17β-HYDROXYSTEROID DEHYDROGENASE TYPE 13 (HSD17B13) iRNA COMPOSITIONS AND METHODS OF USE THEREOF

Related Applications

This application claims the benefit of priority to U.S. Provisional Application No.: 62/645,941, filed on March 21, 2018, U.S. Provisional Application No. 62/770,298, filed on November 21, 2018, and U.S. Provisional Application No.: 62/775,590, filed on December 5, 2018. The entire contents of each of the foregoing provisional patent applications are incorporated herein by reference.

Sequence Listing

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on March 12, 2019, is named 121301-08420_SL.txt and is 1,374,047 bytes in size.

Background of the Invention

17β-hydroxysteroid dehydrogenase Type 13 (HSD17B13) is a member of the 17β-Hydroxysteroid dehydrogenase (HSD17B) family of enzymes whose members have various functions, including, for example, reduction or oxidation of sex hormones, fatty acids, and bile acids *in vivo* (Moeller and Adamski (2009) *Mol Cell Endocrinol* 301:7). Members of the HSD17B family differ in tissue distribution, subcellular localization, catalytic preference, and have diverse substrate specificities as they also catalyze the conversions of other substrates than steroids, as for example lipids and retinoids (Marchais-Oberwinkler, *et al.* (2011) *J Steroid Biochem Mol Biol* 125(1-2):66–82). HSD17B13 has been demonstrated to enhance hepatic lipogenesis in normal mouse liver and cultured human hepatocytes (Su, *et al.* (2014) *Proc Natl Acad Sci USA* 111:11437).

Hepatocytes, which form the parenchymal tissue of the liver, are responsible for mobilizing lipids for energy and storing excess lipids in the form of lipid droplets (LDs) making the liver the primary organ responsible for lipid homeostasis.

LDs are now recognized as bioactive organelles involved in lipid metabolism, membrane traffic and signal transduction. LDs are generally composed of a core of neutral lipids (such as triacylglcerols (TGs) and cholesterol esters surrounded by a phospholipid/cholesterol monolayer. Numerous LD-specific proteins associate with the membrane of LDs and function, *e.g.,* to control the flux of molecules into and out of the LDs. The predominant hepatocellular LD-associated proteins are members of the perilipin family of proteins, but non-perilipin proteins, such as hypoxia-inducible proein 2 (HIG2), patanin-like phospholipase domain-containing 3 (PNPLA3), and HSD17B13, have also been identified as LD-associate proteins (Carr and Ahima (2016) *Exp Cell Res* 15:187; Su, *et al.* (2014) *Proc Natl Acad Sci USA* 111:11437).

Increased accumulation of LDs is associated with many metabolic diseases and chronic fibro-inflammatory liver diseases, such as liver fibrosis, NASH and NAFLD. HSD17B13 has been identified as one of the most abundantly expressed LD proteins specifically localized on the surface of LDs in human subjects and mice with NAFLD. The level of expression of HSD17B13 was also shown to be up-regulated in the livers of patients and mice with NAFLD. Overexpression of HSD17B13 resulted in an increase in the number and size of LDs. Hepatic overexpression of HSD17B13 in C57BL/6 mice significantly increased lipogenesis and TG contents in the livers, leading to a fatty liver phenotype.

There is currently no treatment for chronic fibro-inflammatory liver diseases. The current standard of care for subjects having a chronic fibro-inflammatory liver disease includes, lifestyle modification and managing the associated comorbidities, *e.g.,* hypertension, hyperlipidemia, diabetes, obesity, *etc*. Accordingly, as the prevalence of chronic fibro-inflammatory liver diseases has progressively increased over the past 10 years and is expected to increase, there is a need in the art for alternative treatments for subjects having a chronic fibro-inflammatory liver disease.

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 17β-hydroxysteroid dehydrogenase Type 13 (HSD17B13) gene. The HSD17B13 gene may be within a cell, *e.g.,* a cell within a subject, such as a human. The present invention also provides methods of using the iRNA compositions of the invention for inhibiting the expression of a HSD17B13 gene and/or for treating a subject who would benefit from inhibiting or reducing the expression of a HSD17B13 gene, *e.g.,* a subject suffering or prone to suffering from an HSD17B13-associated disease, for example, a chronic fibro-inflammatory liver disease.

Accordingly, in one aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of 17β-hydroxysteroid dehydrogenases type 13 (HSD17B13) in a cell. The dsRNA agent includes a sense strand and an antisense strand, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 1, 2, or 3 nucleotides from the nucleotide sequence of SEQ ID NO:1 or 2 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 1, 2, or 3 nucleotides from the nucleotide sequence of SEQ ID NO:8 or 9. In some embodiments, the dsRNA agent includes a sense strand and an antisense strand, wherein the sense strand comprises at least 15 contiguous nucleotides from the nucleotide sequence of SEQ ID NO:1 or 2 and the antisense strand comprises at least 15 contiguous nucleotides from the nucleotide sequence of SEQ ID NO:8 or 9.

In another aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of 17β-hydroxysteroid dehydrogenases type 13 (HSD17B13) in a cell. The dsRNA agent includes a sense strand and an antisense strand forming a double stranded region, wherein said antisense strand comprises a region of complementarity to an mRNA encoding HSD17B13 which comprises at least 15 contiguous nucleotides differing by no more than 1, 2, or 3

nucleotides from any one of the antisense sequences listed in any one of Tables 2, 3, 7, 8, 10, 11, or 13. In some embodiments, the dsRNA agent includes a sense strand and an antisense strand forming a double stranded region, wherein said antisense strand comprises a region of complementarity to an mRNA encoding HSD17B13 which comprises at least 15 contiguous nucleotides from any one of the antisense sequences listed in any one of Tables 2, 3, 7, 8, 10, 11, or 13.

In one embodiment, the region of complementarity comprises at least 15 contiguous nucleotides differing by no more than 1, 2, or 3 nucleotides from any one of nucleotides 213-242; 256-287; 361-385; 447-480; 483-529; 489-529; 630-653; 688-711; 752-777; 753-779; 772-806; 781-806; 791-851; 829-858; 870-896; 893-930; 900-930; 910-932; 980-1092; 1101-1158; 1176-1210; 1320-1350; 1335-1373; 1456-1482; 1506-1535; 1558-1588; 1699-1740; 1725-1757; 2182-2210; 2190-2254; 2194-2216; 2240-2373; or 2242-2264 of SEQ ID NO:1. In some embodiments, the region of complementarity comprises at least 15 contiguous nucleotides from any one of nucleotides 213-242; 256-287; 361-385; 447-480; 483-529; 489-529; 630-653; 688-711; 752-777; 753-779; 772-806; 781-806; 791-851; 829-858; 870-896; 893-930; 900-930; 910-932; 980-1092; 1101-1158; 1176-1210; 1320-1350; 1335-1373; 1456-1482; 1506-1535; 1558-1588; 1699-1740; 1725-1757; 2182-2210; 2190-2254; 2194-2216; 2240-2373; or 2242-2264 of SEQ ID NO:1.

In another embodiment, the region of complementarity comprises at least 15 contiguous nucleotides differing by no more than 1, 2, or 3 nucleotides from any one of nucleotides 71-93, 101-123, 108-130, 109-131, 112-134, 123-145; 213-235; 220-242, 256-278;292-314, 293-315, 299-321, 301-323, 324-346, 349-371, 350-372, 351-373, 352-374; 353-375, 355-377, 356-378, 357-379, 361-383; 363-385, 365-387, 402-424, 422-444, 423-445, 427-449, 428-450, 431-453, 447-469, 489-511, 490-512, 507-529, 541-563, 547-569, 548-570, 585-607, 589-611, 592-614, 593-615, 620-642, 630-652, 631-653, 632-654, 649-671, 676-698, 688-710, 723-745, 728-750, 752-774, 753-775, 755-777, 757-779, 763-785, 764-786, 772-794, 778-800, 780-802, 781-803,791-813, 792-814, 794-816, 795-817, 807-829, 828-850, 829-851; 832-854; 836-858; 838-860; 839-861, 840-862, 832-861; 870-892; 874-896, 894-916; 895-917; 896-918; 897-919; 898-920; 899-921; 900-922; 901-923; 902-924; 906-928; 908-930; 894-930; 910-932; 965-987;966-988981-1003; 1005-1027; 1006-1028; 1010-1032; 1005-1032;1052-1074; 1097-1119;1101-1123; 1102-1124; 1103-1125; 1133-1155; 1135-1157; 1136-1158; 1097-1125;1133-1158; 1176-1198;1188-1210;1243-1265;1315-13371320-1342; 1322-1344; 1325-1347; 1327-1349;1328-1350; 1320-1507;1335-1357;1336-1358;1458-1480; 1459-1481; 1460-1482; 1458-1482;1497-1519;1498-1520;1506-1528;1513-1535; 1565-1587;1566-1588;1613-1635;1614-1636;1622-1644;1643-1665; 1699-1721; 1717-1739; 1718-1740; 1724-1746; 1725-1747; 1726-1748; 1727-1749; 1728-1750; 1717-1750; 1737-1759; 1768-1790; 2188-2210; 2190-2212; 2188-2212; 2194-2216; 2195-2217; 2250-2272; 2232-2254; 2240-2262; 2232-2262; 2242-2264; 2245-2267 2249-2271; 2232-2271; 2347-2369; 2351-2373; or 2347-2373 of SEQ ID NO:1. In some embodiments, the region of complementarity comprises at least 15 contiguous nucleotides from any one of nucleotides 71-93, 101-123, 108-130, 109-131, 112-134, 123-145; 213-235; 220-242, 256-278;292-314, 293-315, 299-321, 301-323, 324-346, 349-371, 350-372, 351-373, 352-374; 353-375, 355-377, 356-378, 357-379, 361-383; 363-385, 365-387, 402-424, 422-444, 423-445, 427-

449, 428-450, 431-453, 447-469, 489-511, 490-512, 507-529, 541-563, 547-569, 548-570, 585-607, 589-611, 592-614, 593-615, 620-642, 630-652, 631-653, 632-654, 649-671, 676-698, 688-710, 723-745, 728-750, 752-774, 753-775, 755-777, 757-779, 763-785, 764-786, 772-794, 778-800, 780-802, 781-803,791-813, 792-814, 794-816, 795-817, 807-829, 828-850, 829-851; 832-854; 836-858; 838-860; 839-861, 840-862, 832-861; 870-892; 874-896, 894-916; 895-917; 896-918; 897-919; 898-920; 899-921; 900-922; 901-923; 902-924; 906-928; 908-930; 894-930; 910-932; 965-987;966-988981-1003; 1005-1027; 1006-1028; 1010-1032; 1005-1032;1052-1074; 1097-1119;1101-1123; 1102-1124; 1103-1125; 1133-1155; 1135-1157; 1136-1158; 1097-1125;1133-1158; 1176-1198;1188-1210;1243-1265;1315-13371320-1342; 1322-1344; 1325-1347; 1327-1349;1328-1350; 1320-1507;1335-1357;1336-1358;1458-1480; 1459-1481; 1460-1482; 1458-1482;1497-1519;1498-1520;1506-1528;1513-1535; 1565-1587;1566-1588;1613-1635;1614-1636;1622-1644;1643-1665; 1699-1721; 1717-1739; 1718-1740; 1724-1746; 1725-1747; 1726-1748; 1727-1749; 1728-1750; 1717-1750; 1737-1759; 1768-1790; 2188-2210; 2190-2212; 2188-2212; 2194-2216; 2195-2217; 2250-2272; 2232-2254; 2240-2262; 2232-2262; 2242-2264; 2245-2267 2249-2271; 2232-2271; 2347-2369; 2351-2373; or 2347-2373 of SEQ ID NO:1.

In another embodiment, the region of complementarity comprises at least 15 contiguous nucleotides differing by no more than 1, 2, or 3 nucleotides from any one of nucleotides 108-130; 109-131; 108-131; 112-134; 293-315; 301-323; 293-323; 361-383; 402-424; 423-445; 428-450; 423-450; 428-453; 431-453; 489-511; 490-512; 489-512; 649-671; 753-775; 772-794;791-813; 792-814; 795-817; 791-817; 829-851; 832-854; 836-858; 829-858; 870-892; 874-896; 870-896; 898-920; 900-922; 902-924; 906-928; 908-930; 902-930; 910-932; 966-988;1328-1350; or 2194-2216; 2242-2264; or 2249-2271 of SEQ ID NO:1. In some embodiments, the region of complementarity comprises at least 15 contiguous nucleotides from any one of nucleotides 108-130; 109-131; 108-131; 112-134; 293-315; 301-323; 293-323; 361-383; 402-424; 423-445; 428-450; 423-450; 428-453; 431-453; 489-511; 490-512; 489-512; 649-671; 753-775; 772-794;791-813; 792-814; 795-817; 791-817; 829-851; 832-854; 836-858; 829-858; 870-892; 874-896; 870-896; 898-920; 900-922; 902-924; 906-928; 908-930; 902-930; 910-932; 966-988;1328-1350; or 2194-2216; 2242-2264; or 2249-2271 of SEQ ID NO:1. In another embodiment, the region of complementarity comprises at least 15 contiguous nucleotides differing by no more than 1, 2, or 3 nucleotides from nucleotides 898-930 of SEQ ID NO:1. In some embodiments, the region of complementarity comprises at least 15 contiguous nucleotides from nucleotides 898-930 of SEQ ID NO:1.

In one embodiment, the region of complementarity comprises at least 15 contiguous nucleotides differing by no more than 1, 2, or 3 nucleotides from nucleotides 910-932 of SEQ ID NO:1. In some embodiments, the region of complementarity comprises at least 15 contiguous nucleotides from nucleotides 910-932 of SEQ ID NO:1.

In one embodiment, the region of complementarity comprises at least 15 contiguous nucleotides differing by no more than 1, 2, or 3 nucleotides from nucleotides 2194-2216 of SEQ ID NO:1. In some embodiments, the region of complementarity comprises at least 15 contiguous nucleotides from nucleotides 2194-2216 of SEQ ID NO:1.

In one embodiment, the region of complementarity comprises at least 15 contiguous nucleotides differing by no more than 1, 2, ro 3 nucleotides from nucleotides 2242-2264 of SEQ ID NO:1. In some embodiments, the region of complementarity comprises at least 15 contiguous nucleotides from nucleotides 2242-2264 of SEQ ID NO:1.

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

In one embodiment, substantially all of the nucleotides of the sense strand comprise a modification. In another embodiment, substantially all of the nucleotides of the antisense strand comprise a modification. In yet another embodiment, substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand comprise a modification.

In one aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of 17β-hydroxysteroid dehydrogenases type 13 (HSD17B13) in a cell. The dsRNA agent includes 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 1, 2, or 3 nucleotides from the nucleotide sequence of SEQ ID NO:1 or 2 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 1, 2, or 3 nucleotides from the nucleotide sequence of SEQ ID NO:8 or 9, wherein substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand are modified nucleotides, andwherein the sense strand is conjugated to a ligand attached at the 3'-terminus. In some embodiments, the dsRNA agent includes a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides from the nucleotide sequence of SEQ ID NO:1 or 2 and the antisense strand comprises at least 15 contiguous nucleotides from the nucleotide sequence of SEQ ID NO:8 or 9, wherein substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand are modified nucleotides, andwherein the sense strand is conjugated to a ligand attached at the 3'-terminus.

In one embodiment, all of the nucleotides of the sense strand comprise a modification. In another embodiment, all of the nucleotides of the antisense strand comprise a modification. In yet another embodiment, all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand comprise a modification.

In one embodiment, at least one of said modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 3'-terminal deoxy-thymine (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'-hydroxyl-modified nucleotide, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide

comprising a 5'-phosphate, a nucleotide comprising a 5'-phosphate mimic, a glycol modified nucleotide, and a 2-O-(N-methylacetamide) modified nucleotide, and combinations thereof.

In one embodiment, the nucleotide modifications are 2'-O-methyl and/or 2'-fluoro modifications.

The region of complementarity may be at least 17 nucleotides in length;19 to 30 nucleotides in length;19-25 nucleotides in length; or 21 to 23 nucleotides in length.

Each strand may be no more than 30 nucleotides in length, *e.g.,* each strand is independently 19-30 nucleotides in length; each strand is independently 19-25 nucleotides in length; each strand is independently 21-23 nucleotides in length.

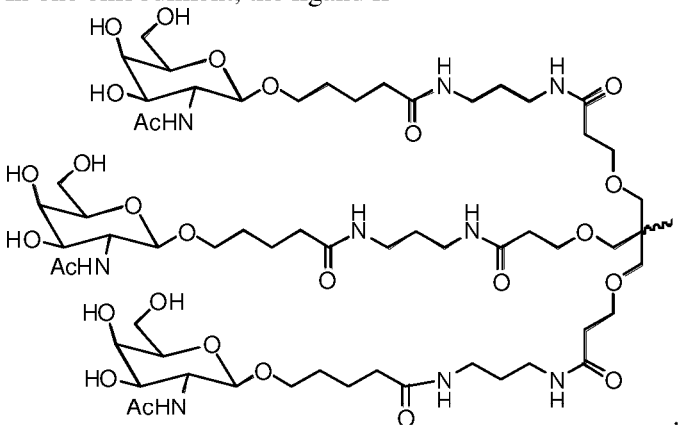
The dsRNA may include at least one strand that comprises a 3' overhang of at least 1 nucleotide; or at least one strand that comprises a 3' overhang of at least 2 nucleotides.

In some embodiment, the dsRNA agent further comprises a ligand.

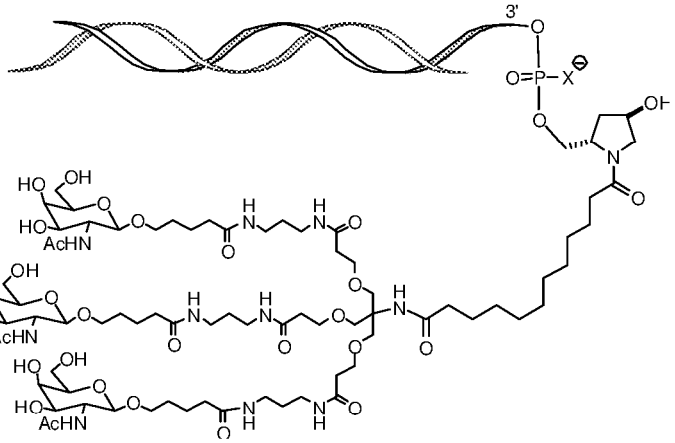
In one embodiment, the ligand is conjugated to the 3' end of the sense strand of the dsRNA agent.

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

In one embodiment, the ligand is



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



and, wherein X is O or S.

In one embodiment, the X is O.

In one embodiment, the region of complementarity comprises any one of the antisense sequences in any one of Tables 2, 3, 7, 8, 10, 11, or 13.

In one aspect, the present invention provides a double stranded for inhibiting expression of 17β-hydroxysteroid dehydrogenases type 13 (HSD17B13) in a cell. The dsRNA agent includes a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding HSD17B13, wherein each strand is about 14 to about 30 nucleotides in length, wherein said dsRNA agent is represented by formula (III):

sense: 5' n_p -N_a -(X X X) $_i$-N_b -Y Y Y -N_b -(Z Z Z)$_j$ -N_a - n_q 3'

antisense: 3' n_p'-N_a'-(X'X'X')$_k$-N_b'-Y'Y'Y'-N_b'-(Z'Z'Z')$_l$-N_a'- n_q' 5' (III)

wherein:

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

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

each N_a and N_a' independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides;

each N_b and N_b' independently represents an oligonucleotide sequence comprising 0-10 nucleotides which are either modified or unmodified or combinations thereof;

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

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

modifications on N_b differ from the modification on Y and modifications on N_b' differ from the modification on Y'; and

wherein the sense strand is conjugated to at least one ligand.

In one embodiment, i is 0; j is 0; i is 1; j is 1; both i and j are 0; or both i and j are 1. In another embodiment, k is 0; l is 0; k is 1; l is 1; both k and l are 0; or both k and l are 1.

In one embodiment, XXX is complementary to X'X'X', YYY is complementary to Y'Y'Y', and ZZZ is complementary to Z'Z'Z'.

In one embodiment, the YYY motif occurs at or near the cleavage site of the sense strand, *e.g.*, the Y'Y'Y' motif occurs at the 11, 12 and 13 positions of the antisense strand from the 5'-end.

In one embodiment, formula (III) is represented by formula (IIIa):

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

antisense: 3' $n_{p'}$-$N_{a'}$- Y'Y'Y'- $N_{a'}$- $n_{q'}$ 5' (IIIa).

In another embodiment, formula (III) is represented by formula (IIIb):

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

antisense: 3' $n_{p'}$-$N_{a'}$- Y'Y'Y'-$N_{b'}$-Z'Z'Z'- $N_{a'}$- $n_{q'}$ 5' (IIIb)

wherein each N_b and N_b' independently represents an oligonucleotide sequence comprising 1-5 modified nucleotides.

In yet another embodiment, formula (III) is represented by formula (IIIc):

sense: 5' n_p -N_a –X X X -N_b -Y Y Y -N_a - n_q 3'

antisense: 3' $n_{p'}$-$N_{a'}$- X′X′X′-$N_{b'}$- Y′Y′Y′- $N_{a'}$- $n_{q'}$ 5' (IIIc)

wherein each N_b and N_b' independently represents an oligonucleotide sequence comprising 1-5 modified nucleotides.

