sense and antisense strand nucleotide sequences selected from the group consisting of

(a) 5'- ACCAGUCGUCCCAGAAUAACU -3' and
5'-AGUUAUTCUGGGACGACUGGUCA -3';
(b) 5'- ACCAGUCGUCCCAGAAUAACU -3' and
5'-AGUUAUTCUGGGACGACUGGUCU -3';
(c) 5'- CCAGAAUAACUCAUCCUCCAU -3' and
5'-ATGGAGGAUGAGUUAUUCUGGGA -3';
(d) 5'- CUGUCACAGACUCCACUUCAU -3' and
5'-AUGAAGTGGAGUCUGUGACAGUA -3';
(e) 5'- UGUCACAGACUCCACUUCAGU -3' and
5'-ACUGAAGUGGAGUCUGUGACAGU -3';
(f) 5'- CUUUGCUUGAGGAUCUUCCGU -3' and
5'-ACGGAAGAUCCTCAAGCAAAGAG -3';
(g) 5'- AAUGGGCACUUUCUUGUCUGU -3' and
5'-ACAGACAAGAAAGUGCCCAUUUG -3';
(h) 5'- GACAAGCAUUUAUACUUUCUU -3' and
5'-AAGAAAGUAUAAAUGCUUGUCUC -3'; and
(i) 5'- ACAAGCAUUUAUACUUUCUUU -3' and
5'-AAAGAAAGUAUAAAUGCUUGUCU -3'.

23. The dsRNA agent of any one of claims 1-22, wherein the dsRNA agent comprises at least one modified nucleotide.

24. The dsRNA agent of any one of claims 1-23, wherein substantially all of the nucleotides of the sense strand are modified nucleotides; substantially all of the nucleotides of the antisense strand are modified nucleotides; or substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand are modified nucleotides.

25. The dsRNA agent of any one of claims 1-24, wherein all of the nucleotides of the sense strand are modified nucleotides; all of the nucleotides of the antisense strand are modified nucleotides; or all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand are modified nucleotides.

26. The dsRNA agent of any one of claims 23-25, 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, 2'-hydroxly-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 thermally destabilizing nucleotide, a glycol modified nucleotide (GNA), a nucleotide comprising a 2' phosphate, and a 2-O-(N-methylacetamide) modified nucleotide; and combinations thereof.

27. The dsRNA agent of any one of claims 23-25, wherein at least one of the modified nucleotides is selected from the group consisting of LNA, HNA, CeNA, 2′-methoxyethyl, 2′-O-alkyl, 2′-O-allyl, 2′-C- allyl, 2′-fluoro, 2′-deoxy, 2'-hydroxyl, and glycol; and combinations thereof.

28. The dsRNA agent of any one of claims 23-25, wherein 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), a nucleotide comprising a 2' phosphate, a nucleotide comprising a phosphorothioate group, and a vinyl-phosphonate nucleotide; and combinations thereof.

29. The dsRNA agent of any one of claims 23-25, wherein at least one of the modified nucleotides is a nucleotide modified with a thermally destabilizing nucleotide modification.

30. The dsRNA agent of claim 29, wherein the thermally destabilizing nucleotide modification is selected from the group consisting of an abasic modification; a mismatch with the opposing nucleotide in the duplex; a destabilizing sugar modification, a 2'-deoxy modification, an acyclic nucleotide, an unlocked nucleic acid (UNA), and a glycerol nucleic acid (GNA).

31. The dsRNA agent of any one of claims 1-30, further comprising a phosphate or phosphate mimic at the 5'-end of the antisense strand.

32. The dsRNA agent of claim 31, wherein the phosphate mimic is a 5'-vinyl phosphonate (VP).

33. The dsRNA agent of any one of claims 1-32, wherein 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.

34. The dsRNA agent of any one of claims 1-33, wherein the double stranded region is 19-30 nucleotide pairs in length.

35. The dsRNA agent of claim 34, wherein the double stranded region is 19-25 nucleotide pairs in length.

36. The dsRNA agent of claim 34, wherein the double stranded region is 19-23 nucleotide pairs in length.

37. The dsRNA agent of claim 34, wherein the double stranded region is 23-27 nucleotide pairs in length.

38. The dsRNA agent of claim 34, wherein the double stranded region is 21-23 nucleotide pairs in length.

39. The dsRNA agent of any one of claims 1-38, wherein each strand is independently no more than 30 nucleotides in length.

40. The dsRNA agent of any one of claims 1-39, wherein the sense strand is 21 nucleotides in length and the antisense strand is 23 nucleotides in length.

41. The dsRNA agent of any one of claims 1-40, wherein the region of complementarity is at least 17 nucleotides in length.

42. The dsRNA agent of any one of claims 1-41, wherein the region of complementarity is between 19 and 23 nucleotides in length.

43. The dsRNA agent of any one of claims 1-42, wherein the region of complementarity is 19 nucleotides in length.

44. The dsRNA agent of any one of claims 1-43, wherein at least one strand comprises a 3' overhang of at least 1 nucleotide.

45. The dsRNA agent of any one of claims 1-43, wherein at least one strand comprises a 3' overhang of at least 2 nucleotides.

46. The dsRNA agent of any one of claims 1-45, wherein one or more C_{22} hydrocarbon chains is conjugated to one or more internal positions on at least one strand.

47. The dsRNA agent of claim 46, wherein the C_{22} hydrocarbon chain is saturated or unsaturated.

48. The dsRNA agent of claim 46 or 47, wherein the C_{22} hydrocarbon chain is linear or branched

49. The dsRNA agent of any one of claims 46-48, wherein the internal positions include all positions except two or three terminal positions from each end of the at least one strand.