In another embodiment, formula (III) is represented by formula (IIId):

sense: 5' n_p -N_a –X X X- N_b -Y Y Y -N_b -Z Z Z -N_a - n_q 3'

antisense: 3' $n_{p'}$-$N_{a'}$- X′X′X′- $N_{b'}$-Y′Y′Y′-$N_{b'}$-Z′Z′Z′- $N_{a'}$- $n_{q'}$ 5' (IIId)

wherein each N_b and N_b' independently represents an oligonucleotide sequence comprising 1-5 modified nucleotides and each N_a and N_a' independently represents an oligonucleotide sequence comprising 2-10 modified nucleotides.

The region of complementarity may be at least 17 nucleotides in length; 19 to 30 nucleotides in length;19-25 nucleotides in length; or 21 to 23 nucleotides in length.

Each strand may be no more than 30 nucleotides in length, *e.g.,* each strand is independently 19-30 nucleotides in length.

In one embodiment, the modifications on the nucleotides are selected from the group consisting of LNA, HNA, CeNA, 2′-methoxyethyl, 2′-O-alkyl, 2′-O-allyl, 2′-C- allyl, 2′-fluoro, 2'-O-methyl, 2′-deoxy, 2'-hydroxyl, and combinations thereof.

In one embodiment, the modifications on the nucleotides are 2′-O-methyl or 2′-fluoro modifications.

In one embodiment, the Y′ is a 2′-O-methyl or 2'-flouro modified nucleotide.

In one embodiment, at least one strand of the dsRNA agent may comprise a 3' overhang of at least 1 nucleotide; or a 3' overhang of at least 2 nucleotides.

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. In one embodiment, the strand is the antisense strand. In anotehr embodiment, the strand is the sense strand.

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

In one embodiment, the strand is the antisense strand. In anotehr embodiment, the strand is the sense strand.

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

In one embodiment, p′>0. In another embodiment, p′=2.

In one embodiment, q'=0, p=0, q=0, and p' overhang nucleotides are complementary to the target mRNA. In another embodiment, q'=0, p=0, q=0, and p' overhang nucleotides are non-complementary to the target mRNA.

In one embodiment, the sense strand has a total of 21 nucleotides and the antisense strand has a total of 23 nucleotides.

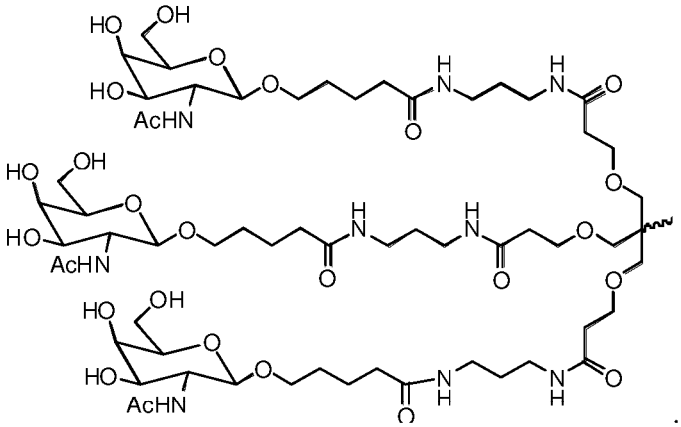
In one embodiment, at least one n_p' is linked to a neighboring nucleotide via a phosphorothioate linkage. In another embodiment, wherein all n_p' are linked to neighboring nucleotides via phosphorothioate linkages.

In one embodiment, all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand comprise a modification.

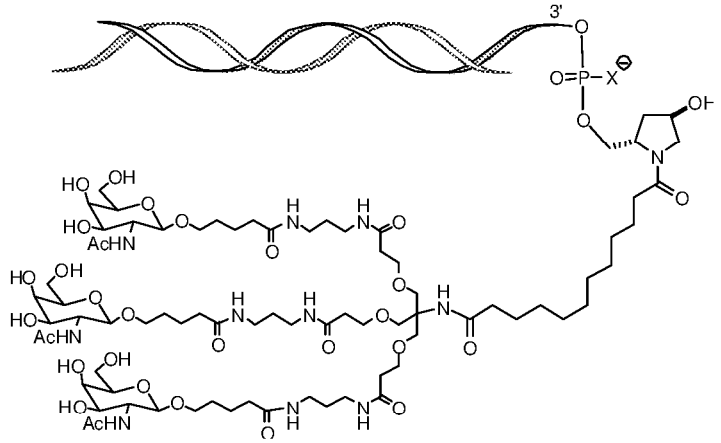
In one embodiment, the ligand is conjugated to the 3' end of the sense strand of the dsRNA agent.

In one embodiment, the ligand is one or more N-acetylgalactosamine (GalNAc) derivatives attached through a monovalent, bivalent, or trivalent branched linker.

In one embodiment, the ligand is



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



and, wherein X is O or S.

In one embodiment, the X is O.

In one aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting the expression of 17β-hydroxysteroid dehydrogenases type 13 (HSD17B13) in a cell. The dsRNA agent includes a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding HSD17B13, wherein each strand is about 14 to about 30 nucleotides in length, wherein the dsRNA agent is represented by formula (III):

sense: 5' n_p -N_a -(X X X) $_i$-N_b -Y Y Y -N_b -(Z Z Z)$_j$ -N_a - n_q 3'

antisense: 3' n_p'-N_a'-(X'X'X')$_k$-N_b'-Y'Y'Y'-N_b'-(Z'Z'Z')$_l$-N_a'- n_q' 5' (III)

wherein:

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

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

each N_a and N_a' independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides;

each N_b and N_b' independently represents an oligonucleotide sequence comprising 0-10 nucleotides which are either modified or unmodified or combinations thereof;

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

XXX, YYY, ZZZ, X'X'X', Y'Y'Y', and Z'Z'Z' each independently represent one motif of three identical modifications on three consecutive nucleotides, and wherein the modifications are 2'-O-methyl or 2'-fluoro modifications;

modifications on N_b differ from the modification on Y and modifications on N_b' differ from the modification on Y'; and

wherein the sense strand is conjugated to at least one ligand.

In one aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting the expression of 17β-hydroxysteroid dehydrogenases type 13 (HSD17B13) in a cell. The dsRNA agent includes a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding HSD17B13, wherein each strand is about 14 to about 30 nucleotides in length, wherein the dsRNA agent is represented by formula (III):

sense: 5' n_p -N_a -(X X X) $_i$-N_b -Y Y Y -N_b -(Z Z Z)$_j$ -N_a - n_q 3'

antisense: 3' n_p'-N_a'-(X'X'X')$_k$-N_b'-Y'Y'Y'-N_b'-(Z'Z'Z')$_l$-N_a'- n_q' 5' (III)

wherein:

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

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

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

n_p' >0 and at least one n_p' is linked to a neighboring nucleotide via a phosphorothioate linkage;

each N_a and N_a' independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides;

each N_b and N_b' independently represents an oligonucleotide sequence comprising 0-10 nucleotides which are either modified or unmodified or combinations thereof;

XXX, YYY, ZZZ, X'X'X', Y'Y'Y', and Z'Z'Z' each independently represent one motif of three identical modifications on three consecutive nucleotides, and wherein the modifications are 2'-O-methyl or 2'-fluoro modifications;

modifications on N_b differ from the modification on Y and modifications on N_b' differ from the modification on Y'; and

wherein the sense strand is conjugated to at least one ligand.

In one aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting the expression of 17β-hydroxysteroid dehydrogenases type 13 (HSD17B13) in a cell. The dsRNA agent includes a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding HSD17B13, wherein each strand is about 14 to about 30 nucleotides in length, wherein the dsRNA agent is represented by formula (III):

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

antisense: $3'\ n_p'\text{-}N_a'\text{-}(X'X'X')_k\text{-}N_b'\text{-}Y'Y'Y'\text{-}N_b'\text{-}(Z'Z'Z')_l\text{-}N_a'\text{-}n_q'\ 5'$ (III)

wherein:

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

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

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

$n_p' > 0$ and at least one n_p' is linked to a neighboring nucleotide via a phosphorothioate linkage;

each N_a and N_a' independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides;

each N_b and N_b' independently represents an oligonucleotide sequence comprising 0-10 nucleotides which are either modified or unmodified or combinations thereof;

XXX, YYY, ZZZ, X'X'X', Y'Y'Y', and Z'Z'Z' each independently represent one motif of three identical modifications on three consecutive nucleotides, and wherein the modifications are 2'-O-methyl or 2'-fluoro modifications;

modifications on N_b differ from the modification on Y and modifications on N_b' differ from the modification on Y'; and

wherein the sense strand is conjugated to at least one ligand, wherein the ligand is one or more GalNAc derivatives attached through a monovalent, bivalent, or trivalent branched linker.

In one aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting the expression of 17β-hydroxysteroid dehydrogenases type 13 (HSD17B13) in a cell. The dsRNA agent includes a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding HSD17B13, wherein each strand is about 14 to about 30 nucleotides in length, wherein the dsRNA agent is represented by formula (III):

sense: 5' n_p -N_a -(X X X) $_i$-N_b -Y Y Y -N_b -(Z Z Z)$_j$ -N_a - n_q 3'

antisense: 3' n_p'-N_a'-(X'X'X')$_k$-N_b'-Y'Y'Y'-N_b'-(Z'Z'Z')$_l$-N_a'- n_q' 5' (III)

wherein:

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

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

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

n_p' >0 and at least one n_p' is linked to a neighboring nucleotide via a phosphorothioate linkage;

each N_a and N_a' independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides;

each N_b and N_b' independently represents an oligonucleotide sequence comprising 0-10 nucleotides which are either modified or unmodified or combinations thereof;

XXX, YYY, ZZZ, X'X'X', Y'Y'Y', and Z'Z'Z' each independently represent one motif of three identical modifications on three consecutive nucleotides, and wherein the modifications are 2'-O-methyl or 2'-fluoro modifications;

modifications on N_b differ from the modification on Y and modifications on N_b' differ from the modification on Y';

wherein the sense strand comprises at least one phosphorothioate linkage; and

wherein the sense strand is conjugated to at least one ligand, wherein the ligand is one or more GalNAc derivatives attached through a monovalent, bivalent, or trivalent branched linker.

In one aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting the expression of 17β-hydroxysteroid dehydrogenases type 13 (HSD17B13) in a cell. The dsRNA agent includes a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding HSD17B13, wherein each strand is about 14 to about 30 nucleotides in length, wherein the dsRNA agent is represented by formula (III):

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

antisense: 3' n_p'-N_a'- Y'Y'Y'- N_a'- n_q' 5' (IIIa)

wherein:

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

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

n_p' >0 and at least one n_p' is linked to a neighboring nucleotide via a phosphorothioate linkage;

each N_a and N_a' independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides;

YYY and Y′Y′Y′ each independently represent one motif of three identical modifications on three consecutive nucleotides, and wherein the modifications are 2′-O-methyl and/or 2′-fluoro modifications;

wherein the sense strand comprises at least one phosphorothioate linkage; and

wherein the sense strand is conjugated to at least one ligand, wherein the ligand is one or more GalNAc derivatives attached through a monovalent, bivalent, or trivalent branched linker.

In one aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting the expression of 17β-hydroxysteroid dehydrogenases type 13 (HSD17B13) in a cell. The dsRNA agent includes 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 1, 2, or 3 nucleotides from the nucleotide sequence of SEQ ID NO:1 or 2 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 1, 2, or 3 nucleotides from the nucleotide sequence of SEQ ID NO:8 or 9, wherein substantially all of the nucleotides of the sense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoro modification, wherein the sense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus, wherein substantially all of the nucleotides of the antisense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoro modification, wherein the antisense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus and two phosphorothioate internucleotide linkages at the 3'-terminus, and wherein the sense strand is conjugated to one or more GalNAc derivatives attached through a monovalent, bivalent or trivalent branched linker at the 3'-terminus. In some embodiments, the dsRNA agent includes a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides from the nucleotide sequence of SEQ ID NO:1 or 2 and the antisense strand comprises at least 15 contiguous nucleotides from the nucleotide sequence of SEQ ID NO:8 or 9, wherein substantially all of the nucleotides of the sense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoro modification, wherein the sense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus, wherein substantially all of the nucleotides of the antisense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoro modification, wherein the antisense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus and two phosphorothioate internucleotide linkages at the 3'-terminus, and wherein the sense strand is

conjugated to one or more GalNAc derivatives attached through a monovalent, bivalent or trivalent branched linker at the 3'-terminus.

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

In one embodiment, the region of complementarity comprises any one of the antisense sequences listed in any one of Tables 2, 3, 7, 8, 10, 11, or 13. In one embodiment, the agent is selected from the group consisting of AD-288917, AD-288996, AD-413639, AD-413644, and AD-413669. In one embodiment, the RNAi agent is AD-288917. In another embodiment, the agent is AD-288996. In another embodiment, the agent is AD-413639. In one embodiment, the agent is AD-413644. In another embodiment, the agent is AD-413669

In one embodiment, the sense strand and the antisense strand comprise nucleotide sequences selected from the group consisting of the nucleotide sequences of any one of the agents listed in any one of Tables 2, 3, 7, 8, 10, 11, or 13.

The present invention also provides cells, vectors, and pharmaceutical compositions which include any of the dsRNA agents of the invention. The dsRNA agents mat be forumated in an unbuffered solution, *e.g.,* saline or water, or in a buffered solution, *e.g.,* a silution comprising acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof. In one embodiment, the buffered solution is phosphate buffered saline (PBS).

In one aspect, the present invention provides a method of inhibiting 17β-hydroxysteroid dehydrogenases type 13 (HSD17B13) expression in a cell. The method includes contacting the cell with a dsRNA agent or a pharmaceutical composition of the invention, thereby inhibiting expression of HSD17B13 in the cell.

The cell may be within a subject, such as a human subject.

In one embodiment, the HSD17B13 expression is inhibited by at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or to below the level of detection of HSD17B13 expression.

In one embodiment, the human subject suffers from an HSD17B13-associated disease, disorder, or condition. In one embodiment, the HSD17B13-associated disease, disorder, or condition is a chronic fibro-inflammatory liver disease. In one embodiment, the chronic fibro-inflammatory liver disease is selected from the group consisting of inflammation of the liver, liver fibrosis, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), cirrhosis of the liver, alcoholic steatohepatitis (ASH), alcoholic liver diseases (ALD), HCV-associated cirrhosis, drug induced liver injury, and hepatocellular necrosis.

In one aspect, the present invention provides a method of inhibiting the expression of HSD17B13 in a subject. The methods include administering to the subject a therapeutically effective amount of a dsRNA agent or a pharmaceutical composition of the invention, thereby inhibiting the expression of HSD17B13 in the subject.

In another aspect, the present invention provides a method of treating a subject suffering from an HSD17B13-associated disease, disorder, or condition. The method includes administering to the subject a therapeutically effective amount of of a dsRNA agent or a pharmaceutical composition

of the invention, thereby treating the subject suffering from an HSD17B13-associated disease, disorder, or condition.

In another aspect, the present invention provides a method of preventing at least one symptom in a subject having a disease, disorder or condition that would benefit from reduction in expression of an HSD17B13 gene. The method includes administering to the subject a prophylactically effective amount of the agent of a dsRNA agent or a pharmaceutical composition of the invention, thereby preventing at least one symptom in a subject having a disease, disorder or condition that would benefit from reduction in expression of an HSD17B13 gene.

In another aspect, the present invention provides a method of reducing the risk of developing chronic liver disease in a subject having steatosis. The method includes administering to the subject a therapeutically effective amount of a dsRNA agent or a pharmaceutical composition of the invention, thereby reducing the risk of developing chronic liver disease in the subject having steatosis.

In yet another aspect, the present invention provides a method of inhibiting the progression of steatosis to steatohepatitis in a subject suffering from steatosis. The method includes administering to the subject a therapeutically effective amount of a dsRNA agent or a pharmaceutical composition of the invention, thereby inhibiting the progression of steatosis to steatohepatitis in the subject.

In one aspect, the present invention provides a method of inhibiting the accumulation of lipid droplets in the liver of a subject suffering from an HSD17B13-associated disease, disorder, or condition. The method includes administering to the subject a therapeutically effective amount of a dsRNA agent or a pharmaceutical composition of the invention, and a dsRNA agent targeting a PNPLA3 gene or a pharmaceutical composition comprising a dsRNA agent targeting a PNPLA3 gene, thereby inhibiting the accumulation of fat in the liver of the subject suffering from an HSD17B13-associated disease, disorder, or condition.

In another aspect, the present invention provides a method of treating a subject suffering from an HSD17B13-associated disease, disorder, or condition. The method includes administering to the subject a therapeutically effective amount of a dsRNA agent or a pharmaceutical composition of the invention, and a dsRNA agent targeting a PNPLA3 gene or a pharmaceutical composition comprising a dsRNA agent targeting a PNPLA3 gene, thereby treating the subject suffering from an HSD17B13-associated disease, disorder, or condition.

In another aspect, the present invention provides a method of preventing at least one symptom in a subject having a disease, disorder or condition that would benefit from reduction in expression of an HSD17B13 gene. The method includes administering to the subject a therapeutically effective amount of a dsRNA agent or a pharmaceutical composition of the invention, and a dsRNA agent targeting a PNPLA3 gene or a pharmaceutical composition comprising a dsRNA agent targeting a PNPLA3 gene, thereby preventing at least one symptom in a subject having a disease, disorder or condition that would benefit from reduction in expression of an HSD17B13 gene.

In another aspect, the present invention provides a method of reducing the risk of developing chronic liver disease in a subject having steatosis. The method includes administering to the subject a therapeutically effective amount of a dsRNA agent or a pharmaceutical composition of the invention, and a dsRNA agent targeting a PNPLA3 gene or a pharmaceutical composition comprising a dsRNA agent targeting a PNPLA3 gene, thereby reducing the risk of developing chronic liver disease in the subject having steatosis.

In another aspect, the present invention provides a method of inhibiting the progression of steatosis to steatohepatitis in a subject suffering from steatosis. The method includes administering to the subject a therapeutically effective amount of a dsRNA agent or a pharmaceutical composition of the invention, and a dsRNA agent targeting a PNPLA3 gene or a pharmaceutical composition comprising a dsRNA agent targeting a PNPLA3 gene, thereby inhibiting the progression of steatosis to steatohepatitis in the subject.

In one embodiment, the administration of the dsRNA agent or the pharmaceutical composition to the subject causes a decrease in HSD17B13 enzymatic activity, a decrease in HSD17B13 protein accumulation, a decrease in PNPLA3 enzymatic activity, a decrease in PNPLA3 protein accumulation, and/or a decrease in accumulation of fat and/or expansion of lipid droplets in the liver of a subject.

In one embodiment, the HSD17B13-associated disease, disorder, or condition is a chronic fibro-inflammatory liver disease.

In one embodiment, the chronic fibro-inflammatory liver disease is selected from the group consisting of accumulation of fat in the liver, inflammation of the liver, liver fibrosis, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), cirrhosis of the liver, alcoholic steatohepatitis (ASH), alcoholic liver diseases (ALD), HCV-associated cirrhosis, drug induced liver injury, and hepatocellular necrosis.

In one embodiment, the chronic fibro-inflammatory liver disease is nonalcoholic steatohepatitis (NASH).

In one embodiment, the subject is obese.

In one embodiment, the methods and uses of the invention further include administering an additional therapeutic to the subject.

In one embodiment, the dsRNA agent is administered to the subject at a dose of about 0.01 mg/kg to about 10 mg/kg or about 0.5 mg/kg to about 50 mg/kg.

The agent may be administered to the subject intravenously, intramuscularly, or subcutaneously. In one embodiment, the agent is administered to the subject subcutaneously.

In one embodiment, the methods and uses of the invention further include determining, the level of HSD17B13 in the subject.

In one aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of 17β-hydroxysteroid dehydrogenases type 13 (HSD17B13) 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 a nucleotide

sequence of any one of the agents in any one of Tables 2, 3, 7, 8, 10, 11, or 13, and the antisense strand comprises a nucleotide sequence of any one of the agents in any one of Tables 2, 3, 7, 8, 10, 11, or 13, wherein substantially all of the nucleotide of the sense strand and substantially all of the nucleotides of the antisense strand are modified nucleotides, and wherein the dsRNA agent is conjugated to a ligand.

Brief Description of the Drawings

Figure 1 shows that HSD17B13 rs72613567:TA is associated with reduced risk of alcoholic and nonalcoholic liver disease phenotypes. Specifically, Figure 1 shows HSD17B13 rs72613567:TA was associated with lower odds of various chronic liver diseases in an allele dosage-dependent manner. Specifically, allele dosage-dependent effects were observed for both alcoholic and non-alcoholic liver diseases, cirrhosis and hepatocellular carcinoma. Odds ratios were calculated using logistic regression, with adjustment for age, gender, BMI, and self-reported ethnicity.

Figure 2A is a graph depicting the effect of a single dose of AD-288917 in mice expressing human HSD17B13.

Figure 2B is a graph depicting the effect of a single dose of AD-288917 in Cynomolgus monkeys.