50. The dsRNA agent of claim 49, wherein the internal positions exclude a cleavage site region of the sense strand.

51. The dsRNA agent of claim 50, wherein the internal positions exclude positions 9-12 or positions 11-13, counting from the 5'-end of the sense strand.

52. The dsRNA agent of claim 49, wherein the internal positions exclude a cleavage site region of the antisense strand.

53. The dsRNA agent of claim 52, wherein the internal positions exclude positions 12-14, counting from the 5'-end of the antisense strand.

54. The dsRNA agent of any one of claims 46-53, wherein the one or more C_{22} hydrocarbon chains are conjugated to one or more of the following internal positions: 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.

55. The dsRNA agent of claim 54, wherein the one or more C_{22} hydrocarbon chains are conjugated to one or more of the following internal positions: 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.

56. The dsRNA agent of claim 55, wherein the one or more C_{22} hydrocarbon chains are conjugated to position 6 on the sense strand, counting from the 5'-end of the sense strand.

57. The dsRNA agent of any one of claims 46-56, wherein the one or more C_{22} hydrocarbon chains is an aliphatic, alicyclic, or polyalicyclic compound.

58. The dsRNA agent of claim 57, wherein the one or more C_{22} hydrocarbon chains contains a functional group selected from the group consisting of hydroxyl, amine, carboxylic acid, sulfonate, phosphate, thiol, azide, and alkyne.

59. The dsRNA agent of any one of claims 46-58, wherein the one or more C_{22} hydrocarbon chains is a C_{22} acid.

60. The dsRNA agent of claim 59, wherein the C_{22} acid is selected from the group consisting of docosanoic acid, 6-octyltetradecanoic acid, 10-hexylhexadecanoic acid, all-cis-7,10,13,16,19-docosapentaenoic acid, all-cis-4,7,10,13,16,19-docosahexaenoic acid, all-cis-13,16-docosadienoic acid, all-cis-7,10,13,16-docosatetraenoic acid, all-cis-4,7,10,13,16-docosapentaenoic acid, and cis-13-docosenoic acid.

61. The dsRNA agent of any one of claims 46-58, wherein the one or more C_{22} hydrocarbon chains is a C_{22} alcohol.

62. The dsRNA agent of claim 61, wherein the C_{22} alcohol is selected from the group consisting of 1-docosanol, 6-octyltetradecan-1-ol, 10-hexylhexadecan-1-ol, cis-13-docosen-1-ol, docosan-9-ol, docosan-2-ol, docosan-10-ol, docosan-11-ol, andcis-4,7,10,13,16,19-docosahexanol.

63. The dsRNA agent of any one of claims 46-58, wherein the one or more C_{22} hydrocarbon chains is a C_{22} amide.

64. The dsRNA agent of claim 63, wherein the C_{22} amide is selected from the group consisting of (E)-Docos-4-enamide, (E)-Docos-5-enamide, (Z)-Docos-9-enamide, (E)-Docos-11-enamide,12-Docosenamide, (Z)-Docos-13-enamide, (Z)-N-Hydroxy-13-docoseneamide, (E)-Docos-14-enamide, 6-cis-Docosenamide, 14-Docosenamide Docos-11-enamide, (4E,13E)-Docosa-4,13-dienamide, and (5E,13E)-Docosa-5,13-dienamide. .

65. The dsRNA agent of any one of claims 46-64, wherein the one or more C_{22} hydrocarbon chains is conjugated via a carrier that replaces one or more nucleotide(s) in the internal position(s).

66. The dsRNA agent of claim 65, wherein 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.

67. The dsRNA agent of any one of claims 46-66, wherein the one or more C_{22} hydrocarbon chains is conjugated to the dsRNA 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.

68. The dsRNA agent of any one of claims 46-67, wherein the one or more C_{22} hydrocarbon chains is conjugated to the dsRNA agent via a linker or a carrier or via internucleotide phosphate linkage.

69. The dsRNA agent of any one of claims 46-68, wherein the one or more C_{22} hydrocarbon chains is conjugated to a nucleobase, sugar moiety, or internucleosidic phosphate linkage.

70. The dsRNA agent of any one of claims 1-69, further comprising a targeting ligand that targets a receptor which mediates delivery to adipose tissue.

71. The dsRNA agent of claim 70, wherein the targeting ligand is selected from the group consisting of Angiopep-2, lipoprotein receptor related protein (LRP) ligand, bEnd.3 cell binding ligand, transferrin receptor (TfR) ligand, manose receptor ligand, glucose transporter protein, LDL receptor ligand, trans-retinol, RGD peptide, LDL receptor ligand, CD63 ligand, and carbohydrate based ligand.

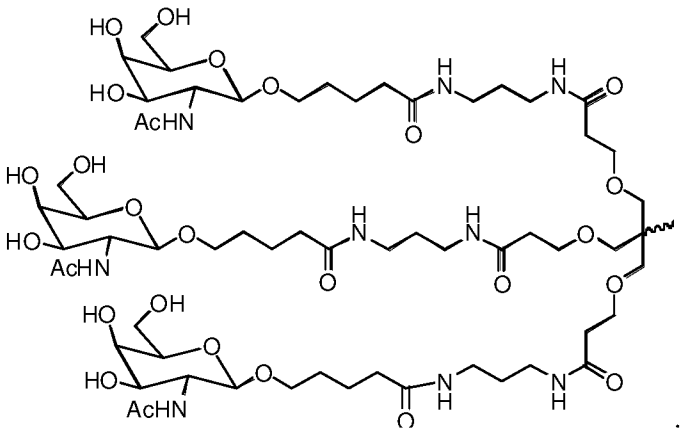
72. The dsRNA agent of any one of claims 1-71, further comprising a targeting ligand that targets a liver tissue.

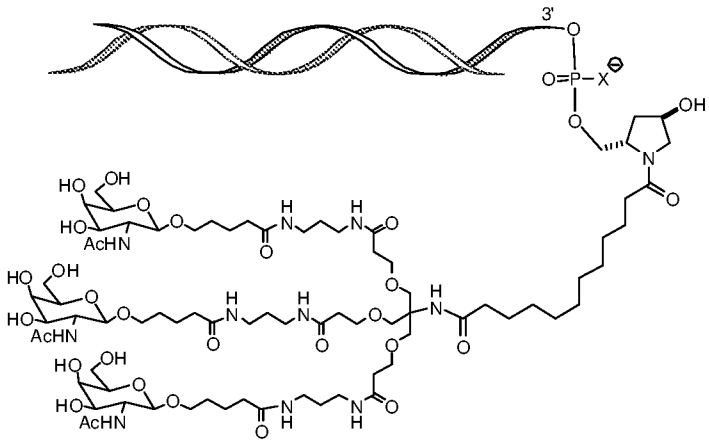
73. The dsRNA agent of claim 72, wherein the targeting ligand is conjugated to the 3' end of the sense strand of the dsRNA agent.

74. The dsRNA agent of claim 72 or 73, wherein the targeting ligand is an N-acetylgalactosamine (GalNAc) derivative.

75. The dsRNA agent of any one of claims 72-74, wherein the targeting ligand is one or more GalNAc derivatives attached through a monovalent, bivalent, or trivalent branched linker.

76. The dsRNA agent of 72-75, wherein the targeting ligand is


HO
OH
O
HO
AcHN
O
H
N
O
O
O



and, wherein X is O or S.

78. The dsRNA agent of claim 77, wherein the X is O.

79. The dsRNA agent of any one of claims 46-78, wherein the one or more C_{22} hydrocarbon chains or targeting ligand is conjugated via a bio-clevable linker selected from the group consisting of DNA, RNA, disulfide, amide, funtionalized monosaccharides or oligosaccharides of galactosamine, glucosamine, glucose, galactose, mannose, and combinations thereof.

80. The dsRNA agent of any one of claims 1-79, wherein the dsRNA agent further comprises at least one phosphorothioate or methylphosphonate internucleotide linkage.

81. The dsRNA agent of claim 80, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at the 3'-terminus of one strand.

82. The dsRNA agent of claim 81, wherein the strand is the antisense strand.

83. The dsRNA agent of claim 81, wherein the strand is the sense strand.

84. The dsRNA agent of claim 80, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at the 5'-terminus of one strand.

85. The dsRNA agent of claim 84, wherein the strand is the antisense strand.

86. The dsRNA agent of claim 84, wherein the strand is the sense strand.

87. The dsRNA agent of claim 80, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at both the 5'- and 3'-terminus of one strand.

88. The dsRNA agent of claim 87, wherein the strand is the antisense strand.

89. The dsRNA agent of any one of claims 1-88, wherein the base pair at the 1 position of the 5′-end of the antisense strand of the duplex is an AU base pair.

90. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of inhibin subunit beta E (INHBE), wherein said dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 4 nucleotides from the nucleotide sequence ascscagucgUfCfCfcagaauaacu (SEQ ID NO:),

wherein the antisense strand comprises at least 15 contiguous nucleotides differenting by no more than 4 nucleotides from the nucleotide sequence asdGsuudAudTcuggdGaCfgacugguscsa (SEQ ID NO:),

wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U; Af, Gf, Cf, and Uf are 2'-fluoro A, G, C and U; dA, dG, dC and dT are 2`-deoxy A, G, C and T; s is a phosphorothioate linkage; and

wherein the dsRNA comprises one or more C22 hydrocarbon chains conjugated to one or more internal positions on at least one strand of the dsRNA agent.

91. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of inhibin subunit beta E (INHBE), wherein said dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 4 nucleotides from the nucleotide sequence ascscagucgUfCfCfcagaauaacu (SEQ ID NO:),

wherein the antisense strand comprises at least 15 contiguous nucleotides differenting by no more than 4 nucleotides from the nucleotide sequence asdGsuudAudTcuggdGaCfgacugguscsu (SEQ ID NO:),

wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U; Af, Gf, Cf, and Uf are 2'-fluoro A, G, C and U; dA, dG, dC and dT are 2`-deoxy A, G, C and T; s is a phosphorothioate linkage; and

wherein the dsRNA comprises one or more C22 hydrocarbon chains conjugated to one or more internal positions on at least one strand of the dsRNA agent.

92. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of inhibin subunit beta E (INHBE), wherein said dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 4 nucleotides from the nucleotide sequence cscsagaauaAfCfUfcauccuccau (SEQ ID NO:),

wherein the antisense strand comprises at least 15 contiguous nucleotides differenting by no more than 4 nucleotides from the nucleotide sequence asdTsggdAgdGaugadGuUfauucuggsgsa (SEQ ID NO:),

wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U; Af, Gf, Cf, and Uf are 2'-fluoro A, G, C and U; dA, dG, dC and dT are 2`-deoxy A, G, C and T; s is a phosphorothioate linkage; and

wherein the dsRNA comprises one or more C22 hydrocarbon chains conjugated to one or more internal positions on at least one strand of the dsRNA agent.

93. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of inhibin subunit beta E (INHBE), wherein said dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 4 nucleotides from the nucleotide sequence csusgucaCfaGfAfCfuccacuucau (SEQ ID NO:),

wherein the antisense strand comprises at least 15 contiguous nucleotides differenting by no more than 4 nucleotides from the nucleotide sequence asUfsgadAg(Tgn)ggagucUfgUfgacagsusa (SEQ ID NO:),

wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U; Af, Gf, Cf, and Uf are 2'-fluoro A, G, C and U; dA, dG, dC and dT are 2`-deoxy A, G, C and T; Tgn is thymidine-glycol nucleic acid (GNA) S-isomer; s is a phosphorothioate linkage; and

wherein the dsRNA comprises one or more C22 hydrocarbon chains conjugated to one or more internal positions on at least one strand of the dsRNA agent.

94. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of inhibin subunit beta E (INHBE), wherein said dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 4 nucleotides from the nucleotide sequence usgsucacagAfCfUfccacuucagu (SEQ ID NO:),

wherein the antisense strand comprises at least 15 contiguous nucleotides differenting by no more than 4 nucleotides from the nucleotide sequence asdCsugdAadGuggadGuCfugugacasgsu (SEQ ID NO:),

wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U; Af, Gf, Cf, and Uf are 2'-fluoro A, G, C and U; dA, dG, dC and dT are 2`-deoxy A, G, C and T; s is a phosphorothioate linkage; and

wherein the dsRNA comprises one or more C22 hydrocarbon chains conjugated to one or more internal positions on at least one strand of the dsRNA agent.

95. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of inhibin subunit beta E (INHBE), wherein said dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 4 nucleotides from the nucleotide sequence csusuugcuuGfAfGfgaucuuccgu (SEQ ID NO:),

wherein the antisense strand comprises at least 15 contiguous nucleotides differenting by no more than 4 nucleotides from the nucleotide sequence asdCsggdAadGauccdTcAfagcaaagsasg (SEQ ID NO:),

wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U; Af, Gf, Cf, and Uf are 2'-fluoro A, G, C and U; dA, dG, dC and dT are 2`-deoxy A, G, C and T; s is a phosphorothioate linkage; and

wherein the dsRNA comprises one or more C22 hydrocarbon chains conjugated to one or more internal positions on at least one strand of the dsRNA agent.

96. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of inhibin subunit beta E (INHBE), wherein said dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 4 nucleotides from the nucleotide sequence asasugggcaCfUfUfucuugucugu (SEQ ID NO:),

wherein the antisense strand comprises at least 15 contiguous nucleotides differenting by no more than 4 nucleotides from the nucleotide sequence asdCsagdAcdAagaadAgUfgcccauususg (SEQ ID NO:),

wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U; Af, Gf, Cf, and Uf are 2'-fluoro A, G, C and U; dA, dG, dC and dT are 2`-deoxy A, G, C and T; s is a phosphorothioate linkage; and

wherein the dsRNA comprises one or more C22 hydrocarbon chains conjugated to one or more internal positions on at least one strand of the dsRNA agent.

97. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of inhibin subunit beta E (INHBE), wherein said dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 4 nucleotides from the nucleotide sequence gsascaagcaUfUfUfauacuuucuu (SEQ ID NO:),

wherein the antisense strand comprises at least 15 contiguous nucleotides differenting by no more than 4 nucleotides from the nucleotide sequence asdAsgadAadGuauadAaUfgcuugucsusc (SEQ ID NO:),

wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U; Af, Gf, Cf, and Uf are 2'-fluoro A, G, C and U; dA, dG, dC and dT are 2`-deoxy A, G, C and T; s is a phosphorothioate linkage; and

wherein the dsRNA comprises one or more C22 hydrocarbon chains conjugated to one or more positions on at least one strand of the dsRNA agent.

98. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of inhibin subunit beta E (INHBE), wherein said dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 4 nucleotides from the nucleotide sequence ascsaagcauUfUfAfuacuuucuuu (SEQ ID NO:),

wherein the antisense strand comprises at least 15 contiguous nucleotides differenting by no more than 4 nucleotides from the nucleotide sequence asdAsagdAadAguaudAaAfugcuuguscsu (SEQ ID NO:),

wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U; Af, Gf, Cf, and Uf are 2'-fluoro A, G, C and U; dA, dG, dC and dT are 2`-deoxy A, G, C and T; s is a phosphorothioate linkage; and

wherein the dsRNA comprises one or more C22 hydrocarbon chains conjugated to one or more internal positions on at least one strand of the dsRNA agent.

99. The dsRNA agent of any one of claims 90-98, wherein the C_{22} hydrocarbon chain is saturated or unsaturated.

100. The dsRNA agent of any one of claims 90-99, wherein the C_{22} hydrocarbon chain is linear or branched

101. The dsRNA agent of any one of claims 90-100, wherein the internal positions include all positions except two or three terminal positions from each end of the at least one strand.

102. The dsRNA agent of claim 101, wherein the internal positions exclude a cleavage site region of the sense strand.

103. The dsRNA agent of claim 102, wherein the internal positions exclude positions 9-12 or positions 11-13, counting from the 5'-end of the sense strand.

104. The dsRNA agent of claim 101, wherein the internal positions exclude a cleavage site region of the antisense strand.