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 an HSD17B13 gene. The HSD17B13 gene may be within a cell, *e.g.,* a cell within a subject, such as a human. The present invention also provides methods of using the iRNA compositions of the invention for inhibiting the expression of an HSD17B13 gene, and for treating a subject who would benefit from inhibiting or reducing the expression of an HSD17B13 gene, *e.g.,* a subject that would benefit from a reduction in inflammation of the liver, *e.g.,* a subject suffering or prone to suffering from an HSD17B13-associated disease disorder, or condition, such as a subject suffering or prone to suffering from liver fibrosis, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), alcoholic steatohepatitis (ASH), alcoholic liver diseases (ALD), cirrhosis of the liver, HCV-associated cirrhosis, drug induced liver injury, and hepatocellular necrosis.

The iRNAs of the invention targeting HSD17B13 may include an RNA strand (the antisense strand) having a region which is about 30 nucleotides or less in length, *e.g.*, 15-30, 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, which region is substantially complementary to at least part of an mRNA transcript of an HSD17B13 gene.

In some 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 an HSD17B13 gene. In some embodiments, such iRNA agents having longer length antisense strands may 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 the iRNA agents described herein enables the targeted degradation of mRNAs of an HSD17B13 gene in mammals.

Very low dosages of the iRNAs, in particular, can specifically and efficiently mediate RNA interference (RNAi), resulting in significant inhibition of expression of an HSD17B13 gene. Thus, methods and compositions including these iRNAs are useful for treating a subject who would benefit from inhibiting or reducing the expression of an HSD17B13 gene, *e.g.,* a subject that would benefit from a reduction of inflammation of the liver, *e.g.,* a subject suffering or prone to suffering from an HSD17B13-associated disease disorder, or condition, such as a subject suffering or prone to suffering from liver fibrosis, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), alcoholic steatohepatitis (ASH), alcoholic liver diseases (ALD), cirrhosis of the liver, HCV-associated cirrhosis, drug induced liver injury, and hepatocellular necrosis.

The following detailed description discloses how to make and use compositions containing iRNAs to inhibit the expression of an HSD17B13 gene, as well as compositions and methods for treating subjects having diseases and disorders that would benefit from inhibition and/or reduction of the expression of this gene.

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.

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 $\pm$10%. In certain embodiments, about means $\pm$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 "HSD17B13," also known as "hydroxysteroid 17-beta dehydrogenase 13," "short chain dehydrogenase/reductase family 16C member," "short-chain dehydrogenase/reductase 9," "17-beta-HSD 13," "17β-HSD13," "SDR16C3," "SCDR9," "short chain dehydrogenase/reductase family 16C, Member 3," "hydroxysteroid (17-beta) dehydrogenase 13," "17-beta-hydroxysteroid dehydrogenase 13," "17-beta hydroxysteroid dehydrogenase," "HMFN0376," and "NIIL497," refers to the well known gene encoding a 17β-hydroxysteroid dehydrogenase type 13 protein from any vertebrate or mammalian source, including, but not limited to, human, bovine, chicken, rodent, mouse, rat, porcine, ovine, primate, monkey, and guinea pig, unless specified otherwise.

The term also refers to fragments and variants of native HSD17B13 that maintain at least one *in vivo* or *in vitro* activity of a native HSD17B13. The term encompasses full-length unprocessed precursor forms of HSD17B13 as well as mature forms resulting from post-translational cleavage of the signal peptide and forms resulting from proteolytic processing.

Two variants of the human HSD17B13 gene were previously identified, variant A (or Transcript A) and variant B (or Transcript B). Transcript A includes all seven exons of the HSD17B13 gene, whereas exon 2 is skipped in Transcript B. The nucleotide and amino acid sequence of a human HSD17B13 variant A can be found in, for example, GenBank Reference Sequence: NM_178135.4; SEQ ID NO:1); and the nucleotide and amino acid sequence of a human HSD17B13 variant B can be found in, for example, GenBank Reference Sequence: NM_001136230.2; SEQ ID NO:2. As described in U.S. Patent Application No.: 15/875,514, filed on January 19, 2018, and PCT Application No.: PCT/US2018/014357, filed on January 19, 2018 (the entire contents of each of which are incorporated herein by reference), six additional HSD17B13 transcripts that are expressed (C-H, SEQ ID NOS: 17, 18, 19, 20, 21, and 22, respectively) have been identified. In Transcript C, exon 6 is skipped compared to Transcript A. In Transcript D, there is an insertion of a guanine 3' of exon 6, resulting in a frameshift in and premature truncation of exon 7 compared to Transcript A. In Transcript E, there is an additional exon between exons 3 and 4 compared to Transcript A. In Transcript F, which is expressed only in HSD17B13 rs72613567 variant carriers, there is read-through from exon 6 into intron 6 compared to Transcript A. In Transcript G, exon 2 is skipped, and there is an insertion of a guanine 3' of exon 6, resulting in a frameshift in and premature truncation of exon 7 compared to Transcript A. In Transcript H, there is an additional exon between exons 3 and 4, and there is an insertion of a guanine 3' of exon 6, resulting in a frameshift in and premature truncation of exon 7 compared to Transcript A.

One additional *HSD17B13* transcript that is expressed at low levels (F', SEQ ID NO: 23) has also been identified. Like Transcript F, Transcript F' also includes a read-through from exon 6 into intron 6 compared to Transcript A, but, in contrast to Transcript F, the read-through does not include the inserted thymine present in the *HSD17B13* rs72613567 variant gene. The nucleotide positions of the exons within the *HSD17B13* genes for each Transcript are provided below.

SEQ ID NO:15 is the nucleotide sequence of the HSD17B13 Wild Type Genomic Sequence (Human Genome Assembly GRCh38) and SEQ ID NO: 16 is the nucleotide sequence of HSD17B13 Genomic Sequence Variant (Human Genome Assembly GRCh38; rs72613567—insertion of T at chr4: 87310241-87310240): Insertion of T at position 12666.

Nucleotide Positions in SEQ ID NO: 15 for Exons of HSD17B13 Transcripts More Prevalent in Subjects Homozygous for Wild Type *HSD17B13* Gene.

	Transcript A	**Transcript B**	**Transcript E**	**Transcript F'**
Exon 1	1-275	1-275	1-275	1-275
Exon 2	4471-4578	skipped	4471-4578	4471-4578
Exon 3	5684-5815	5684-5815	5684-5815	5684-5815
Exon 3'	not present	not present	6210-6281	not present
Exon 4	7308-7414	7308-7414	7308-7414	7308-7414
Exon 5	8947-9084	8947-9084	8947-9084	8947-9084
Exon 6	12548-12664	12548-12664	12548-12664	12548-13501*
Exon 7	17599-19118	17599-19118	17599-19118	skipped

*Includes read-through from exon 6 into intron 6; read-through = positions 12665-13501

Nucleotide Positions in SEQ ID NO: 16 for Exons of HSD17B13 Transcripts More Prevalent in Subjects Homozygous for rs72613567 *HSD17B13* Variant Gene (Insertion of T at Position 12666).

	Transcript C	**Transcript D**	**Transcript F**	**Transcript G**	**Transcript H**
Exon 1	1-275	1-275	1-275	1-275	1-275
Exon 2	4471-4578	4471-4578	4471-4578	skipped	4471-4578
Exon 3	5684-5815	5684-5815	5684-5815	5684-5815	5684-5815
Exon 3'	not present	not present	not present	not present	6210-6281
Exon 4	7308-7414	7308-7414	7308-7414	7308-7414	7308-7414
Exon 5	8947-9084	8947-9084	8947-9084	8947-9084	8947-9084
Exon 6	skipped	12548-12665^	12548-13502*	12548-12665^	12548-12665^
Exon 7	17600-19119	17600-19119	skipped	17600-19119	17600-19119

^Includes additional residue 12665 at 3' end compared to Transcript A

*Includes read-through from exon 6 into intron 6; read-through = positions 12665-13502

There are two variants of the mouse HSD17B13 gene; the nucleotide and amino acid sequence of a mouse Hsd17b13, transcript variant 1 can be found in, for example, GenBank Reference Sequence: NM_001163486.1; SEQ ID NO:3); and the nucleotide and amino acid sequence of a mouse Hsd17b13, transcript variant 2 can be found in, for example, GenBank Reference Sequence: NM_198030.2; SEQ ID NO:4. The nucleotide and amino acid sequence of a rat Hsd17b13 gene can be found in, for example, GenBank Reference Sequence: NM_001009684.1; SEQ ID NO:5). The nucleotide and amino acid sequence of a *Macaca mulatta* HSD17B13 gene can be found in, for example, GenBank Reference Sequence: XM_015138766.1; SEQ ID NO:6). The

nucleotide and amino acid sequence of a *Macaca fascicularis* HSD17B13 gene can be found in, for example, GenBank Reference Sequence: XM_005555367.2; SEQ ID NO:7).

Additional examples of HSD17B13 mRNA sequences are readily available using publicly available databases, *e.g.*, GenBank, UniProt, and OMIM.

The term"HSD17B13" as used herein also refers to a particular polypeptide expressed in a cell by naturally occurring DNA sequence variations of the HSD17B13 gene, such as a single nucleotide polymorphism in the HSD17B13 gene. Numerous SNPs within the HSD17B13 gene have been identified and may be found at, for example, NCBI dbSNP (see, *e.g.*, www.ncbi.nlm.nih.gov/snp).

As used herein, "target sequence" refers to a contiguous portion of the nucleotide sequence of an mRNA molecule formed during the transcription of a HSD17B13 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 iRNA-directed cleavage at or near that portion of the nucleotide sequence of an mRNA molecule formed during the transcription of a HSD17B13 gene.

The target sequence of an HSD17B13 gene may be from about 9-36 nucleotides in length, *e.g.*, about 15-30 nucleotides in length. For example, the target sequence can be from about 15-30 nucleotides, 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. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the invention.

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 HSD17B13 gene in a cell, *e.g.,* a cell 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.,* an HSD17B13 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 (sssiRNA) generated within a cell and which promotes the formation of a RISC complex to effect silencing of the target gene, *i.e.,* an HSD17B13 gene. Accordingly, the term "siRNA" is also used herein to refer to an RNAi as described above.

In another embodiment, the RNAi agent may be a single-stranded RNAi agent that is introduced into a cell or organism to inhibit a target mRNA. Single-stranded RNAi agents (ssRNAi) 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 RNAi agents 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 another embodiment, an "iRNA" for use in the compositions and methods of the invention is a double-stranded RNA and is referred to herein as a "double stranded RNAi 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.,* an HSD17B13 gene. 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 and/or a modified nucleotide. In addition, as used in this specification, an "RNAi agent" may include ribonucleotides with chemical modifications; an RNAi agent 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, and/or a modified nucleobase. 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 "RNAi agent" for the purposes of this specification and claims.

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 9 to 36 base pairs in length, *e.g.*, about 15-30 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 15-30, 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. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the invention.

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, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 20, at least 23 or more unpaired nucleotides.

Where the two substantially complementary strands of a dsRNA are comprised by separate RNA molecules, those molecules need not, but can be covalently connected. 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, an RNAi agent of the invention is a dsRNA, each strand of which comprises less than 30 nucleotides, *e.g.,* 17-27, 19-27, 17-25, 19-25, or 19-23, that interacts with a target RNA sequence, *e.g.*, an HSD17B13 target mRNA sequence, to direct the cleavage of the target RNA. In another embodiment, an RNAi agent of the invention is a dsRNA, each strand of which comprises 19-23 nucleotides, that interacts with a target RNA sequence, *e.g.*, an HSD17B13 target mRNA sequence, to direct the cleavage of the target RNA. In one embodiment, the sense strand is 21 nucleotides in length. In another embodiment, the antiosense strand is 23 nucleotides in length.

As used herein, the term "nucleotide overhang" refers to at least one unpaired nucleotide that protrudes from the duplex structure of an iRNA, *e.g.*, a dsRNA. For example, when a 3'-end of one strand of a dsRNA extends beyond the 5'-end of the other strand, or vice versa, there is a nucleotide overhang. A dsRNA can comprise an overhang of at least one nucleotide; alternatively the overhang can comprise at least two nucleotides, at least three nucleotides, at least four nucleotides, 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 and/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 and/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 overhang on the sense strand or the antisense strand, or both, can include extended lengths longer than 10 nucleotides, *e.g.*, 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.

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

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.,* an HSD17B13 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 HSD17B13 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, 3, or 2 nucleotides of the 5'- and/or 3'-terminus of the iRNA.

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, 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 via a RISC pathway. 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 and/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 Hoogstein 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 the antisense strand of an iRNA agent and a target sequence, as will be understood from the context of their use.

As used herein, a polynucleotide that is "substantially complementary to at least part of" a messenger RNA (mRNA) refers to a polynucleotide that is substantially complementary to a contiguous portion of the mRNA of interest (*e.g.*, an mRNA encoding HSD17B13). For example, a polynucleotide is complementary to at least a part of an HSD17B13 mRNA if the sequence is substantially complementary to a non-interrupted portion of an mRNA encoding HSD17B13.

Accordingly, in some embodiments, the antisense strand polynucleotides disclosed herein are fully complementary to the target HSD17B13 sequence. In other embodiments, the antisense strand polynucleotides disclosed herein are substantially complementary to the target HSD17B13 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 NO:1, or a fragment of SEQ ID NO:1, such as about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about % 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% complementary.

In one embodiment, an RNAi agent of the invention includes a sense strand that is substantially complementary to an antisense polynucleotide which, in turn, is complementary to a target HSD17B13 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 NO:8, or a fragment of any one of SEQ ID NO:8, such as about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about % 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% complementary.

In some embodiments, an iRNA of the invention includes an antisense strand that is substantially complementary to the target HSD17B13 sequence and 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 any one of the sense strands in any one of Tables 2, 3, 7, 8, 10, 11, or 13, or a fragment of any one of the sense strands in any one of Tables 2, 3, 7, 8, 10, 11, or 13, such as about about 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% complementary, or 100% complementary.

The term "inhibiting," as used herein, is used interchangeably with "reducing," "silencing," "downregulating," "suppressing" and other similar terms, and includes any level of inhibition.

The phrase "inhibiting expression of an HSD17B13 gene," as used herein, includes inhibition of expression of any HSD17B13 gene (such as, *e.g.*, a mouse HSD17B13 gene, a rat HSD17B13 gene, a monkey HSD17B13 gene, or a human HSD17B13 gene) as well as variants or mutants of an HSD17B13 gene that encode an HSD17B13 protein.

"Inhibiting expression of an HSD17B13 gene" includes any level of inhibition of an HSD17B13 gene, *e.g.*, at least partial suppression of the expression of an HSD17B13 gene, such as an inhibition by at least about 20%. In certain embodiments, inhibition is by at least about 25%, at least about 30%, at least about 35%,at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99%.

The expression of an HSD17B13 gene may be assessed based on the level of any variable associated with HSD17B13 gene expression, *e.g.*, HSD17B13 mRNA level or HSD17B13 protein level. The expression of an HSD17B13 gene may also be assessed indirectly based on, for example, the levels of circulating alanine aminotransferase (ALT), or the enzymatic activity of HSD17B13 in a tissue sample, such as a liver sample. 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 one embodiment, at least partial suppression of the expression of an HSD17B13 gene, is assessed by a reduction of the amount of HSD17B13 mRNA which can be isolated from, or detected, in a first cell or group of cells in which an HSD17B13 gene is transcribed and which has or have been treated such that the expression of an HSD17B13 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 or have not been so treated (control cells).

The degree of inhibition may be expressed in terms of:

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

The phrase "contacting a cell with an RNAi agent," such as a dsRNA, as used herein, includes contacting a cell by any possible means. Contacting a cell with an RNAi agent 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 RNAi agent may be put into physical contact with the cell by the individual performing the method, or alternatively, the RNAi agent may be put into a situation that will permit or cause it to subsequently come into contact with the cell.

Contacting a cell *in vitro* may be done, for example, by incubating the cell with the RNAi agent. Contacting a cell *in vivo* may be done, for example, by injecting the RNAi agent into or near the tissue where the cell is located, or by injecting the RNAi agent into another area, *e.g.*, 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 RNAi agent may contain and/or be coupled to a ligand, *e.g.*, GalNAc3, that directs the RNAi agent to a site of interest, *e.g.*, the liver. 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 one embodiment, 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 diffusive or active cellular processes, or by auxiliary agents or devices. Introducing an iRNA into a cell may be *in vitro* and/or *in vivo*. For example, for *in vivo* introduction, iRNA can be injected into a tissue site or administered systemically. *In vivo* delivery can also be done by a beta-glucan delivery system, such as those described in U.S. Patent Nos. 5,032,401 and 5,607,677, and U.S. Publication No. 2005/0281781, the entire contents of which are hereby incorporated herein by reference. *In vitro* introduction into a cell includes methods known in the art such as electroporation and lipofection. Further approaches are described herein below and/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 camel, a llama, a horse, a goat, a rabbit, a sheep, a hamster, a guinea pig, a cat, a dog, a rat, a mouse, a horse, and a whale), or a bird (*e.g.*, a duck or a goose).

In an embodiment, the subject is a human, such as a human being treated or assessed for a disease, disorder or condition that would benefit from reduction in HSD17B13 expression; a human at risk for a disease, disorder or condition that would benefit from reduction in HSD17B13 expression; a human having a disease, disorder or condition that would benefit from reduction in HSD17B13 expression; and/or human being treated for a disease, disorder or condition that would benefit from reduction in HSD17B13 expression as described herein.

In one embodiment, the subject is heterozygous for the gene encoding the patatin like phospholipase domain containg 3 (PNPLA3) I148M variation. In another embodiment, the subject is homozygous for the gene encoding the PNPLA3 I148M variation. In one embodiment, the subject is heterozygous for the gene encoding the patatin like phospholipase domain containg 3 (PNPLA3) I144M variation. In another embodiment, the subject is homozygous for the gene encoding the PNPLA3 I144M variation. In one embodiment, the subject is homozygous for the gene encoding a functional HSD17B13 protein. In another embodiment, the subject is heterozygous for the gene encoding a functional HSD17B13 protein. In yet another embodiment, the subject is heterozygous for the gene encoding a functional HSD17B13 protein and a gene encoding a loss of function variant of HSD17B13. In another embodiment, the subject is not a carrier of the *HSD17B13* rs72613567 variant, *e.g.,* HSD17B13 rs72613567:TA.

As used herein, the terms "treating" or "treatment" refer to a beneficial or desired result including, but not limited to, alleviation or amelioration of one or more symptoms associated with HSD17B13 gene expression and/or HSD17B13 protein production, *e.g.,* an HSD17B13-associated disease, such as a chronic fibro-inflammatory liver disease, *e.g.,* inflammation of the liver, liver fibrosis, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), cirrhosis of the liver,alcoholic steatohepatitis (ASH), alcoholic liver diseases (ALD), HCV-associated cirrhosis, drug induced liver injury, hepatocellular necrosis, and/or hepatocellular carcinoma. "Treatment" can also mean prolonging survival as compared to expected survival in the absence of treatment.

The term "lower" in the context of an HSD17B13-associated disease refers to a statistically significant decrease in such level. The decrease can be, for example, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or more. In certain embodiments, a decrease is at least 20%. "Lower" in the context of the level of HSD17B13 in a subject is preferably down to a level accepted as within the range of normal for an individual without such disorder.

As used herein, "prevention" or "preventing," when used in reference to a disease, disorder or condition thereof, that would benefit from a reduction in expression of an HSD17B13 gene, refers to a reduction in the likelihood that a subject will develop a symptom associated with such disease, disorder, or condition, *e.g.,* a symptom of HSD17B13 gene expression, such as inflammation of the liver, liver fibrosis, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), cirrhosis of the liver, alcoholic steatohepatitis (ASH), alcoholic liver diseases (ALD), HCV-associated cirrhosis, drug induced liver injury, hepatocellular necrosis, and/or hepatocellular carcinoma. 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 (*e.g.,* reduction in lipid accumulation in the liver and/or lipid droplet expansion in the liver) delayed (*e.g.*, by days, weeks, months or years) is considered effective prevention.

As used herein, the term "HSD17B13-associated disease," is a disease or disorder that is caused by, or associated with, HSD17B13 gene expression or HSD17B13 protein production. The term "HSD17B13-associated disease" includes a disease, disorder or condition that would benefit from a decrease in HSD17B13 gene expression or protein activity.

In one embodiment, an "HSD17B13-associated disease" is a chronic fibro-inflammatory liver disease. A "chronic fibro-inflammatory liver disease" is any disease, disorder, or condition associated with chronic liver inflammation and/or fibrosis. Non-limiting examples of a chronic fibro-inflammatory liver disease include, for example, inflammation of the liver, liver fibrosis, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), cirrhosis of the liver, alcoholic steatohepatitis (ASH), alcoholic liver diseases (ALD), HCV-associated cirrhosis, drug induced liver injury, hepatocellular necrosis, and/or hepatocellular carcinoma.