105. The dsRNA agent of claim 104, wherein the internal positions exclude positions 12-14, counting from the 5'-end of the antisense strand.

106. The dsRNA agent of any one of claims 90-105, wherein the one or more C_{22} hydrocarbon chains are conjugated to one or more of the following internal positions: 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.

107. The dsRNA agent of claim 106, wherein the one or more C_{22} hydrocarbon chains are conjugated to one or more of the following internal positions: 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.

108. The dsRNA agent of claim 107, wherein the one or more C_{22} hydrocarbon chains are conjugated to position 6 on the sense strand, counting from the 5'-end of the sense strand.

109. The dsRNA agent of any one of claims 90-108, wherein the one or more C_{22} hydrocarbon chains is an aliphatic, alicyclic, or polyalicyclic compound.

110. The dsRNA agent of claim 109, wherein the one or more C_{22} hydrocarbon chains contains a functional group selected from the group consisting of hydroxyl, amine, carboxylic acid, sulfonate, phosphate, thiol, azide, and alkyne.

111. The dsRNA agent of any one of claims 90-110, wherein the one or more C_{22} hydrocarbon chains is a C_{22} acid.

112. The dsRNA agent of claim 111, wherein the C_{22} acid is selected from the group consisting of docosanoic acid, 6-octyltetradecanoic acid, 10-hexylhexadecanoic acid, all-cis-7,10,13,16,19-docosapentaenoic acid, all-cis-4,7,10,13,16,19-docosahexaenoic acid, all-cis-13,16-docosadienoic acid, all-cis-7,10,13,16-docosatetraenoic acid, all-cis-4,7,10,13,16-docosapentaenoic acid, and cis-13-docosenoic acid.

113. The dsRNA agent of any one of claims 90-110, wherein the one or more C_{22} hydrocarbon chains is a C_{22} alcohol.

114. The dsRNA agent of claim 113, wherein the C_{22} alcohol is selected from the group consisting of 1-docosanol, 6-octyltetradecan-1-ol, 10-hexylhexadecan-1-ol, cis-13-docosen-1-ol, docosan-9-ol, docosan-2-ol, docosan-10-ol, docosan-11-ol, andcis-4,7,10,13,16,19-docosahexanol.

115. The dsRNA agent of any one of claims 90-110, wherein the one or more C_{22} hydrocarbon chains is a C_{22} amide.

116. The dsRNA agent of claim 115, wherein the C_{22} amide is selected from the group consisting of (E)-Docos-4-enamide, (E)-Docos-5-enamide, (Z)-Docos-9-enamide, (E)-Docos-11-enamide,12-Docosenamide, (Z)-Docos-13-enamide, (Z)-N-Hydroxy-13-docoseneamide, (E)-Docos-14-enamide, 6-cis-Docosenamide, 14-Docosenamide Docos-11-enamide, (4E,13E)-Docosa-4,13-dienamide, and (5E,13E)-Docosa-5,13-dienamide. .

117. The dsRNA agent of any one of claims 109-116, wherein the one or more C_{22} hydrocarbon chains is conjugated via a carrier that replaces one or more nucleotide(s) in the internal position(s).

118. The dsRNA agent of claim 117, wherein 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.

119. The dsRNA agent of any one of claims 90-118, wherein the one or more C_{22} hydrocarbon chains is conjugated to the dsRNA 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.

120. The dsRNA agent of any one of claims 90-119, wherein the one or more C_{22} hydrocarbon chains is conjugated to the dsRNA agent via a linker or a carrier or via internucleotide phosphate linkage.

121. The dsRNA agent of any one of claims 90-120, wherein the one or more C_{22} hydrocarbon chains is conjugated to a nucleobase, sugar moiety, or internucleosidic phosphate linkage.

122. A cell containing the dsRNA agent of any one of claims 1-121.

123. A pharmaceutical composition for inhibiting expression of a metabolic disorder-associated target gene selected from the group consisting of inhibin subunit beta E (INHBE), activin A receptor type 1C (ACVR1C), perilipin-1 (PLIN1), phosphodiesterase 3B (PDE3B), and inhibin subunit beta C (INHBC) comprising the dsRNA agent of any one of claims 1-121 and a pharmaceutically acceptable carrier.

124. The pharmaceutical composition of claim 123, wherein dsRNA agent is in an unbuffered solution.

125. The pharmaceutical composition of claim 124, wherein the unbuffered solution is saline or water.

126. The pharmaceutical composition of claim 123, wherein said dsRNA agent is in a buffer solution.

127. The pharmaceutical composition of claim 126, wherein the buffer solution comprises acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof.

128. The pharmaceutical composition of claim 127, wherein the buffer solution is phosphate buffered saline (PBS).

129. A method of inhibiting expression of a metabolic disorder-associated target gene selected from the group consisting of inhibin subunit beta E (INHBE), activin A receptor type 1C (ACVR1C), perilipin-1 (PLIN1), phosphodiesterase 3B (PDE3B), and inhibin subunit beta C (INHBC) in a cell, the method comprising contacting the cell with the dsRNA agent of any one of claims 1-121, or the pharmaceutical composition of any one of claims 123-128, thereby inhibiting expression of the metabolic disorder-associated target gene in the cell.