"Therapeutically effective amount," as used herein, is intended to include the amount of an RNAi agent that, when administered to a subject having an HSD17B13-associated disease, disorder, or condition, is sufficient to effective 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 iRNA that, when administered to a subject having an HSD17B13-associated disease, disorder, or condition, 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 iRNA, 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 "prophylacticaly effective amount" also includes an amount of an RNAi agent that produces some desired local or systemic effect at a reasonable benefit/risk ratio applicable to any treatment. 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, and/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. Some examples of materials which can serve as pharmaceutically-acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) lubricating agents, such as magnesium state, sodium lauryl sulfate and talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) pH buffered solutions; (21) polyesters, polycarbonates and/or polyanhydrides; (22) bulking agents, such as polypeptides and amino acids (23) serum component, such as serum albumin, HDL and LDL; and (22) other non-toxic compatible substances employed in pharmaceutical formulations.

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 blood or plasma drawn from the subject.

II. iRNAs of the Invention

Described herein are iRNAs which inhibit the expression of a target gene. In one embodiment, the iRNAs inhibit the expression of an HSD17B13 gene. In one embodiment, the iRNA agent includes double stranded ribonucleic acid (dsRNA) molecules for inhibiting the expression of an HSD17B13 gene in a cell, such as a liver cell, such as a liver cell within a subject, *e.g.*, a mammal, such as a human having a chronic fibro-inflammatory liver disease, disorder, or condition, *e.g.*, a disease, disorder, or condition associated with, *e.g.*, accumulation and/or expansion of lipid droplets in the liver and/or fibrosis of the liver.

The dsRNA includes an antisense strand having a region of complementarity which is complementary to at least a part of an mRNA formed in the expression of an HSD17B13 gene. The region of complementarity is about 30 nucleotides or less in length (*e.g.*, about 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, or 18 nucleotides or less 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 bird target gene) by at least about 10% 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 flowcytometric techniques.

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 HSD17B13 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 between 15 and 30 base pairs in length, *e.g.,* between, 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. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the invention.

Similarly, the region of complementarity to the target sequence is between 15 and 30 nucleotides in length, *e.g.,* between 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. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the invention.

In some embodiments, the sense and antisense strands of the dsRNA are each independently about 15 to about 30 nucleotides in length, or about 25 to about 30 nucleotides in length, *e.g.,* each strand is independently between 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. In some embodiments, the dsRNA is between about 15 and about 23 nucleotides in length, or between about 25 and 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 can 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 9 to 36 base pairs, *e.g.*, about 10-36, 11-36, 12-36, 13-36, 14-36, 15-36, 9-35, 10-35, 11-35, 12-35, 13-35, 14-35, 15-35, 9-34, 10-34, 11-34, 12-34, 13-34, 14-34, 15-34, 9-33, 10-33, 11-33, 12-33, 13-33, 14-33, 15-33, 9-32, 10-32, 11-32, 12-32, 13-32, 14-32, 15-32, 9-31, 10-31, 11-31, 12-31, 13-32, 14-31, 15-31, 15-30, 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. 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 HSD17B13 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, 2, 3, or 4 nucleotides. dsRNAs having at least one nucleotide overhang can have unexpectedly 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 either an antisense or sense strand of a dsRNA.

A dsRNA can be synthesized by standard methods known in the art as further discussed below, *e.g.*, by use of an automated DNA synthesizer, such as are commercially available from, for example, Biosearch, Applied Biosystems, Inc.

iRNA 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. Single-stranded oligonucleotides of the invention can be prepared using solution-phase or solid-phase organic synthesis or both.

In one aspect, a dsRNA of the invention includes at least two nucleotide sequences, a sense sequence and an anti-sense sequence. The sense strand sequence is selected from the group of sequences provided in any one of Tables 2, 3, 7, 8, 10, 11 or 13, and the corresponding nucleotide sequence of the antisense strand of the sense strand is selected from the group of sequences of any one of Tables 2, 3, 7, 8, 10, 11, or 13. 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 an HSD17B13 gene. As such, in this aspect, a dsRNA will include two oligonucleotides, where one oligonucleotide is described as the sense strand (passenger strand) in any one of Tables 2, 3, 7, 8, 10, 11, or 13, and the second oligonucleotide is described as the corresponding antisense strand (guide strand) of the sense strand in any one of Tables 2, 3, 7, 8, 10, 11, or 13. In one embodiment, the substantially complementary sequences of the dsRNA are contained on separate oligonucleotides. In another embodiment, the substantially complementary sequences of the dsRNA are contained on a single oligonucleotide.

It will be understood that, although the sequences in Tables 2, 3, 7, 8, 10, 11, or 13 are described as modified, unmodified, unconjugated. and/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, 3, 7, 8, 10, 11, or 13 that is un-modified, un-conjugated, and/or modified and/or conjugated differently than described therein.

The skilled person is well aware that dsRNAs having a duplex structure of between about 20 and 23 base pairs, *e.g.,* 21, base pairs have been hailed as particularly effective in inducing RNA interference (Elbashir *et al.*, (2001) *EMBO J.*, 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 herein, dsRNAs described herein can include at least one strand of a length of minimally 21 nucleotides. It can be reasonably expected that shorter duplexes 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 15, 16, 17, 18, 19, 20, or more contiguous nucleotides derived from one of the sequences provided herein, and differing in their ability to inhibit the expression of an HSD17B13 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 described in any one of Tables 2, 3, 7, 8, 10, 11, or 13 identify a site(s) in an HSD17B13 transcript that is susceptible to RISC-mediated cleavage. As such, the present invention further features iRNAs that target within this site(s). 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 15 contiguous nucleotides from one of the sequences provided herein coupled to additional nucleotide sequences taken from the region contiguous to the selected sequence in the gene.

While a target sequence is generally about 15-30 nucleotides in length, there is wide variation in the suitability of particular sequences in this range for directing cleavage of any given target RNA. Various software packages and the guidelines set out herein provide guidance for the identification of optimal target sequences for any given gene target, but an empirical approach can also be taken in which a "window" or "mask" of a given size (as a non-limiting example, 21 nucleotides) is literally or figuratively (including, *e.g.*, in silico) placed on the target RNA sequence

to identify sequences in the size range that can serve as target sequences. By moving the sequence "window" progressively one nucleotide upstream or downstream of an initial target sequence location, the next potential target sequence can be identified, until the complete set of possible sequences is identified for any given target size selected. This process, coupled with systematic synthesis and testing of the identified sequences (using assays as described herein or as known in the art) to identify those sequences that perform optimally can identify those RNA sequences that, when targeted with an iRNA agent, mediate the best inhibition of target gene expression. Thus, while the sequences identified herein represent effective target sequences, it is contemplated that further optimization of inhibition efficiency can be achieved by progressively "walking the window" one nucleotide upstream or downstream of the given sequences to identify sequences with equal or better inhibition characteristics.

Further, it is contemplated that for any sequence identified herein, further optimization could be achieved by systematically either adding or removing nucleotides to generate longer or shorter sequences and testing those sequences generated by walking a window of the longer or shorter size up or down the target RNA from that point. Again, coupling this approach to generating new candidate targets with testing for effectiveness of iRNAs based on those target sequences in an inhibition assay as known in the art and/or as described herein can lead to further improvements in the efficiency of inhibition. Further still, such optimized sequences can be adjusted by, *e.g.*, the introduction of modified nucleotides as described herein or as known in the art, addition or changes in overhang, or other modifications as known in the art and/or discussed herein to further optimize the molecule (*e.g.*, increasing serum stability or circulating half-life, increasing thermal stability, enhancing transmembrane delivery, targeting to a particular location or cell type, increasing interaction with silencing pathway enzymes, increasing release from endosomes) as an expression inhibitor.

An iRNA agent as described herein can contain one or more mismatches to the target sequence. In one embodiment, an iRNA as described herein contains no more than 3 mismatches. If the antisense strand of the iRNA contains mismatches to a target sequence, it is preferable that the area of mismatch is not located in the center of the region of complementarity. If the antisense strand of the iRNA contains mismatches to the target sequence, it is preferable that the mismatch be restricted to be within the last 5 nucleotides from either the 5'- or 3'-end of the region of complementarity. For example, for a 23 nucleotide iRNA agent the strand which is complementary to a region of an HSD17B13 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 iRNA containing a mismatch to a target sequence is effective in inhibiting the expression of an HSD17B13 gene. Consideration of the efficacy of iRNAs with mismatches in inhibiting expression of an HSD17B13 gene is important, especially if the particular region of complementarity in an HSD17B13 gene is known to have polymorphic sequence variation within the population.

III. Modified iRNAs of the Invention

In one embodiment, the RNA of the iRNA of the invention *e.g.*, a dsRNA, is un-modified, and does not comprise, *e.g.,* chemical modifications and/or conjugations known in the art and described herein. In another embodiment, 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 of the invention are modified. iRNAs of the invention in which "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.

In some aspects of the invention, substantially all of the nucleotides of an iRNA of the invention are modified and the iRNA agents comprise no more than 10 nucleotides comprising 2'-fluoro modifications (*e.g.,* no more than 9 2′-fluoro modifications, no more than 8 2′-fluoro modifications, no more than 7 2′-fluoro modifications, no more than 6 2′-fluoro modifications, no more than 5 2′-fluoro modifications, no more than 4 2′-fluoro modifications, no more than 5 2′-fluoro modifications, no more than 4 2′-fluoro modifications, no more than 3 2′-fluoro modifications, or no more than 2 2′-fluoro modifications). For example, in some embodiments, the sense strand comprises no more than 4 nucleotides comprising 2′-fluoro modifications (*e.g.,* no more than 3 2′-fluoro modifications, or no more than 2 2′-fluoro modifications). In other embodiments, the antisense strand comprises no more than 6 nucleotides comprising 2′-fluoro modifications (*e.g.,* no more than 5 2′-fluoro modifications, no more than 4 2′-fluoro modifications, no more than 4 2′-fluoro modifications, or no more than 2 2′-fluoro modifications).

In other aspects of the invention, all of the nucleotides of an iRNA of the invention are modified and the iRNA agents comprise no more than 10 nucleotides comprising 2'-fluoro modifications (*e.g.,* no more than 9 2′-fluoro modifications, no more than 8 2′-fluoro modifications, no more than 7 2′-fluoro modifications, no more than 6 2′-fluoro modifications, no more than 5 2′-fluoro modifications, no more than 4 2′-fluoro modifications, no more than 5 2′-fluoro modifications, no more than 4 2′-fluoro modifications, no more than 3 2′-fluoro modifications, or no more than 2 2′-fluoro modifications).

In one embodiment, the double stranded RNAi agent of the invention further comprises a 5'-phosphate or a 5'-phosphate mimic at the 5' nucleotide of the antisense strand. In another embodiment, the double stranded RNAi agent further comprises a 5'-phosphate mimic at the 5' nucleotide of the antisense strand. In a specific embodiment, the 5'-phosphate mimic is a 5'-vinyl phosphate (5'-VP).

The nucleic acids featured in the invention can be synthesized and/or modified by methods well established in the art, such as those described in "Current protocols in nucleic acid chemistry," Beaucage, S.L. *et al.* (Edrs.), John Wiley & Sons, Inc., New York, NY, USA, which is hereby incorporated herein by reference. Modifications include, for example, 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; and/or backbone modifications, including modification or replacement of the phosphodiester linkages. Specific examples of iRNA compounds 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 iRNA will have a phosphorus atom in its internucleoside backbone.

Modified RNA backbones include, for example, phosphorothioates, chiral phosphorothioates, phosphorodithioates, phosphotriesters, aminoalkylphosphotriesters, methyl and other alkyl phosphonates including 3'-alkylene phosphonates and chiral phosphonates, phosphinates, phosphoramidates including 3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, and boranophosphates having normal 3'-5' linkages, 2'-5'-linked analogs of these, and those having inverted polarity wherein the adjacent pairs of nucleoside units are linked 3'-5' to 5'-3' or 2'-5' to 5'-2'. Various salts, mixed salts and free acid forms are also included. In some embodiments of the invention, the dsRNA agents of the invention are in a free acid form. In other embodiments of the invention, the dsRNA agents of the invention are in a salt form. In one embodiment, the dsRNA agents of the invention are in a sodium salt form. In certain embodiments, when the dsRNA agents of the invention are in the sodium salt form, sodium ions are present in the agent as counterions for substantially all of the phosphodiester and/or phosphorothiotate groups present in the agent. Agents in which substantially all of the phosphodiester and/or phosphorothioate linkages have a sodium counterion include not more than 5, 4, 3, 2, or 1 phosphodiester and/or phosphorothioate linkages without a sodium counterion. In some embodiments, when the dsRNA agents of the invention are in the sodium salt form, sodium ions are present in the agent as counterions for all of the phosphodiester and/or phosphorothiotate groups present in the agent.

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

Modified RNA backbones that do not include a phosphorus atom therein have backbones that are formed by short chain alkyl or cycloalkyl internucleoside linkages, mixed heteroatoms and alkyl or cycloalkyl internucleoside linkages, or one or more short chain heteroatomic or heterocyclic internucleoside linkages. These include those having morpholino linkages (formed in part from the

sugar portion of a nucleoside); siloxane backbones; sulfide, sulfoxide and sulfone backbones; formacetyl and thioformacetyl backbones; methylene formacetyl and thioformacetyl backbones; alkene containing backbones; sulfamate backbones; methyleneimino and methylenehydrazino backbones; sulfonate and sulfonamide backbones; amide backbones; and others having mixed N, O, S and CH_2 component parts.

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

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

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

Modified RNAs can also contain one or more substituted sugar moieties. The iRNAs, *e.g.*, dsRNAs, featured herein can include one of the following at the 2'-position: OH; F; O-, S-, or N-alkyl; O-, S-, or N-alkenyl; O-, S- or N-alkynyl; or O-alkyl-O-alkyl, wherein the alkyl, alkenyl and alkynyl can be substituted or unsubstituted C_1 to C_{10} alkyl or C_2 to C_{10} alkenyl and alkynyl. Exemplary suitable modifications include O[$(CH_2)_nO$] $_mCH_3$, O$(CH_2)._nOCH_3$, O$(CH_2)_nNH_2$, O(CH_2) $_nCH_3$, O$(CH_2)_nONH_2$, and O$(CH_2)_nON[(CH_2)_nCH_3)]_2$, where n and m are from 1 to about 10. In other embodiments, dsRNAs include one of the following at the 2' position: C_1 to C_{10} lower alkyl, substituted lower alkyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH_3, OCN, Cl, Br, CN, CF_3,

OCF_3, $SOCH_3$, SO_2CH_3, ONO_2, NO_2, N_3, NH_2, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, an RNA cleaving group, a reporter group, an intercalator, a group for improving the pharmacokinetic properties of an iRNA, or a group for improving the pharmacodynamic properties of an iRNA, and other substituents having similar properties. In some embodiments, the modification includes a 2'-methoxyethoxy (2'-O--$CH_2CH_2OCH_3$, also known as 2'-O-(2-methoxyethyl) or 2'-MOE) (Martin *et al.*, *Helv. Chim. Acta*, 1995, 78:486-504) *i.e.*, an alkoxy-alkoxy group. Another exemplary modification is 2'-dimethylaminooxyethoxy, *i.e.*, a $O(CH_2)_2ON(CH_3)_2$ group, also known as 2'-DMAOE, as described in examples herein below, and 2'-dimethylaminoethoxyethoxy (also known in the art as 2'-O-dimethylaminoethoxyethyl or 2'-DMAEOE), *i.e.*, 2'-O--CH_2--O--CH_2--$N(CH_2)_2$. Further exemplary modifications include : 5'-Me-2'-F nucleotides, 5'-Me-2'-OMe nucleotides, 5'-Me-2'-deoxynucleotides, (both R and S isomers in these three families); 2'-alkoxyalkyl; and 2'-NMA (N-methylacetamide).

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

An iRNA of the invention 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). Modified nucleobases include other synthetic and natural nucleobases such as 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl uracil and cytosine, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl anal other 8-substituted adenines and guanines, 5-halo, particularly 5-bromo, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine and 7-methyladenine, 8-azaguanine and 8-azaadenine, 7-deazaguanine and 7-daazaadenine and 3-deazaguanine and 3-deazaadenine. Further nucleobases include those disclosed in U.S. Pat. No. 3,687,808, those disclosed in Modified Nucleosides in Biochemistry, Biotechnology and Medicine, Herdewijn, P. ed. Wiley-VCH, 2008; those disclosed in The Concise Encyclopedia Of Polymer Science And Engineering, pages 858-859, Kroschwitz, J. L, ed. John Wiley & Sons, 1990, these disclosed by Englisch *et al.*, (1991) *Angewandte Chemie, International*

Edition, 30:613, and those disclosed by Sanghvi, Y S., Chapter 15, dsRNA Research and Applications, pages 289-302, Crooke, S. T. and Lebleu, B., Ed., CRC Press, 1993. Certain of these nucleobases are particularly useful for increasing the binding affinity of the oligomeric compounds featured in the invention. These include 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and 0-6 substituted purines, including 2-aminopropyladenine, 5-propynyluracil and 5-propynylcytosine. 5-methylcytosine substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2 °C (Sanghvi, Y. S., Crooke, S. T. and Lebleu, B., Eds., dsRNA Research and Applications, CRC Press, Boca Raton, 1993, pp. 276-278) and are exemplary base substitutions, even more particularly when combined with 2'-O-methoxyethyl sugar modifications.

Representative U.S. patents that teach the preparation of certain of the above noted modified nucleobases as well as other modified nucleobases include, but are not limited to, the above noted U.S. Patent Nos. 3,687,808, 4,845,205; 5,130,30; 5,134,066; 5,175,273; 5,367,066; 5,432,272; 5,457,187; 5,459,255; 5,484,908; 5,502,177; 5,525,711; 5,552,540; 5,587,469; 5,594,121, 5,596,091; 5,614,617; 5,681,941; 5,750,692; 6,015,886; 6,147,200; 6,166,197; 6,222,025; 6,235,887; 6,380,368; 6,528,640; 6,639,062; 6,617,438; 7,045,610; 7,427,672; and 7,495,088, the entire contents of each of which are hereby incorporated herein by reference.

An iRNA of the invention can also be modified to include one or more locked nucleic acids (LNA). A locked nucleic acid is a nucleotide having a modified ribose moiety in which the ribose moiety comprises an extra bridge connecting the 2' and 4' carbons. This structure effectively "locks" the ribose in the 3'-endo structural conformation. The addition of locked nucleic acids to siRNAs has been shown to increase siRNA stability in serum, and to reduce off-target effects (Elmen, J. *et al.*, (2005) *Nucleic Acids Research* 33(1):439-447; Mook, OR. *et al.*, (2007) *Mol Canc Ther* 6(3):833-843; Grunweller, A. *et al.*, (2003) *Nucleic Acids Research* 31(12):3185-3193).

An iRNA of the invention can also be modified to include one or more bicyclic sugar moities. A "bicyclic sugar" is a furanosyl ring modified by the bridging of two atoms. A"bicyclic nucleoside" ("BNA") is a nucleoside having a sugar moiety comprising a bridge connecting two carbon atoms of the sugar ring, thereby forming a bicyclic ring system. In certain embodiments, the bridge connects the 4′-carbon and the 2′-carbon of the sugar ring. Thus, in some embodiments an agent of the invention may include one or more locked nucleic acids (LNA). A locked nucleic acid is a nucleotide having a modified ribose moiety in which the ribose moiety comprises an extra bridge connecting the 2' and 4' carbons. In other words, an LNA is a nucleotide comprising a bicyclic sugar moiety comprising a 4'-CH2-O-2' bridge. This structure effectively "locks" the ribose in the 3'-endo structural conformation. The addition of locked nucleic acids to siRNAs has been shown to increase siRNA stability in serum, and to reduce off-target effects (Elmen, J. *et al.*, (2005) *Nucleic Acids Research* 33(1):439-447; Mook, OR. *et al.*, (2007) *Mol Canc Ther* 6(3):833-843; Grunweller, A. *et al.*, (2003) *Nucleic Acids Research* 31(12):3185-3193). Examples of bicyclic nucleosides for use in the polynucleotides of the invention include without limitation nucleosides comprising a bridge between the 4′ and the 2′ ribosyl ring atoms. In certain embodiments, the antisense polynucleotide agents of the invention include one or more bicyclic nucleosides comprising a 4′ to 2′ bridge.

Examples of such 4′ to 2′ bridged bicyclic nucleosides, include but are not limited to 4′-(CH2)—O-2′ (LNA); 4′-(CH2)—S-2′; 4′-(CH2)2—O-2′ (ENA); 4′-CH(CH3)—O-2′ (also referred to as "constrained ethyl" or "cEt") and 4′-CH(CH2OCH3)—O-2′ (and analogs thereof; see, *e.g.*, U.S. Pat. No. 7,399,845); 4′-C(CH3)(CH3)—O-2′ (and analogs thereof; see *e.g.*, US Patent No. 8,278,283); 4′-CH2—N(OCH3)-2′ (and analogs thereof; see *e.g.*, US Patent No. 8,278,425); 4′-CH2—O—N(CH3)-2′ (see, e.g.,U.S. Patent Publication No. 2004/0171570); 4′-CH2—N(R)—O-2′, wherein R is H, C1-C12 alkyl, or a protecting group (see, *e.g.*, U.S. Pat. No. 7,427,672); 4′-CH2—C(H)(CH3)-2′ (see, *e.g.*, Chattopadhyaya *et al., J. Org. Chem.*, 2009, 74, 118-134); and 4′-CH2—C(=CH2)-2′ (and analogs thereof; see, *e.g.*, US Patent No. 8,278,426). The entire contents of each of the foregoing are hereby incorporated herein by reference.

Additional representative U.S. Patents and US Patent Publications that teach the preparation of locked nucleic acid nucleotides include, but are not limited to, the following: U.S. Patent Nos. 6,268,490; 6,525,191; 6,670,461; 6,770,748; 6,794,499; 6,998,484; 7,053,207; 7,034,133;7,084,125; 7,399,845; 7,427,672; 7,569,686; 7,741,457; 8,022,193; 8,030,467; 8,278,425; 8,278,426; 8,278,283; US 2008/0039618; and US 2009/0012281, the entire contents of each of which are hereby incorporated herein by reference.

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

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

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

Representative publications that teach the preparation of certain of the above noted CRN include, but are not limited to, US Patent Publication No. 2013/0190383; and PCT publication WO 2013/036868, the entire contents of each of which are hereby incorporated herein by reference.

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

Representative U.S. publications that teach the preparation of UNA include, but are not limited to, US Patent No. 8,314,227; and US Patent Publication Nos. 2013/0096289; 2013/0011922; and 2011/0313020, the entire contents of each of which are hereby incorporated herein by reference.

Potentially stabilizing modifications to the ends of RNA molecules can include N-(acetylaminocaproyl)-4-hydroxyprolinol (Hyp-C6-NHAc), N-(caproyl-4-hydroxyprolinol (Hyp-C6), N-(acetyl-4-hydroxyprolinol (Hyp-NHAc), thymidine-2'-0-deoxythymidine (ether), N-(aminocaproyl)-4-hydroxyprolinol (Hyp-C6-amino), 2-docosanoyl-uridine-3"- phosphate, inverted base dT(idT) and others. Disclosure of this modification can be found in PCT Publication No. WO 2011/005861.

Other modifications of an iRNA of the invention include a 5' phosphate or 5' phosphate mimic, *e.g.,* a 5'-terminal phosphate or phosphate mimic on the antisense strand of an RNAi agent. Suitable phosphate mimics are disclosed in, for example US Patent Publication No. 2012/0157511, the entire contents of which are incorporated herein by reference.

In certain specific embodiments, an RNAi agent of the present invention is an agent that inhibits the expression of an HSD17B13 gene which is selected from the group of agents listed in any one of Tables 2, 3, 7, 8, 10, 11, or 13. Any of these agents may further comprise a ligand.

A. Modified iRNAs Comprising Motifs of the Invention

In certain aspects of the invention, the double stranded RNAi agents of the invention include agents with chemical modifications as disclosed, for example, in WO 2013/075035, filed on November 16, 2012, the entire contents of which are incorporated herein by reference.

Accordingly, the invention provides double stranded RNAi agents capable of inhibiting the expression of a target gene (*i.e.*, an HSD17B13 gene) *in vivo*. The RNAi agent comprises a sense strand and an antisense strand. Each strand of the RNAi agent may range from 12-30 nucleotides in length. For example, each strand may be between 14-30 nucleotides in length, 17-30 nucleotides in length, 25-30 nucleotides in length, 27-30 nucleotides in length, 17-23 nucleotides in length, 17-21 nucleotides in length, 17-19 nucleotides in length, 19-25 nucleotides in length, 19-23 nucleotides in length, 19-21 nucleotides in length, 21-25 nucleotides in length, or 21-23 nucleotides in length. In one embodiment, the sense strand is 21 nulceotides in length. In one embodiment, the antisense strand is 23 nucleotides in length.

The sense strand and antisense strand typically form a duplex double stranded RNA ("dsRNA"), also referred to herein as an "RNAi agent." The duplex region of an RNAi agent may be 12-30 nucleotide pairs in length. For example, the duplex region can be between 14-30 nucleotide pairs in length, 17-30 nucleotide pairs in length, 27-30 nucleotide pairs in length, 17 - 23 nucleotide pairs in length, 17-21 nucleotide pairs in length, 17-19 nucleotide pairs in length, 19-25 nucleotide pairs in length, 19-23 nucleotide pairs in length, 19- 21 nucleotide pairs in length, 21-25 nucleotide pairs in length, or 21-23 nucleotide pairs in length. In another example, the duplex region is selected from 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, and 27 nucleotides in length.

In one embodiment, the RNAi agent may contain one or more overhang regions and/or capping groups at the 3'-end, 5'-end, or both ends of one or both strands. The overhang can be 1-6 nucleotides in length, for instance 2-6 nucleotides in length, 1-5 nucleotides in length, 2-5 nucleotides in length, 1-4 nucleotides in length, 2-4 nucleotides in length, 1-3 nucleotides in length, 2-3 nucleotides in length, or 1-2 nucleotides in length. The overhangs can be the result of one strand being longer than the other, or the result of two strands of the same length being staggered. The overhang can form a mismatch with the target mRNA or it can be complementary to the gene sequences being targeted or can be another sequence. The first and second strands can also be joined, *e.g.*, by additional bases to form a hairpin, or by other non-base linkers.

In one embodiment, the nucleotides in the overhang region of the RNAi agent can each independently be a modified or unmodified nucleotide including, but no limited to 2'-sugar modified, such as, 2-F, 2'-Omethyl, thymidine (T), 2`-O-methoxyethyl-5-methyluridine (Teo), 2`-O-methoxyethyladenosine (Aeo), 2`-O-methoxyethyl-5-methylcytidine (m5Ceo), and any combinations thereof. For example, TT can be an overhang sequence for either end on either strand. The overhang can form a mismatch with the target mRNA or it can be complementary to the gene sequences being targeted or can be another sequence.

The 5'- or 3'- overhangs at the sense strand, antisense strand or both strands of the RNAi agent may be phosphorylated. In some embodiments, the overhang region(s) contains two nucleotides having a phosphorothioate between the two nucleotides, where the two nucleotides can be the same or different. In one embodiment, the overhang is present at the 3'-end of the sense strand, antisense strand, or both strands. In one embodiment, this 3'-overhang is present in the antisense strand. In one embodiment, this 3'-overhang is present in the sense strand.

The RNAi agent may contain only a single overhang, which can strengthen the interference activity of the RNAi, without affecting its overall stability. For example, the single-stranded overhang may be located at the 3'-terminal end of the sense strand or, alternatively, at the 3'-terminal end of the antisense strand. The RNAi may also have a blunt end, located at the 5'-end of the antisense strand (or the 3'-end of the sense strand) or *vice versa*. Generally, the antisense strand of the RNAi has a nucleotide overhang at the 3'-end, and the 5'-end is blunt. While not wishing to be bound by theory, the asymmetric blunt end at the 5'-end of the antisense strand and 3'-end overhang of the antisense strand favor the guide strand loading into RISC process.

In one embodiment, the RNAi agent is a double ended bluntmer of 19 nucleotides 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 another embodiment, the RNAi agent is a double ended bluntmer of 20 nucleotides 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 yet another embodiment, the RNAi agent is a double ended bluntmer of 21 nucleotides 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 RNAi agent comprises a 21 nucleotide sense strand and a 23 nucleotide antisense strand, 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 RNAi agent is blunt, while the other end comprises a 2 nucleotide overhang. Preferably, the 2 nucleotide overhang is at the 3'-end of the antisense strand.

When the 2 nucleotide overhang is at the 3'-end of the antisense strand, there may be two phosphorothioate internucleotide linkages between the terminal three nucleotides, wherein two of the three nucleotides are the overhang nucleotides, and the third nucleotide is a paired nucleotide next to the overhang nucleotide. In one embodiment, the RNAi agent additionally has two phosphorothioate internucleotide linkages between the terminal three nucleotides at both the 5'-end of the sense strand and at the 5'-end of the antisense strand. In one embodiment, every nucleotide in the sense strand and the antisense strand of the RNAi agent, including the nucleotides that are part of the motifs are modified nucleotides. In one embodiment each residue is independently modified with a 2'-O-methyl or 3'-fluoro, *e.g.,* in an alternating motif. Optionally, the RNAi agent further comprises a ligand (preferably $GalNAc_3$).

In one embodiment, the RNAi agent comprises a sense and an antisense strand, 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 the first strand comprise at least 8 ribonucleotides; the 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 the 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 RNAi agent comprises sense and antisense strands, wherein the RNAi 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 the 3' end of the first strand and the 5' end of the second strand form a blunt end and the 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 the second strand is sufficiently complemenatary to a target mRNA along at least 19 nucleotide of the second strand length to reduce target gene expression when the RNAi agent is introduced into a mammalian cell, and wherein dicer cleavage of the RNAi agent preferentially results in an siRNA comprising the 3' end of the second strand, thereby reducing expression of the target gene in the mammal. Optionally, the RNAi agent further comprises a ligand.

In one embodiment, the sense strand of the RNAi 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.

In one embodiment, the antisense strand of the RNAi 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 an RNAi agent having a duplex region of 17-23 nucleotide 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 RNAi from the 5'-end.

The sense strand of the RNAi agent may contain at least one motif of three identical modifications on three consecutive nucleotides at the cleavage site of the strand; and the antisense strand may have at least one motif of three identical modifications on three consecutive nucleotides at or near the cleavage site of the strand. When the sense strand and the antisense strand form a dsRNA duplex, the sense strand and the antisense strand can be so aligned that one motif of the three nucleotides on the sense strand and one motif of the three nucleotides on the antisense strand have at least one nucleotide overlap, *i.e.*, at least one of the three nucleotides of the motif in the sense strand forms a base pair with at least one of the three nucleotides of the motif in the antisense strand. Alternatively, at least two nucleotides may overlap, or all three nucleotides may overlap.

In one embodiment, the sense strand of the RNAi agent may contain more than one motif of three identical modifications on three consecutive nucleotides. The first motif may occur at or near the cleavage site of the strand and the other motifs may be a wing modification. The term "wing modification" herein refers to a motif occurring at another portion of the strand that is separated from the motif at or near the cleavage site of the same strand. The wing modification is either adajacent to the first motif or is separated by at least one or more nucleotides. When the motifs are immediately adjacent to each other then the chemistry of the motifs are distinct from each other and when the motifs are separated by one or more nucleotide than the chemistries can be the same or different. Two or more wing modifications may be present. For instance, when two wing modifications are present, each wing modification may occur at one end relative to the first motif which is at or near cleavage site or on either side of the lead motif.

Like the sense strand, the antisense strand of the RNAi agent may contain more than one motifs of three identical modifications on three consecutive nucleotides, with at least one of the motifs occurring at or near the cleavage site of the strand. This antisense strand may also contain one or more wing modifications in an alignment similar to the wing modifications that may be present on the sense strand.

In one embodiment, the wing modification on the sense strand or antisense strand of the RNAi agent typically does not include the first one or two terminal nucleotides at the 3'-end, 5'-end or both ends of the strand.

In another embodiment, the wing modification on the sense strand or antisense strand of the RNAi agent typically does not include the first one or two paired nucleotides within the duplex region at the 3'-end, 5'-end or both ends of the strand.

When the sense strand and the antisense strand of the RNAi agent each contain at least one wing modification, the wing modifications may fall on the same end of the duplex region, and have an overlap of one, two or three nucleotides.

When the sense strand and the antisense strand of the RNAi agent each contain at least two wing modifications, the sense strand and the antisense strand can be so aligned that two modifications each from one strand fall on one end of the duplex region, having an overlap of one, two or three nucleotides; two modifications each from one strand fall on the other end of the duplex region, having an overlap of one, two or three nucleotides; two modifications one strand fall on each side of the lead motif, having an overlap of one, two or three nucleotides in the duplex region.

In one embodiment, every nucleotide in the sense strand and antisense strand of the RNAi agent, including the nucleotides that are part of the motifs, may be modified. Each nucleotide may be modified with the same or different modification which can include one or more alteration of one or both of the non-linking phosphate oxygens and/or of one or more of the linking phosphate oxygens; alteration of a constituent of the ribose sugar, *e.g.*, of the 2′ hydroxyl on the ribose sugar; wholesale replacement of the phosphate moiety with "dephospho" linkers; modification or replacement of a naturally occurring base; and replacement or modification of the ribose-phosphate backbone.

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

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

In one embodiment, each residue of the sense strand and antisense strand is independently modified with LNA, CRN, cET, UNA, HNA, CeNA, 2'-methoxyethyl, 2'- O-methyl, 2'-O-allyl, 2'-C- allyl, 2'-deoxy, 2'-hydroxyl, or 2'-fluoro. The strands can contain more than one modification. In one embodiment, each residue of the sense strand and antisense strand is independently modified with 2'- O-methyl or 2'-fluoro.

At least two different modifications are typically present on the sense strand and antisense strand. Those two modifications may be the 2'- O-methyl or 2'-fluoro modifications, or others.

In one embodiment, the N_a and/or N_b comprise modifications of an alternating pattern. The term "alternating motif" as used herein refers to a motif having one or more modifications, each modification occurring on alternating nucleotides of one strand. The alternating nucleotide may refer to one per every other nucleotide or one per every three nucleotides, or a similar pattern. For example, if A, B and C each represent one type of modification to the nucleotide, the alternating motif can be "ABABABABABAB…," "AABBAABBAABB…," "AABAABAABAAB…," "AAABAAABAAAB…," "AAABBBAAABBB…," or "ABCABCABCABC…," *etc.*

The type of modifications contained in the alternating motif may be the same or different. For example, if A, B, C, D each represent one type of modification on the nucleotide, the alternating pattern, *i.e.*, modifications on every other nucleotide, may be the same, but each of the sense strand

or antisense strand can be selected from several possibilities of modifications within the alternating motif such as "ABABAB…", "ACACAC…" "BDBDBD…" or "CDCDCD…," *etc.*

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

In one embodiment, the RNAi agent comprises the pattern of the alternating motif of 2'-O-methyl modification and 2'-F modification on the sense strand initially has a shift relative to the pattern of the alternating motif of 2'-O-methyl modification and 2'-F modification on the antisense strand initially, *i.e.*, the 2'-O-methyl modified nucleotide on the sense strand base pairs with a 2'-F modified nucleotide on the antisense strand and vice versa. The 1 position of the sense strand may start with the 2'-F modification, and the 1 position of the antisense strand may start with the 2'- O-methyl modification.

The introduction of one or more motifs of three identical modifications on three consecutive nucleotides to the sense strand and/or antisense strand interrupts the initial modification pattern present in the sense strand and/or antisense strand. This interruption of the modification pattern of the sense and/or antisense strand by introducing one or more motifs of three identical modifications on three consecutive nucleotides to the sense and/or antisense strand surprisingly enhances the gene silencing acitivty to the target gene.

In one embodiment, when the motif of three identical modifications on three consecutive nucleotides is introduced to any of the strands, the modification of the nucleotide next to the motif is a different modification than the modification of the motif. For example, the portion of the sequence containing the motif is "…N_aYYYN_b…," where "Y" represents the modification of the motif of three identical modifications on three consecutive nucleotide, and "N_a" and "N_b" represent a modification to the nucleotide next to the motif "YYY" that is different than the modification of Y, and where N_a and N_b can be the same or different modifications. Altnernatively, N_a and/or N_b may be present or absent when there is a wing modification present.

The RNAi agent 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 strands in any position of the strand. For instance, the internucleotide linkage modification may occur on every

nucleotide on the sense strand and/or antisense strand; each internucleotide linkage modification may occur in an alternating pattern on the sense strand and/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, a double-standed RNAi agent comprises 6-8phosphorothioate internucleotide linkages. In one embodiment, the antisense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus and two phosphorothioate internucleotide linkages at the 3'-terminus, and the sense strand comprises at least two phosphorothioate internucleotide linkages at either the 5'-terminus or the 3'-terminus.

In one embodiment, the RNAi comprises a 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 the duplex region. For example, at least 2, 3, 4, or all the overhang nucleotides may be linked through phosphorothioate or methylphosphonate internucleotide linkage, and optionally, there may be additional phosphorothioate or methylphosphonate internucleotide linkages linking the overhang nucleotide with a paired nucleotide that is next to the overhang nucleotide. For instance, there may be at least two phosphorothioate internucleotide linkages between the terminal three nucleotides, in which two of the three nucleotides are overhang nucleotides, and the third is a paired nucleotide next to the overhang nucleotide. These terminal three nucleotides may be at the 3'-end of the antisense strand, the 3'-end of the sense strand, the 5'-end of the antisense strand, and/or the 5'end of the antisense strand.

In one embodiment, the 2 nucleotide overhang is at the 3'-end of the antisense strand, and there are two phosphorothioate internucleotide linkages between the terminal three nucleotides, wherein two of the three nucleotides are the overhang nucleotides, and the third nucleotide is a paired nucleotide next to the overhang nucleotide. Optionally, the RNAi agent may additionally have two phosphorothioate internucleotide linkages between the terminal three nucleotides at both the 5'-end of the sense strand and at the 5'-end of the antisense strand.

In one embodiment, the RNAi agent comprises mismatch(es) with the target, within the duplex, or combinations thereof. The mistmatch may occur in the overhang region or the duplex region. The base pair may 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 RNAi agent 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 independently selected 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 deoxy-thymine (dT). In another embodiment, the nucleotide at the 3'-end of the antisense strand is deoxy-thymine (dT). In one embodiment, there is a short sequence of deoxy-thymine nucleotides, for example, two dT nucleotides on the 3'-end of the sense and/or antisense strand.

In one embodiment, the sense strand sequence may be represented by formula (I):

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

wherein:

i and j are each independently 0 or 1;

p and q are each independently 0-6;

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

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

each n_p and n_q independently represent an overhang nucleotide;

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

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

In one embodiment, the N_a and/or N_b comprise modifications of alternating pattern.

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

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

$5'\ n_p\text{-}N_a\text{-}YYY\text{-}N_b\text{-}ZZZ\text{-}N_a\text{-}n_q\ 3'$ (Ib);

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

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

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

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

When the sense strand is represented as formula (Id), each N_b independently represents an oligonucleotide sequence comprising 0-10, 0-7, 0-5, 0-4, 0-2 or 0 modified nucleotides. Preferably, N_b is 0, 1, 2, 3, 4, 5 or 6. Each N_a can independently represent an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

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

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

5' n_p-N_a-YYY- N_a-n_q 3' (Ia).

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

In one embodiment, the antisense strand sequence of the RNAi may be represented by formula (II):

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

wherein:

k and l are each independently 0 or 1;

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

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

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

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

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

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

In one embodiment, the N_a' and/or N_b' comprise modifications of alternating pattern.

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

paired nucleotide within the duplex region, from the 5'- end. Preferably, the Y′Y′Y′ motif occurs at positions 11, 12, 13.

In one embodiment, Y′Y′Y′ motif is all 2'-OMe modified nucleotides.

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

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

5' $n_{q'}$-N_a′-Z′Z′Z′-N_b′-Y′Y′Y′-N_a′-$n_{p'}$ 3' (IIb);

5' $n_{q'}$-N_a′-Y′Y′Y′-N_b′-X′X′X′-$n_{p'}$ 3' (IIc); or

5' $n_{q'}$-N_a′- Z′Z′Z′-N_b′-Y′Y′Y′-N_b′- X′X′X′-N_a′-$n_{p'}$ 3' (IId).

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

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

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

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

5' $n_{p'}$-$N_{a'}$-Y'Y'Y'- $N_{a'}$-$n_{q'}$ 3' (Ia).

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

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

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

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

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

The sense strand represented by any one of the above formulas (Ia), (Ib), (Ic), and (Id) forms a duplex with a antisense strand being represented by any one of formulas (IIa), (IIb), (IIc), and (IId), respectively.

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

sense: 5' np -Na-(X X X)i -Nb- Y Y Y -Nb -(Z Z Z)j-Na-nq 3'

antisense: 3' np'-Na'-(X'X'X')k-Nb'-Y'Y'Y'-Nb'-(Z'Z'Z')l-Na'-nq' 5'

(III)

wherein:

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

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

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

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

wherein each np', np, nq', and nq, each of which may or may not be present, independently represents an overhang nucleotide; and

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

In one embodiment, i is 0 and j is 0; or i is 1 and j is 0; or i is 0 and j is 1; or both i and j are 0; or both i and j are 1. In another embodiment, k is 0 and l is 0; or k is 1 and l is 0; k is 0 and l is 1; or both k and l are 0; or both k and l are 1.

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

5' np - Na -Y Y Y -Na-nq 3'

3' np'-Na'-Y′Y′Y′ -Na'nq' 5'

(IIIa)

5' np -Na -Y Y Y -Nb -Z Z Z -Na-nq 3'

3' np'-Na'-Y′Y′Y′-Nb'-Z′Z′Z′-Na'nq' 5'

(IIIb)

5' np-Na- X X X -Nb -Y Y Y - Na-nq 3'

3' np'-Na'-X′X′X′-Nb'-Y′Y′Y′-Na'-nq' 5'

(IIIc)

5' np -Na -X X X -Nb-Y Y Y -Nb- Z Z Z -Na-nq 3'

3' np'-Na'-X′X′X′-Nb'-Y′Y′Y′-Nb'-Z′Z′Z′-Na-nq' 5'

(IIId)

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

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

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

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

Each of X, Y and Z in formulas (III), (IIIa), (IIIb), (IIIc), and (IIId) may be the same or different from each other.

When the RNAi agent is represented by formula (III), (IIIa), (IIIb), (IIIc), and (IIId), at least one of the Y nucleotides may form a base pair with one of the Y′ nucleotides. Alternatively, at least two of the Y nucleotides form base pairs with the corresponding Y′ nucleotides; or all three of the Y nucleotides all form base pairs with the corresponding Y′ nucleotides.