130. The method of claim 129, wherein the target gene is INHBE.

131. The method of claim 129, wherein the target gene is ACVR1C.

132. The method of claim 129, wherein the target gene is PLIN1.

133. The method of claim 129, wherein the target gene is PDE3B.

134. The method of claim 129, wherein the target gene is INHBC.

135. The method of any one of claims 129-134, wherein the cell is an adipocyte.

136. The method of any one of claims 129-134, wherein the cell is a hepatocyte.

137. The method of any one of claims 129-136, wherein the cell is within a subject.

138. The method of claim 137, wherein the subject is a human.

139. The method of claim 138, wherein the subject has a metabolic disorder.

140. The method of claim 139, wherein the metabolic disorder is metabolic syndrome.

141. The method of claim 139, wherein the metabolic disorder is cardiovascular disease.

142. The method of claim 139, wherein the metabolic disorder is is hypertension.

143. The method of any one of claims 129-142, wherein contacting the cell with the dsRNA agent inhibits the expression of the metabolic disorder-associated target gene by at least 50%, 60%, 70%, 80%, 90%, or 95%.

144. The method of any one of claims 129-143, wherein inhibiting expression of the metabolic disorder-associated target gene decreases metabolic disorder-associated target gene protein level in serum of the subject by at least 50%, 60%, 70%, 80%, 90%, or 95%.

145. A method of treating a subject having a metabolic disorder, comprising administering to the subject a therapeutically effective amount of the dsRNA agent of any one of claims 1-121, or the pharmaceutical composition of any one of claims 123-128, thereby treating the subject having the metabolic disorder.

146. A method of preventing at least one symptom in a subject having a metabolic disorder, comprising administering to the subject a prophylactically effective amount of the dsRNA agent of any one of claims 1-121, or the pharmaceutical composition of any one of claims 123-128, thereby preventing at least one symptom in the subject having the metabolic disorder.

147. The method of claim 145 or 146, wherein the metabolic disorder is metabolic syndrome.

148. The method of claim 145 or 146, wherein the metabolic disorder is type 2 diabetes.

149. The method of claim 145 or 146, wherein the metabolic disorder is obesity.

150. The method of claim 145 or 146, wherein the metabolic disorder is elevated triglyceride level.

151. The method of claim 145 or 146, wherein the metabolic disorder is lipodystrophy.

152. The method of claim 145 or 146, wherein the metabolic disorder is liver inflammation.

153. The method of claim 145 or 146, wherein the metabolic disorder is fatty liver disease.

154. The method of claim 145 or 146, wherein the metabolic disorder is hypercholesterolemia.

155. The method of claim 145 or 146, wherein the metabolic disorder is a disorder associated with elevated liver enzymes.

156. The method of claim 145 or 146, wherein the metabolic disorder is nonalcoholic steatohepatitis (NASH).

157. The method of claim 145 or 146, wherein the metabolic disorder is cardiovascular disease.

158. The method of claim 145 or 146, wherein the metabolic disorder is hypertension.

159. The method of claim 145 or 146, wherein the metabolic disorder is cardiomyopathy.

160. The method of claim 145 or 146, wherein the metabolic disorder is heart failure.

161. The method of claim 145 or 146, wherein the metabolic disorder is kidney disease.

162. The method of any one of claims 145-161, wherein the subject is a human.

163. The method of any one of claims 145-162, wherein administration of the dsRNA agent to the subject causes a decrease in metabolic disorder-associated target gene protein accumulation in the subject.

164. The method of any one of claims 145-163, wherein the dsRNA agent is administered to the subject at a dose of about 0.01 mg/kg to about 50 mg/kg.

165. The method of any one of claims 145-164, wherein the dsRNA agent is administered to the subject subcutaneously.

166. The method of any one of claims 145-165, further comprising determining the level of INHBE in a sample(s) from the subject.

167. The method of claim 166, wherein the level of metabolic disorder-associated target gene in the subject sample(s) is a metabolic disorder-associated target gene protein level in a blood or serum or liver tissue sample(s).

168. The method of any one of claims 145-167, further comprising administering to the subject an additional therapeutic agent for treatment of a metabolic disorder.

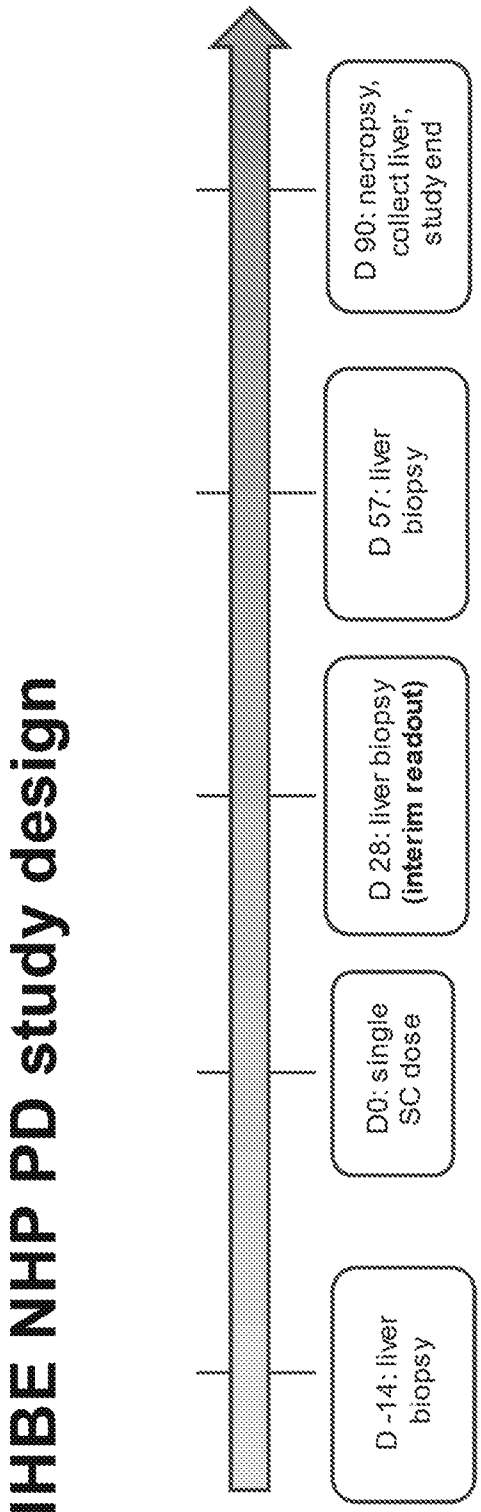
169. The method of claim 168, wherein the additional therapeutic agent is selected from the group consisting of insulin, a glucagon-like peptide 1 agonist, a sulfonylurea, a seglitinide, a biguanide, a thiazolidinedione, an alpha-glucosidase inhibitor, an SGLT2 inhibitor, a DPP-4 inhibitor, an HMG-CoA reductase inhibitor, a statin, and a combination of any of the foregoing.