When the RNAi agent is represented by formula (IIIb) or (IIId), at least one of the Z nucleotides may form a base pair with one of the Z′ nucleotides. Alternatively, at least two of the Z nucleotides form base pairs with the corresponding Z′ nucleotides; or all three of the Z nucleotides all form base pairs with the corresponding Z′ nucleotides.

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

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

In one embodiment, when the RNAi agent is represented by formula (IIId), the Na modifications are 2′-O-methyl or 2′–fluoro modifications. In another embodiment, when the RNAi agent is represented by formula (IIId), the Na modifications are 2′-O-methyl or 2′-fluoro modifications and np′ >0 and at least one np′ is linked to a neighboring nucleotide a via phosphorothioate linkage. In yet another embodiment, when the RNAi agent is represented by formula (IIId), the Na modifications are 2′-O-methyl or 2′-fluoro modifications , np′ >0 and at least one np′ is linked to a neighboring nucleotide via phosphorothioate linkage, and the sense strand is conjugated to one or more GalNAc derivatives attached through a bivalent or trivalent branched linker (described below). In another embodiment, when the RNAi agent is represented by formula (IIId), the Na modifications are 2′-O-methyl or 2′-fluoro modifications , np′ >0 and at least one np′ is linked to a neighboring nucleotide via phosphorothioate linkage, the sense strand comprises at least one phosphorothioate linkage, and the sense strand is conjugated to one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

In one embodiment, when the RNAi agent is represented by formula (IIIa), the Na modifications are 2′-O-methyl or 2′-fluoro modifications , np′ >0 and at least one np′ is linked to a neighboring nucleotide via phosphorothioate linkage, the sense strand comprises at least one phosphorothioate linkage, and the sense strand is conjugated to one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

In one embodiment, the RNAi agent is a multimer containing at least two duplexes represented by formula (III), (IIIa), (IIIb), (IIIc), and (IIId), wherein the duplexes are connected by a linker. The linker can be cleavable or non-cleavable. Optionally, the multimer further comprises a ligand. Each of the duplexes can target the same gene or two different genes; or each of the duplexes can target same gene at two different target sites.

In one embodiment, the RNAi agent is a multimer containing three, four, five, six or more duplexes represented by formula (III), (IIIa), (IIIb), (IIIc), and (IIId), wherein the duplexes are connected by a linker. The linker can be cleavable or non-cleavable. Optionally, the multimer further comprises a ligand. Each of the duplexes can target the same gene or two different genes; or each of the duplexes can target same gene at two different target sites.

In one embodiment, two RNAi agents represented by formula (III), (IIIa), (IIIb), (IIIc), and (IIId) are linked to each other at the 5' end, and one or both of the 3' ends and are optionally conjugated to to a ligand. Each of the agents can target the same gene or two different genes; or each of the agents can target same gene at two different target sites.

In certain embodiments, an RNAi agent of the invention may contain a low number of nucleotides containing a 2'-fluoro modification, e.g., 10 or fewer nucleotides with 2'-fluoro modification. For example, the RNAi agent may contain 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 or 0 nucleotides with a 2'-fluoro modification. In a specific embodiment, the RNAi agent of the invention contains 10 nucleotides with a 2'-fluoro modification, e.g., 4 nucleotides with a 2'-fluoro modification in the sense strand and 6 nucleotides with a 2'-fluoro modification in the antisense strand. In another specific embodiment, the RNAi agent of the invention contains 6 nucleotides with a 2'-fluoro

modification, e.g., 4 nucleotides with a 2'-fluoro modification in the sense strand and 2 nucleotides with a 2'-fluoro modification in the antisense strand.

In other embodiments, an RNAi agent of the invention may contain an ultra low number of nucleotides containing a 2'-fluoro modification, e.g., 2 or fewer nucleotides containing a 2'-fluoro modification. For example, the RNAi agent may contain 2, 1 of 0 nucleotides with a 2'-fluoro modification. In a specific embodiment, the RNAi agent may contain 2 nucleotides with a 2'-fluoro modification, *e.g.*, 0 nucleotides with a 2-fluoro modification in the sense strand and 2 nucleotides with a 2'-fluoro modification in the antisense strand.

Various publications describe multimeric RNAi agents that can be used in the methods of the invention. Such publications include WO2007/091269, US Patent No. 7858769, WO2010/141511, WO2007/117686, WO2009/014887 and WO2011/031520 the entire contents of each of which are hereby incorporated herein by reference.

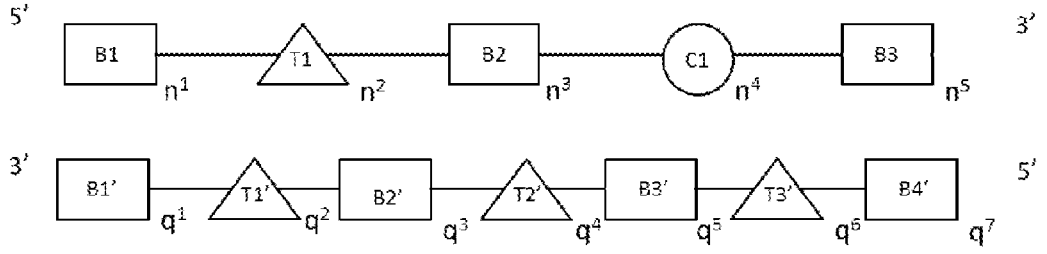
As described in more detail below, the RNAi agent that contains conjugations of one or more carbohydrate moieties to a RNAi agent can optimize one or more properties of the RNAi agent. In many cases, the carbohydrate moiety will be attached to a modified subunit of the RNAi agent. For example, the ribose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

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

The RNAi agents may be conjugated to a ligand *via* a carrier, wherein the carrier can be cyclic group or acyclic group; 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.

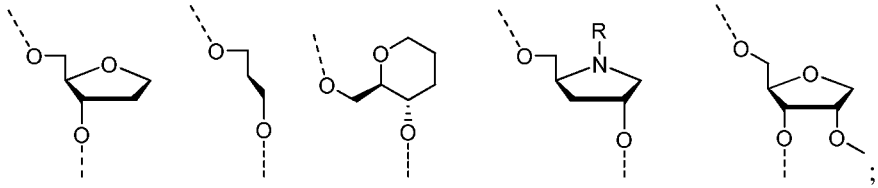
In another embodiment of the invention, an iRNA agent comprises a sense strand and an antisense strand, each strand having 14 to 40 nucleotides. The RNAi agent may be represented by formula (L):



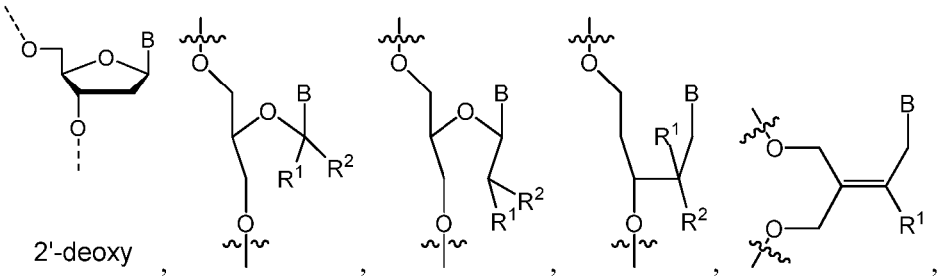
(L),

In formula (L), B1, B2, B3, B1', B2', B3', and B4' each are independently a nucleotide containing a modification selected from the group consisting of 2'-O-alkyl, 2'-substituted alkoxy, 2'-substituted alkyl, 2'-halo, ENA, and BNA/LNA. In certain embodiments, B1, B2, B3, B1', B2', B3', and B4' each contain 2'-OMe modifications. In certain embodiments, B1, B2, B3, B1', B2', B3', and B4' each contain 2'-OMe or 2'-F modifications. In certain embodiments, at least one of B1, B2, B3, B1', B2', B3', and B4' contain 2'-O-N-methylacetamido (2'-O-NMA) modification.

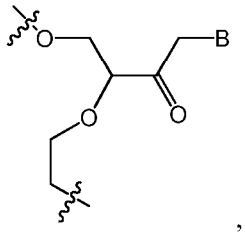
C1 is a thermally destabilizing nucleotide placed at a site opposite to the seed region of the antisense strand (i.e., at positions 2-8 of the 5'-end of the antisense strand). For example, C1 is at a position of the sense strand that pairs with a nucleotide at positions 2-8 of the 5'-end of the antisense strand. In one example, C1 is at position 15 from the 5'-end of the sense strand. C1 nucleotide bears the thermally destabilizing modification which can include abasic modification; mismatch with the opposing nucleotide in the duplex; and sugar modification such as 2'-deoxy modification or acyclic nucleotide *e.g.*, unlocked nucleic acids (UNA) or glycerol nucleic acid (GNA). In certain embodiments, C1 has thermally destabilizing modification selected from the group consisting of: i) mismatch with the opposing nucleotide in the antisense strand; ii) abasic modification selected from the group consisting of:



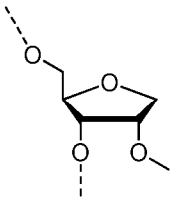
; and iii) sugar modification selected from the group consisting of:



, and



, 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 certain embodiments, the thermally destabilizing modification in C1 is a mismatch selected from the group consisting of G:G, G:A, G:U, G:T, A:A, A:C, C:C, C:U, C:T, U:U, T:T, and U:T; and optionally, at least one nucleobase in the mismatch pair is a 2'-deoxy nucleobase. In one example, the thermally destabilizing modification in C1 is GNA or



.

T1, T1', T2', and T3' each independently represent a nucleotide comprising a modification providing the nucleotide a steric bulk that is less or equal to the steric bulk of a 2'-OMe modification. A steric bulk refers to the sum of steric effects of a modification. Methods for determining steric effects of a modification of a nucleotide are known to one skilled in the art. The modification can be at the 2' position of a ribose sugar of the nucleotide, or a modification to a non-ribose nucleotide, acyclic nucleotide, or the backbone of the nucleotide that is similar or equivalent to the 2' position of the ribose sugar, and provides the nucleotide a steric bulk that is less than or equal to the steric bulk of a 2'-OMe modification. For example, T1, T1', T2', and T3' are each independently selected from DNA, RNA, LNA, 2'-F, and 2'-F-5'-methyl. In certain embodiments, T1 is DNA. In certain embodiments, T1' is DNA, RNA or LNA. In certain embodiments, T2' is DNA or RNA. In certain embodiments, T3' is DNA or RNA.

n^1, n^3, and q^1 are independently 4 to 15 nucleotides in length.

n^5, q^3, and q^7 are independently 1-6 nucleotide(s) in length.

n^4, q^2, and q^6 are independently 1-3 nucleotide(s) in length; alternatively, n^4 is 0.

q^5 is independently 0-10 nucleotide(s) in length.

n^2 and q^4 are independently 0-3 nucleotide(s) in length.

Alternatively, n^4 is 0-3 nucleotide(s) in length.

In certain embodiments, n^4 can be 0. In one example, n^4 is 0, and q^2 and q^6 are 1. In another example, n^4 is 0, and q^2 and q^6 are 1, 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).

In certain embodiments, n^4, q^2, and q^6 are each 1.

In certain embodiments, n^2, n^4, q^2, q^4, and q^6 are each 1.

In certain embodiments, C1 is at position 14-17 of the 5'-end of the sense strand, when the sense strand is 19-22 nucleotides in length, and n^4 is 1. In certain embodiments, C1 is at position 15 of the 5'-end of the sense strand

In certain embodiments, T3' starts at position 2 from the 5' end of the antisense strand. In one example, T3' is at position 2 from the 5' end of the antisense strand and q^6 is equal to 1.

In certain embodiments, T1' starts at position 14 from the 5' end of the antisense strand. In one example, T1' is at position 14 from the 5' end of the antisense strand and q^2 is equal to 1.

In an exemplary embodiment, T3' starts from position 2 from the 5' end of the antisense strand and T1' starts from position 14 from the 5' end of the antisense strand. In one example, T3' starts from position 2 from the 5' end of the antisense strand and q^6 is equal to 1 and T1' starts from position 14 from the 5' end of the antisense strand and q^2 is equal to 1.

In certain embodiments, T1' and T3' are separated by 11 nucleotides in length (*i.e.* not counting the T1' and T3' nucleotides).

In certain embodiments, T1' is at position 14 from the 5' end of the antisense strand. In one example, T1' is at position 14 from the 5' end of the antisense strand and q^2 is equal to 1, and the modification at the 2' position or positions in a non-ribose, acyclic or backbone that provide less steric bulk than a 2'-OMe ribose.

In certain embodiments, T3' is at position 2 from the 5' end of the antisense strand. In one example, T3' is at position 2 from the 5' end of the antisense strand and q^6 is equal to 1, and the modification at the 2' position or positions in a non-ribose, acyclic or backbone that provide less than or equal to steric bulk than a 2'-OMe ribose.

In certain embodiments, T1 is at the cleavage site of the sense strand. In one example, T1 is at position 11 from the 5' end of the sense strand, when the sense strand is 19-22 nucleotides in length, and n^2 is 1. In an exemplary embodiment, T1 is at the cleavage site of the sense strand at position 11 from the 5' end of the sense strand, when the sense strand is 19-22 nucleotides in length, and n^2 is 1,

In certain embodiments, T2' starts at position 6 from the 5' end of the antisense strand. In one example, T2' is at positions 6-10 from the 5' end of the antisense strand, and q^4 is 1.

In an exemplary embodiment, T1 is at the cleavage site of the sense strand, for instance, at position 11 from the 5' end of the sense strand, when the sense strand is 19-22 nucleotides in length, and n^2 is 1; T1' is at position 14 from the 5' end of the antisense strand, and q^2 is equal to 1, and the modification to T1' is at the 2' position of a ribose sugar or at positions in a non-ribose, acyclic or backbone that provide less steric bulk than a 2'-OMe ribose; T2' is at positions 6-10 from the 5' end of the antisense strand, and q^4 is 1; and T3' is at position 2 from the 5' end of the antisense strand, and q^6 is equal to 1, and the modification to T3' is at the 2' position or at positions in a non-ribose, acyclic or backbone that provide less than or equal to steric bulk than a 2'-OMe ribose.

In certain embodiments, T2' starts at position 8 from the 5' end of the antisense strand. In one example, T2' starts at position 8 from the 5' end of the antisense strand, and q^4 is 2.

In certain embodiments, T2' starts at position 9 from the 5' end of the antisense strand. In one example, T2' is at position 9 from the 5' end of the antisense strand, and q^4 is 1.

In certain embodiments, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 1, B3' is 2'-OMe or 2'-F, q^5 is 6, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within positions 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).

In certain embodiments, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 1, B3' is 2'-OMe or 2'-F, q^5 is 6, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within positions 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).

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within positions 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).

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 6, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 7, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 6, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 7, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within positions 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).

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 1, B3' is 2'-OMe or 2'-F, q^5 is 6, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 1, B3' is 2'-OMe or 2'-F, q^5 is 6, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within positions 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).

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 5, T2' is 2'-F, q^4 is 1, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; optionally with at least 2 additional TT at the 3'-end of the antisense strand.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 5, T2' is 2'-F, q^4 is 1, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; optionally with at least 2 additional TT at the 3'-end of the antisense strand; with two phosphorothioate internucleotide linkage modifications within positions 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).

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within positions 1-5 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end).

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1.

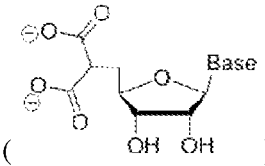
In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within positions 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).

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1.

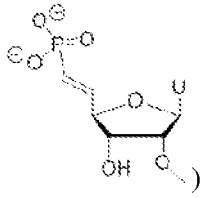
In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within positions 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).

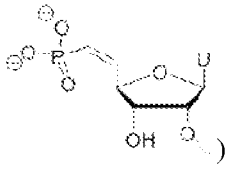
The RNAi agent can comprise a phosphorus-containing group at the 5'-end of the sense strand or antisense strand. The 5'-end phosphorus-containing group can be 5'-end phosphate (5'-P), 5'-end phosphorothioate (5'-PS), 5'-end phosphorodithioate (5'-PS_2), 5'-end vinylphosphonate (5'-VP), 5'-end methylphosphonate (MePhos), or 5'-deoxy-5'-*C*-malonyl



( ). When the 5'-end phosphorus-containing group is 5'-end vinylphosphonate (5'-VP), the 5'-VP can be either 5'-*E*-VP isomer (i.e., *trans*-vinylphosphate,



), 5'-*Z*-VP isomer (i.e., *cis*-vinylphosphate,



), or mixtures thereof.

In certain embodiments, the RNAi agent comprises a phosphorus-containing group at the 5'-end of the sense strand. In certain embodiments, the RNAi agent comprises a phosphorus-containing group at the 5'-end of the antisense strand.

In certain embodiments, the RNAi agent comprises a 5'-P. In certain embodiments, the RNAi agent comprises a 5'-P in the antisense strand.

In certain embodiments, the RNAi agent comprises a 5'-PS. In certain embodiments, the RNAi agent comprises a 5'-PS in the antisense strand.

In certain embodiments, the RNAi agent comprises a 5'-VP. In certain embodiments, the RNAi agent comprises a 5'-VP in the antisense strand. In certain embodiments, the RNAi agent comprises a 5'-*E*-VP in the antisense strand. In certain embodiments, the RNAi agent comprises a 5'-*Z*-VP in the antisense strand.

In certain embodiments, the RNAi agent comprises a 5'-PS_2. In certain embodiments, the RNAi agent comprises a 5'-PS_2 in the antisense strand.

In certain embodiments, the RNAi agent comprises a 5'-PS_2. In certain embodiments, the RNAi agent comprises a 5'-deoxy-5'-*C*-malonyl in the antisense strand.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1. The RNAi agent also comprises a 5'-PS.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1. The RNAi agent also comprises a 5'-P.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1. The RNAi agent also comprises a 5'-VP. The 5'-VP may be 5'-*E*-VP, 5'-*Z*-VP, or combination thereof.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1. The RNAi agent also comprises a 5'- PS_2.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1. The RNAi agent also comprises a 5'-deoxy-5'-*C*-malonyl.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; 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). The RNAi agent also comprises a 5'-P.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; 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). The RNAi agent also comprises a 5'-PS.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; 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). The RNAi agent also comprises a 5'-VP. The 5'-VP may be 5'-*E*-VP, 5'-*Z*-VP, or combination thereof.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; 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). The RNAi agent also comprises a 5'-PS_2.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; 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). The RNAi agent also comprises a 5'-deoxy-5'-*C*-malonyl.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1. The RNAi agent also comprises a 5'-P.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1. The dsRNA agent also comprises a 5'-PS.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1. The RNAi agent also comprises a 5'-VP. The 5'-VP may be 5'-*E*-VP, 5'-*Z*-VP, or combination thereof.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1. The RNAi agent also comprises a 5'- PS_2.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1. The RNAi agent also comprises a 5'-deoxy-5'-*C*-malonyl.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end). The RNAi agent also comprises a 5'-P.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end). The RNAi agent also comprises a 5'-PS.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting

from the 5'-end). The RNAi agent also comprises a 5'-VP. The 5'-VP may be 5'-*E*-VP, 5'-*Z*-VP, or combination thereof.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end). The RNAi agent also comprises a 5'- PS_2.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end). The RNAi agent also comprises a 5'-deoxy-5'-*C*-malonyl.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1. The RNAi agent also comprises a 5'- P.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1. The RNAi agent also comprises a 5'- PS.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1. The RNAi agent also comprises a 5'- VP. The 5'-VP may be 5'-*E*-VP, 5'-*Z*-VP, or combination thereof.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1. The dsRNA RNA agent also comprises a 5'- PS_2.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1. The RNAi agent also comprises a 5'-deoxy-5'-*C*-malonyl.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1; 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). The RNAi agent also comprises a 5'-P.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1; 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). The RNAi agent also comprises a 5'-PS.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1; 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). The RNAi agent also comprises a 5'-VP. The 5'-VP may be 5'-*E*-VP, 5'-*Z*-VP, or combination thereof.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1; 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). The RNAi agent also comprises a 5'-PS_2.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1; 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). The RNAi agent also comprises a 5'-deoxy-5'-*C*-malonyl.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1. The RNAi agent also comprises a 5'- P.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1. The RNAi agent also comprises a 5'- PS.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1. The RNAi agent also comprises a 5'- VP. The 5'-VP may be 5'-*E*-VP, 5'-*Z*-VP, or combination thereof.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1. The RNAi agent also comprises a 5'- PS_2.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1. The RNAi agent also comprises a 5'-deoxy-5'-*C*-malonyl.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1; 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). The RNAi agent also comprises a 5'- P.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1; 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). The RNAi agent also comprises a 5'- PS.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1; 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). The RNAi agent also comprises a 5'- VP. The 5'-VP may be 5'-*E*-VP, 5'-*Z*-VP, or combination thereof.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1; 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). The RNAi agent also comprises a 5'- PS_2.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1; 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). The RNAi agent also comprises a 5'-deoxy-5'-*C*-malonyl.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; 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). The RNAi agent also comprises a 5'-P and a targeting ligand. In certain embodiments, the 5'-P is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; 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). The RNAi agent also comprises a 5'-PS and a targeting ligand. In certain embodiments, the 5'-PS is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; 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). The RNAi agent also comprises a 5'-VP (*e.g.*, a 5'-*E*-VP, 5'-*Z*-VP, or combination thereof), and a targeting ligand.