170. A kit comprising the dsRNA agent of any one of claims 1-121 or the pharmaceutical composition of any one of claims 123-128.

171. A vial comprising the dsRNA agent of any one of claims 1-121 or the pharmaceutical composition of any one of claims 123-128.

172. A syringe comprising the dsRNA agent of any one of claims 1-121 or the pharmaceutical composition of any one of claims 123-128.

173. An RNA-induced silencing complex (RISC) comprising an antisense strand of any of the dsRNA agents of claims 1-121.



Group No.	Test Material	Dose Level (mg/kg)	No. of females
1	PBS (control)	0	3
2-9	INHBE siRNAs	3	3

Female monkeys used, starting weights 1.5 -1.9kg

FIG. 1

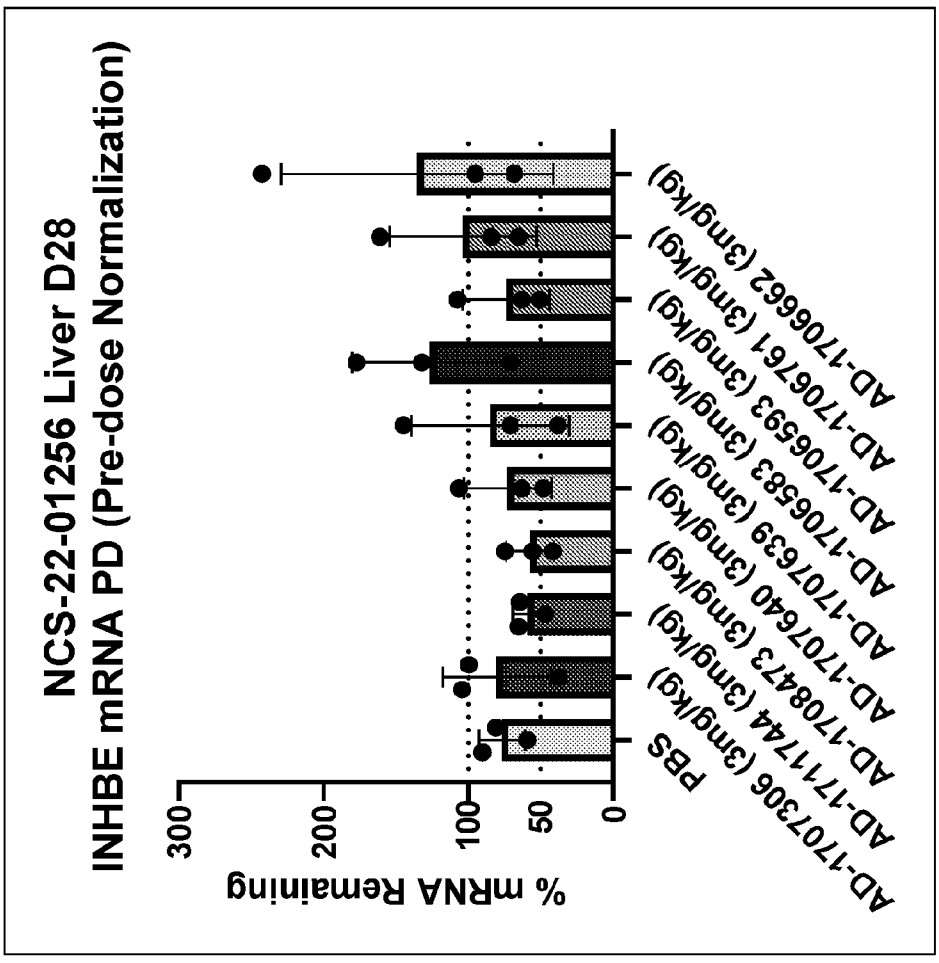

NCS-22-01256 Liver D28
INHBE mRNA PD (Pre-dose Normalization)
% mRNA Remaining
300
200
100
50
0
PBS
AD-1707306 (3mg/kg)
AD-1711744 (3mg/kg)
AD-1708473 (3mg/kg)
AD-1707640 (3mg/kg)
AD-1707639 (3mg/kg)
AD-1706583 (3mg/kg)
AD-1706593 (3mg/kg)
AD-1706761 (3mg/kg)
AD-1706662 (3mg/kg)