In certain embodiments, the 5'-VP is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; 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). The RNAi agent also comprises a 5'-PS_2 and a targeting ligand. In certain embodiments, the 5'-PS_2 is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; 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). The RNAi agent also comprises a 5'-deoxy-5'-*C*-malonyl and a targeting ligand. In certain embodiments, the 5'-deoxy-5'-*C*-malonyl is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end). The RNAi agent also comprises a 5'-P and a targeting ligand. In certain embodiments, the 5'-P is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end). The RNAi agent also comprises a 5'-PS and a targeting ligand. In certain embodiments, the 5'-PS is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end). The RNAi agent also comprises a 5'-VP (*e.g.*, a 5'-*E*-VP, 5'-*Z*-VP, or combination thereof) and a targeting ligand. In certain embodiments, the 5'-VP is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end). The RNAi agent also comprises a 5'-PS_2 and a targeting ligand. In certain embodiments, the 5'-PS_2 is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end). The RNAi agent also comprises a 5'-deoxy-5'-*C*-malonyl and a targeting ligand. In certain embodiments, the 5'-deoxy-5'-*C*-malonyl is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1; 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). The RNAi agent also comprises a 5'-P and a targeting ligand. In certain embodiments, the 5'-P is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1; 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). The RNAi agent also comprises a 5'-PS and a targeting ligand. In certain embodiments, the 5'-PS is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1; 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). The RNAi agent also comprises a 5'-VP (*e.g.*, a 5'-*E*-VP, 5'-*Z*-VP, or combination thereof) and a targeting ligand. In certain embodiments, the 5'-VP is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1; 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). The RNAi agent also comprises a 5'-PS_2 and a targeting ligand. In certain embodiments, the 5'-PS_2 is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1,

B4' is 2'-F, and q^7 is 1; 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). The RNAi agent also comprises a 5'-deoxy-5'-*C*-malonyl and a targeting ligand. In certain embodiments, the 5'-deoxy-5'-*C*-malonyl is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1; 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). The RNAi agent also comprises a 5'-P and a targeting ligand. In certain embodiments, the 5'-P is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1; 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). The RNAi agent also comprises a 5'- PS and a targeting ligand. In certain embodiments, the 5'-PS is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1; 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). The RNAi agent also comprises a 5'- VP (*e.g.*, a 5'-*E*-VP, 5'-*Z*-VP, or combination thereof) and a targeting ligand. In certain embodiments, the 5'-VP

is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1; 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). The RNAi agent also comprises a 5'- PS_2 and a targeting ligand. In certain embodiments, the 5'-PS_2 is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1; 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). The RNAi agent also comprises a 5'-deoxy-5'-*C*-malonyl and a targeting ligand. In certain embodiments, the 5'-deoxy-5'-*C*-malonyl is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

In a particular embodiment, an RNAi agent of the present invention comprises:

(a) a sense strand having:

(i) a length of 21 nucleotides;

(ii) 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, an RNAi agent of the present invention comprises:

(a) a sense strand having:

(i) a length of 21 nucleotides;

(ii) 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 RNAi 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, an RNAi agent of the present invention comprises:

(a) a sense strand having:

(i) a length of 21 nucleotides;

(ii) 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 RNAi 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, an RNAi agent of the present invention comprises:

(a) a sense strand having:

(i) a length of 21 nucleotides;

(ii) 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 RNAi 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, an RNAi agent of the present invention comprises:

(a) a sense strand having:

(i) a length of 21 nucleotides;

(ii) 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 RNAi 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, a RNAi agent of the present invention comprises:

(a) a sense strand having:

(i) a length of 21 nucleotides;

(ii) 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 RNAi 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, an RNAi agent of the present invention comprises:

(a) a sense strand having:

(i) a length of 21 nucleotides;

(ii) 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 RNAi 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, a RNAi agent of the present invention comprises:

(a) a sense strand having:

(i) a length of 21 nucleotides;

(ii) 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 RNAi 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, a RNAi agent of the present invention comprises:

(a) a sense strand having:

(i) a length of 21 nucleotides;

(ii) 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 RNAi 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, a RNAi agent of the present invention comprises:

(a) a sense strand having:

(i) a length of 19 nucleotides;

(ii) 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 RNAi 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 certain embodiments, the iRNA for use in the methods of the invention is an agent selected from agents listed in Tables 2, 3, 7, 8, 10, 11, or 13. In one embodiment, the agent is AD-288917. In another embodiment, the agent is AD-288996. In another embodiment, the agent is AD-413639. In one embodiment, the agent is AD-413644. In another embodiment, the agent is AD-413669. These agents may further comprise a ligand.

IV. iRNAs Conjugated to Ligands

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

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

Ligands can include a naturally occurring substance, such as a protein (*e.g.*, human serum albumin (HSA), low-density lipoprotein (LDL), or globulin); carbohydrate (*e.g.*, a dextran, pullulan, chitin, chitosan, inulin, cyclodextrin, N-acetylglucosamine, N-acetylgalactosamine or hyaluronic acid); or a lipid. The ligand can also be a recombinant or synthetic molecule, such as a synthetic polymer, *e.g.*, a synthetic polyamino acid. Examples of polyamino acids include polyamino acid is a polylysine (PLL), poly L-aspartic acid, poly L-glutamic acid, styrene-maleic acid anhydride copolymer, poly(L-lactide-co-glycolied) copolymer, divinyl ether-maleic anhydride copolymer, N-(2-hydroxypropyl)methacrylamide copolymer (HMPA), polyethylene glycol (PEG), polyvinyl alcohol (PVA), polyurethane, poly(2-ethylacryllic acid), N-isopropylacrylamide polymers, or polyphosphazine. Example of polyamines include: polyethylenimine, polylysine (PLL), spermine, spermidine, polyamine, pseudopeptide-polyamine, peptidomimetic polyamine, dendrimer polyamine, arginine, amidine, protamine, cationic lipid, cationic porphyrin, quaternary salt of a polyamine, or an alpha helical peptide.

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

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

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

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

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

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

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

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

or nucleoside-conjugate precursors that already bear the ligand molecule, or non-nucleoside ligand-bearing building blocks.

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

A. Lipid Conujugates

In one embodiment, the ligand or conjugate is a lipid or lipid-based molecule. Such a lipid or lipid-based molecule preferably binds a serum protein, *e.g.*, human serum albumin (HSA). An HSA binding ligand allows for distribution of the conjugate to a target tissue, *e.g.*, a non-kidney target tissue of the body. For example, the target tissue can be the liver, including parenchymal cells of the liver. Other molecules that can bind HSA can also be used as ligands. For example, neproxin or aspirin can be used. A lipid or lipid-based ligand can (a) increase resistance to degradation of the conjugate, (b) increase targeting or transport into a target cell or cell membrane, and/or (c) can be used to adjust binding to a serum protein, *e.g.*, HSA.

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

In a preferred embodiment, the lipid based ligand binds HSA. Preferably, it binds HSA with a sufficient affinity such that the conjugate will be preferably distributed to a non-kidney tissue. However, it is preferred that the affinity not be so strong that the HSA-ligand binding cannot be reversed.

In another preferred embodiment, the lipid based ligand binds HSA weakly or not at all, such that the conjugate will be preferably distributed to the kidney. Other moieties that target to kidney cells can also be used in place of or in addition to the lipid based ligand.

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

B. Cell Permeation Agents

In another aspect, the ligand is a cell-permeation agent, preferably a helical cell-permeation agent. Preferably, the agent is amphipathic. An exemplary agent is a peptide such as tat or antennopedia. If the agent is a peptide, it can be modified, including a peptidylmimetic, invertomers,

non-peptide or pseudo-peptide linkages, and use of D-amino acids. The helical agent is preferably an alpha-helical agent, which preferably has a lipophilic and a lipophobic phase.

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

A peptide or peptidomimetic can be, for example, a cell permeation peptide, cationic peptide, amphipathic peptide, or hydrophobic peptide (*e.g.*, consisting primarily of Tyr, Trp or Phe). The peptide moiety can be a dendrimer peptide, constrained peptide or crosslinked peptide. In another alternative, the peptide moiety can include a hydrophobic membrane translocation sequence (MTS). An exemplary hydrophobic MTS-containing peptide is RFGF having the amino acid sequence AAVALLPAVLLALLAP (SEQ ID NO: 2977). An RFGF analogue (*e.g.*, amino acid sequence AALLPVLLAAP (SEQ ID NO:2978) containing a hydrophobic MTS can also be a targeting moiety. The peptide moiety can be a "delivery" peptide, which can carry large polar molecules including peptides, oligonucleotides, and protein across cell membranes. For example, sequences from the HIV Tat protein (GRKKRRQRRRPPQ (SEQ ID NO: 2979) and the Drosophila Antennapedia protein (RQIKIWFQNRRMKWKK (SEQ ID NO: 2980) have been found to be capable of functioning as delivery peptides. A peptide or peptidomimetic can be encoded by a random sequence of DNA, such as a peptide identified from a phage-display library, or one-bead-one-compound (OBOC) combinatorial library (Lam *et al.*, Nature, 354:82-84, 1991). Examples of a peptide or peptidomimetic tethered to a dsRNA agent via an incorporated monomer unit for cell targeting purposes is an arginine-glycine-aspartic acid (RGD)-peptide, or RGD mimic. A peptide moiety can range in length from about 5 amino acids to about 40 amino acids. The peptide moieties can have a structural modification, such as to increase stability or direct conformational properties. Any of the structural modifications described below can be utilized.

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

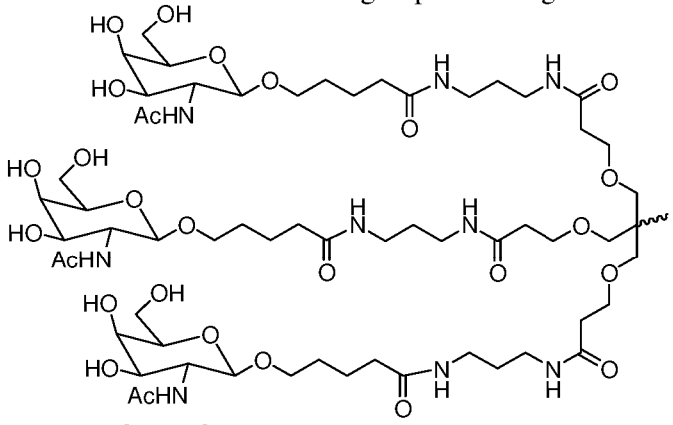
A "cell permeation peptide" is capable of permeating a cell, *e.g.,* a microbial cell, such as a bacterial or fungal cell, or a mammalian cell, such as a human cell. A microbial cell-permeating peptide can be, for example, a α-helical linear peptide (*e.g.*, LL-37 or Ceropin P1), a disulfide bond-containing peptide (*e.g.*, α -defensin, β-defensin or bactenecin), or a peptide containing only one or two dominating amino acids (*e.g.*, PR-39 or indolicidin). A cell permeation peptide can also include a nuclear localization signal (NLS). For example, a cell permeation peptide can be a bipartite

amphipathic peptide, such as MPG, which is derived from the fusion peptide domain of HIV-1 gp41 and the NLS of SV40 large T antigen (Simeoni *et al.*, Nucl. Acids Res. 31:2717-2724, 2003).

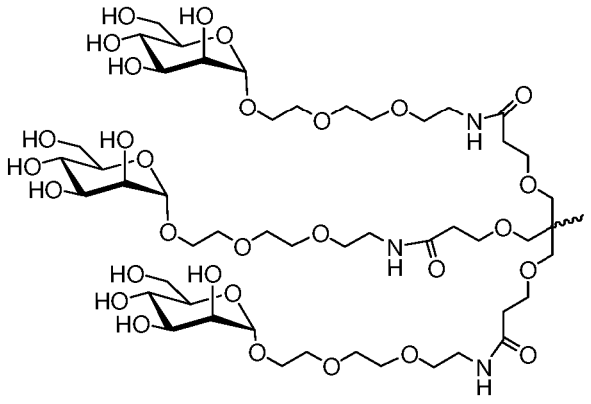
C. Carbohydrate Conjugates

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

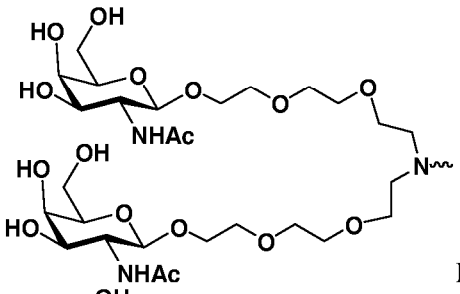
In one embodiment, a carbohydrate conjugate for use in the compositions and methods of the invention is selected from the group consisting of:



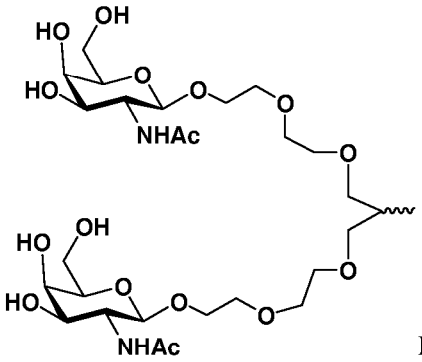
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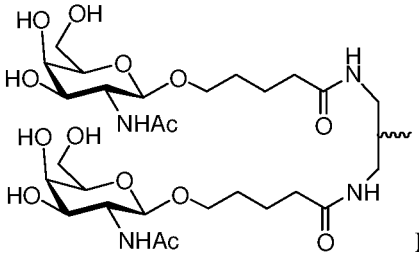
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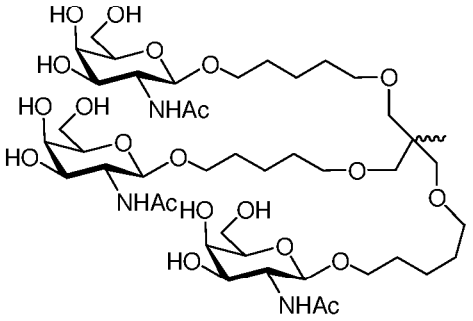
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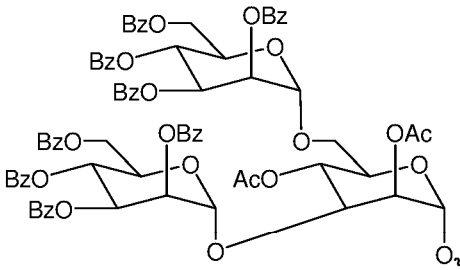
Formula V,



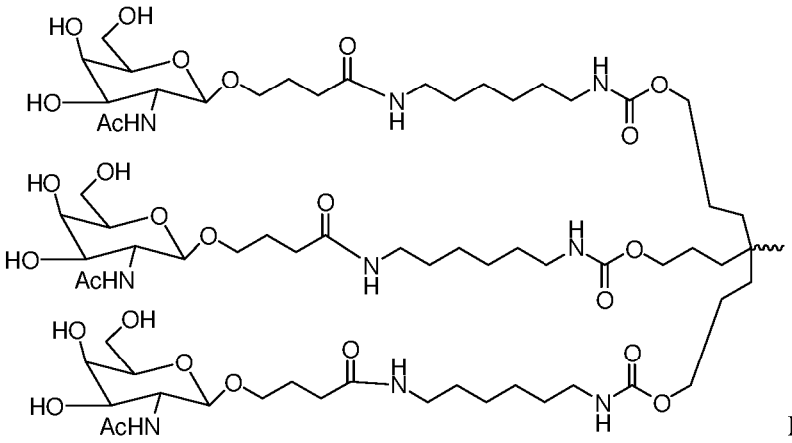
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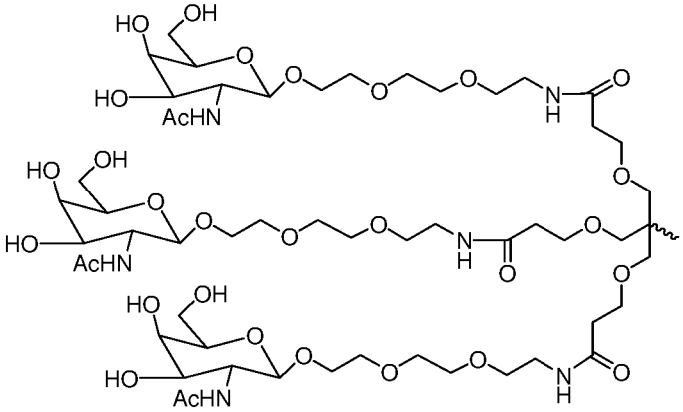
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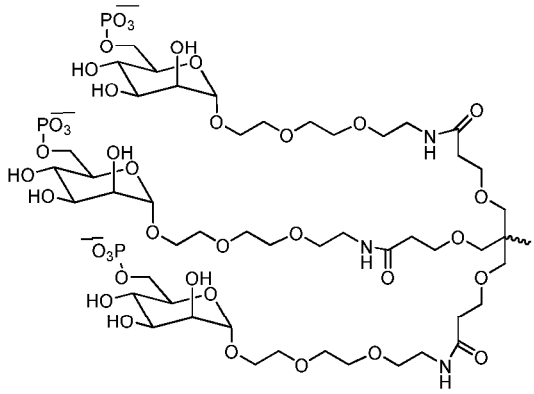
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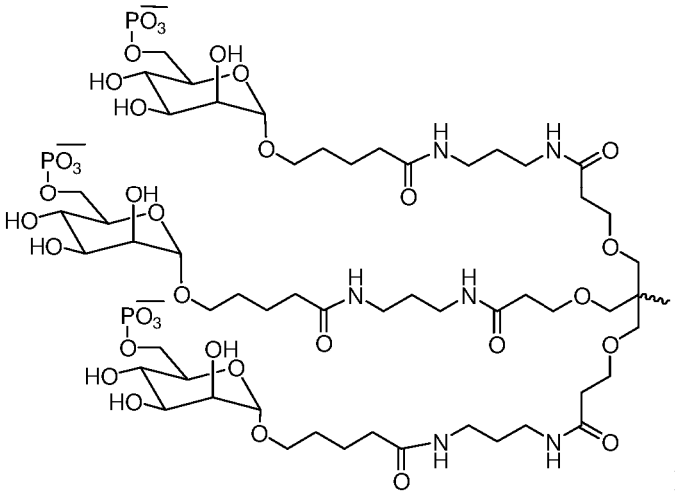
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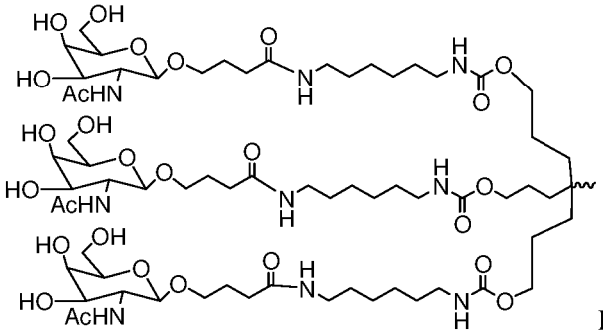
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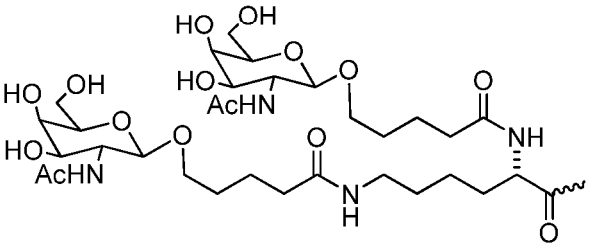
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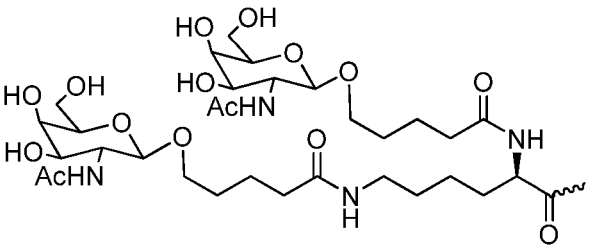
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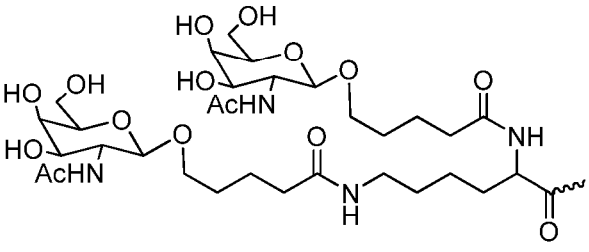
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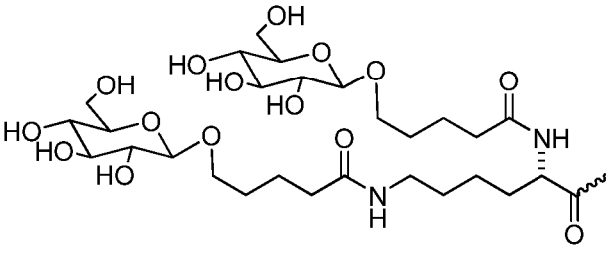
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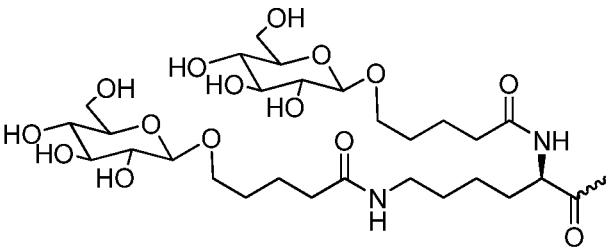
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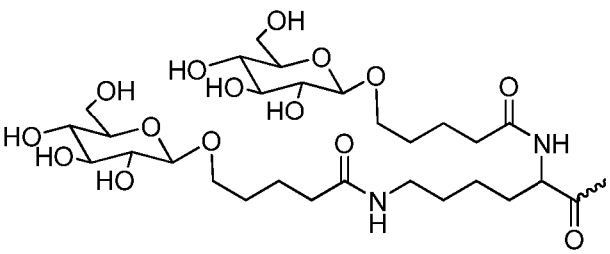
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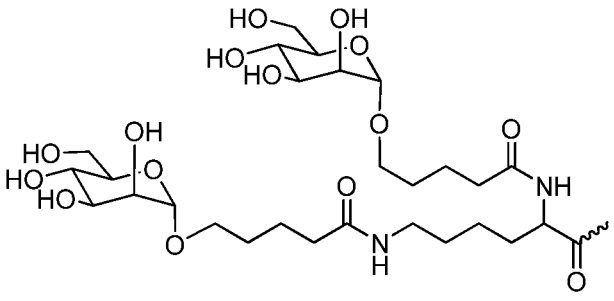
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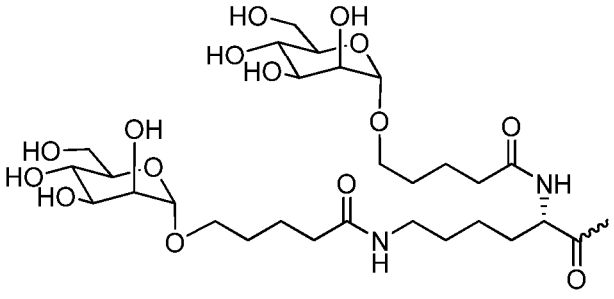
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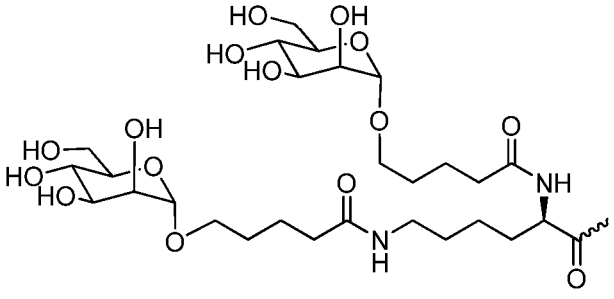
Formula XIX,