FIG. 2A

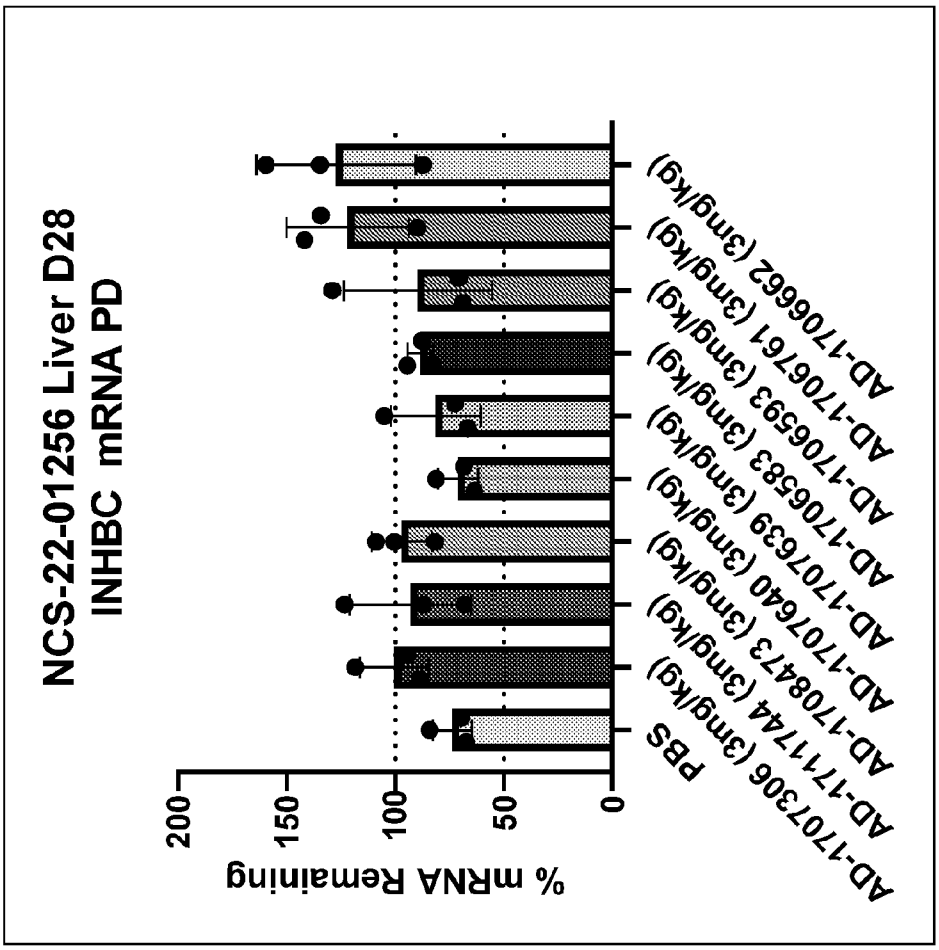

NCS-22-01256 Liver D28
INHBC mRNA PD
% mRNA Remaining
200
150
100
50
0
PBS
AD-1707306 (3mg/kg)
AD-1711744 (3mg/kg)
AD-1708473 (3mg/kg)
AD-1707640 (3mg/kg)
AD-1707639 (3mg/kg)
AD-1706583 (3mg/kg)
AD-1706593 (3mg/kg)
AD-1706761 (3mg/kg)
AD-1706662 (3mg/kg)

FIG. 2B

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2022/037658

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12N15/113 A61K31/713 A61K31/7125 A61K31/712
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C12N A61K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data, Sequence Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SUGIYAMA MASAKAZU ET AL: "Inhibin [beta]E (INHBE) is a possible insulin resistance-associated hepatokine identified by comprehensive gene expression analysis in human liver biopsy samples", PLOS ONE, vol. 13, no. 3, 29 March 2018 (2018-03-29), page e0194798, XP055898904, DOI: 10.1371/journal.pone.0194798 the whole document	1-7, 22-89, 99-130, 135-173
X,P	WO 2022/132666 A1 (REGENERON PHARMA [US]) 23 June 2022 (2022-06-23) the whole document	1-7, 22-89, 99-130, 135-173

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 November 2022	12/01/2023

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Romano, Alper

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2022/037658

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

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed.

   b. ☒ furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)).

      ☒ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.

2. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2022/037658

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims;; it is covered by claims Nos.:

1-7, 22-89, 99-130, 135-173(all partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-7, 22-89, 99-130, 135-173(all partially)

iRNA/siRNA targeting the region defined by nucleotide positions 1-98 of human inhibin subunit beta E (INHBE) as determined according to table 19 and as depicted in tables 2,3,19 and 20

2-20. claims: 1-7, 12-130, 135-173(all partially)

other iRNAs/siRNAs targeting the other non-overlapping target regions of human inhibin subunit beta E (INHBE) defined by nucleotide positions such as 120-148, 168-206, 339-433, 474-557, 588-614, (...) ,1849-1887 as determined according to table 19 and as depicted in tables 2,3,19 and 20

21-24. claims: 1-6, 8-11, 22-89, 99-129, 131-173(all partially)

iRNAs/siRNAs targeting each of activin A receptor type 1C (ACVR1C), perilipin-1 (PLIN1), phosphodiesterase 3B (PDE3B), or inhibin subunit beta C (INHBC) for treatment of metabolic disorders

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2022/037658

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2022132666 A1	23-06-2022	US 2022184114 A1	16-06-2022
		US 2022313726 A1	06-10-2022
		WO 2022132666 A1	23-06-2022