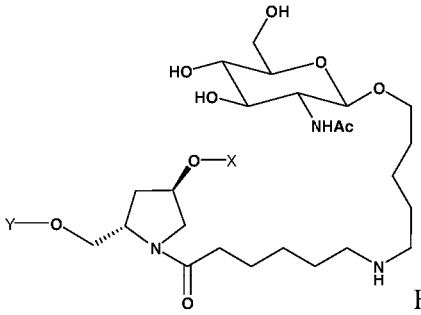
Formula XX,



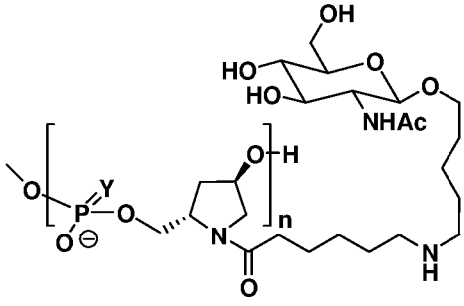
Formula XXI,



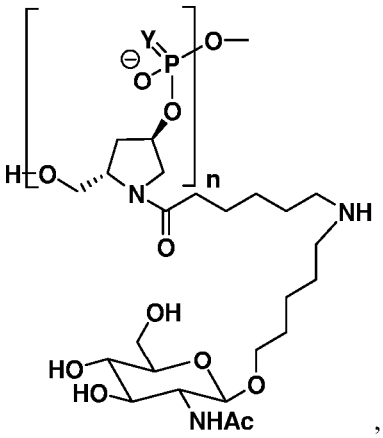
Formula XXII,



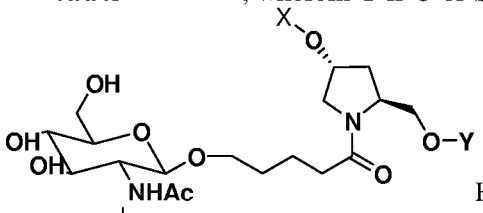
Formula XXIII;



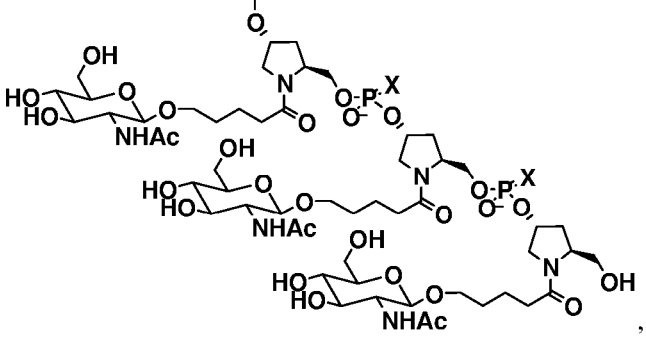
, wherein Y is O or S and n is 3 -6 (Formula XXIV);



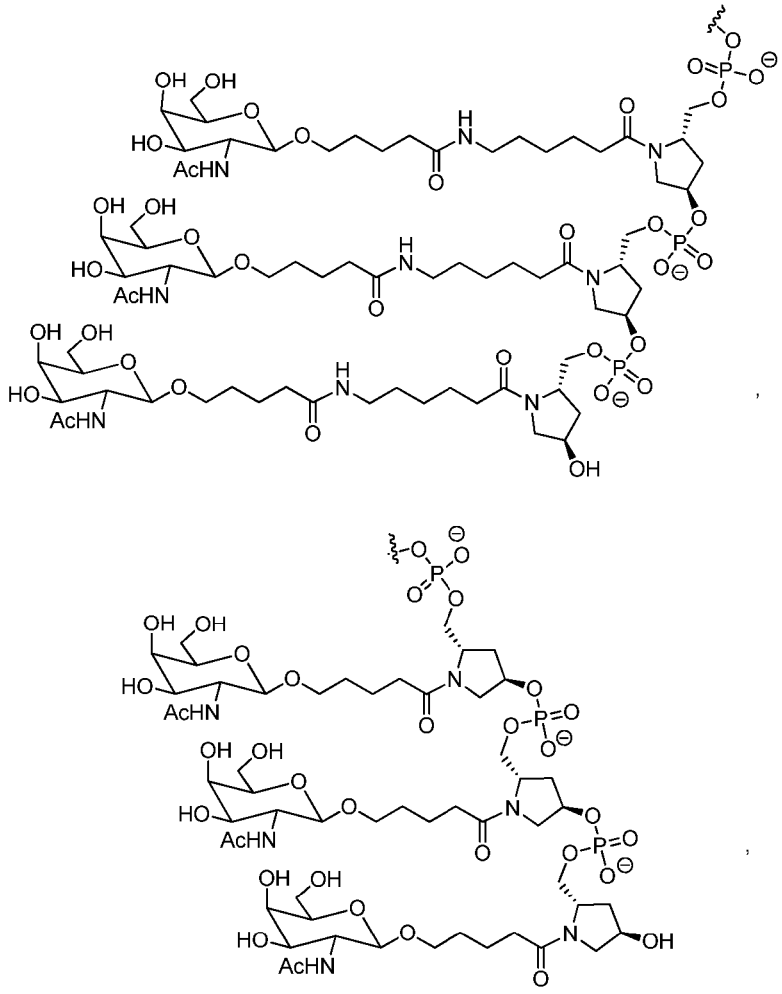
, wherein Y is O or S and n is 3-6 (Formula XXV);



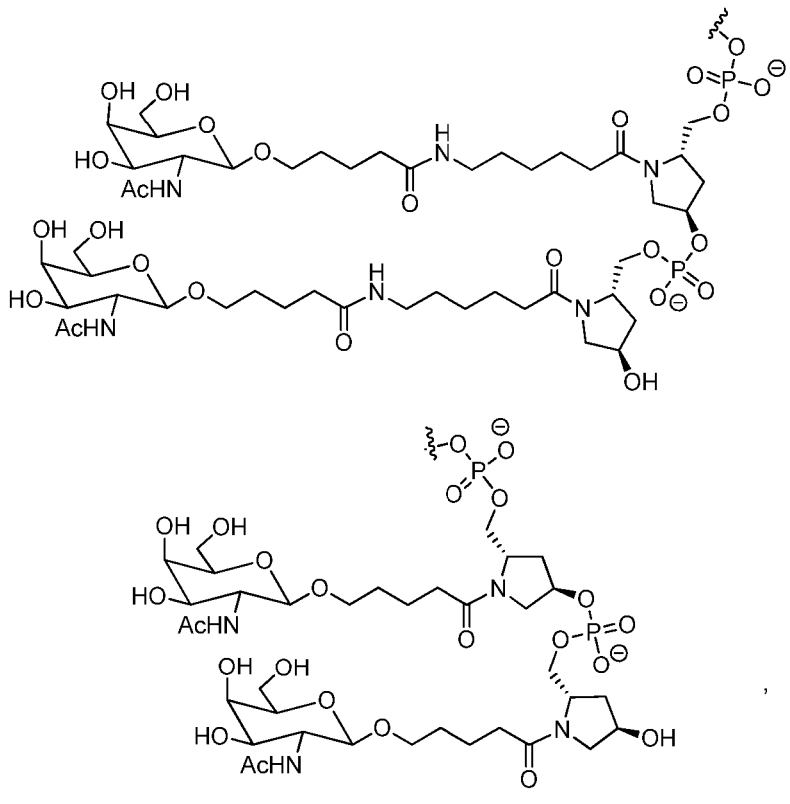
Formula XXVI;



, wherein X is O or S (Formula XXVII);

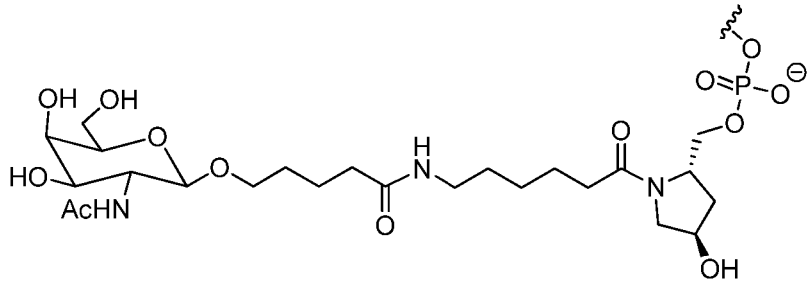


Formula XXVIII; Formula XXIX;

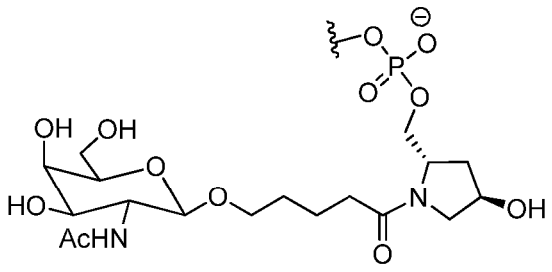


Formula XXX;

Formula XXXI;

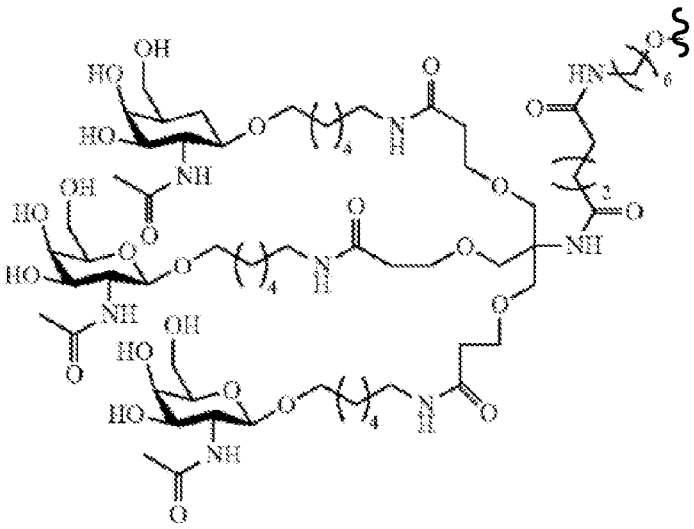


, and



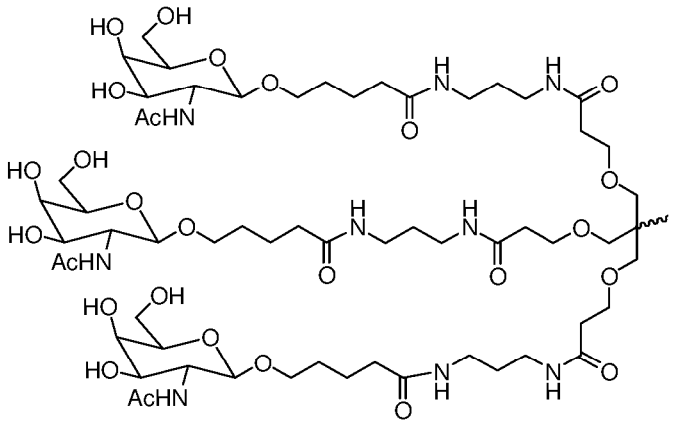
Formula XXXII;

Formula XXXIII.



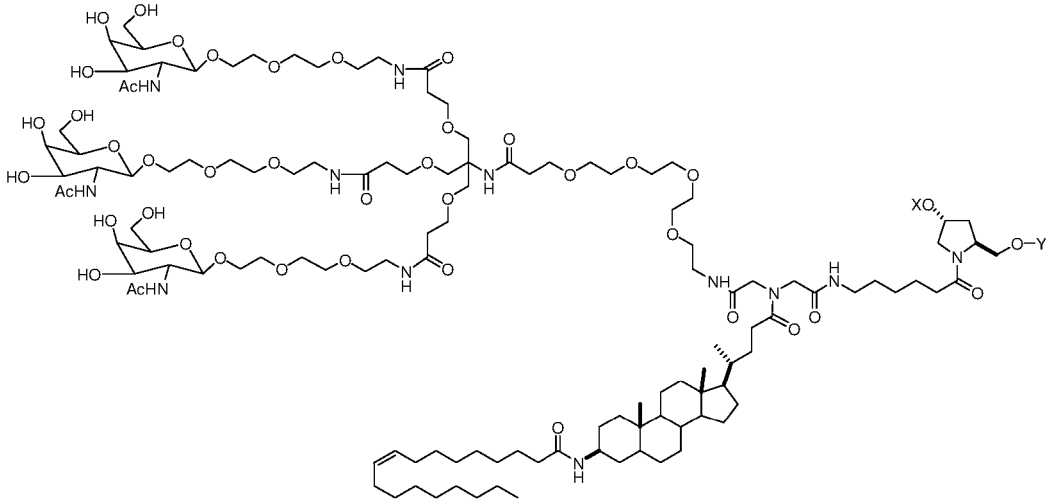
Formula XXXIV.

In another embodiment, a carbohydrate conjugate for use in the compositions and methods of the invention is a monosaccharide. In one embodiment, the monosaccharide is an N-acetylgalactosamine, such as



Formula II.

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



(Formula XXXVI),

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

In certain embodiments of the invention, the GalNAc or GalNAc derivative is attached to an iRNA agent of the invention *via* a monovalent linker. In some embodiments, the GalNAc or GalNAc derivative is attached to an iRNA agent of the invention *via* a bivalent linker. In yet other embodiments of the invention, the GalNAc or GalNAc derivative is attached to an iRNA agent of the invention *via* a trivalent linker.

In one embodiment, the double stranded RNAi agents of the invention comprise one GalNAc or GalNAc derivative attached to the iRNA agent, *e.g.,* the 3' or 5'end of the sense strand of a dsRNA agent as described herein. In another embodiment, the double stranded RNAi agents of the invention comprise a plurality (*e.g.,* 2, 3, 4, 5, or 6) of GalNAc or GalNAc derivatives, each independently attached to a plurality of nucleotides of the double stranded RNAi agent through a plurality of monovalent linkers.

In some embodiments, for example, when the two strands of an iRNA agent of the invention are part of one larger molecule connected by an uninterrupted chain of nucleotides between the 3'-end of one strand and the 5'-end of the respective other strand forming a hairpin loop comprising, a plurality of unpaired nucleotides, each unpaired nucleotide within the hairpin loop may independently comprise a GalNAc or GalNAc derivative attached *via* a monovalent linker.

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

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

D. Linkers

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

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

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

Cleavable linking groups are susceptible to cleavage agents, *e.g.*, pH, redox potential or the presence of degradative molecules. Generally, cleavage agents are more prevalent or found at higher levels or activities inside cells than in serum or blood. Examples of such degradative agents include:

redox agents which are selected for particular substrates or which have no substrate specificity, including, *e.g.*, oxidative or reductive enzymes or reductive agents such as mercaptans, present in cells, that can degrade a redox cleavable linking group by reduction; esterases; endosomes or agents that can create an acidic environment, *e.g.*, those that result in a pH of five or lower; enzymes that can hydrolyze or degrade an acid cleavable linking group by acting as a general acid, peptidases (which can be substrate specific), and phosphatases.

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

A linker can include a cleavable linking group that is cleavable by a particular enzyme. The type of cleavable linking group incorporated into a linker can depend on the cell to be targeted. For example, a liver-targeting ligand can be linked to a cationic lipid through a linker that includes an ester group. Liver cells are rich in esterases, and therefore the linker will be cleaved more efficiently in liver cells than in cell types that are not esterase-rich. Other cell-types rich in esterases include cells of the lung, renal cortex, and testis.

Linkers that contain peptide bonds can be used when targeting cell types rich in peptidases, such as liver cells and synoviocytes.

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

i. Redox cleavable linking groups

In one embodment, a cleavable linking group is a redox cleavable linking group that is cleaved upon reduction or oxidation. An example of reductively cleavable linking group is a disulphide linking group (-S-S-). To determine if a candidate cleavable linking group is a suitable "reductively cleavable linking group," or for example is suitable for use with a particular iRNA moiety and particular targeting agent one can look to methods described herein. For example, a

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

*ii. Phosphate-based cleavable linking groups*In another embodiment, a cleavable linker comprises a phosphate-based cleavable linking group. A phosphate-based cleavable linking group is cleaved by agents that degrade or hydrolyze the phosphate group. An example of an agent that cleaves phosphate groups in cells are enzymes such as phosphatases in cells. Examples of phosphate-based linking groups are -O-P(O)(ORk)-O-, -O-P(S)(ORk)-O-, -O-P(S)(SRk)-O-, -S-P(O)(ORk)-O-, -O-P(O)(ORk)-S-, -S-P(O)(ORk)-S-, -O-P(S)(ORk)-S-, -S-P(S)(ORk)-O-, -O-P(O)(Rk)-O-, -O-P(S)(Rk)-O-, -S-P(O)(Rk)-O-, -S-P(S)(Rk)-O-, -S-P(O)(Rk)-S-, -O-P(S)(Rk)-S-. 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.

iii. Acid cleavable linking groups

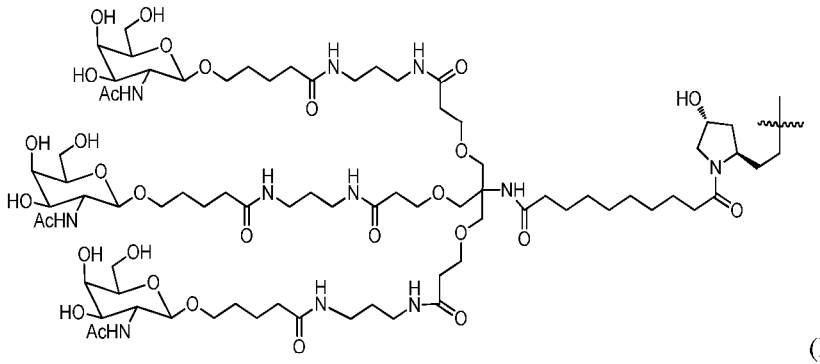
In another embodiment, a cleavable linker comprises an acid cleavable linking group. An *a*cid cleavable linking group is a linking group that is cleaved under acidic conditions. In preferred embodiments acid cleavable linking groups are cleaved in an acidic environment with a pH of about 6.5 or lower (*e.g.*, about 6.0, 5.75, 5.5, 5.25, 5.0, or lower), or by agents such as enzymes that can act as a general acid. In a cell, specific low pH organelles, such as endosomes and lysosomes can provide a cleaving environment for acid cleavable linking groups. Examples of acid cleavable linking groups include but are not limited to hydrazones, esters, and esters of amino acids. Acid cleavable groups can have the general formula -C=NN-, C(O)O, or -OC(O). 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.

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

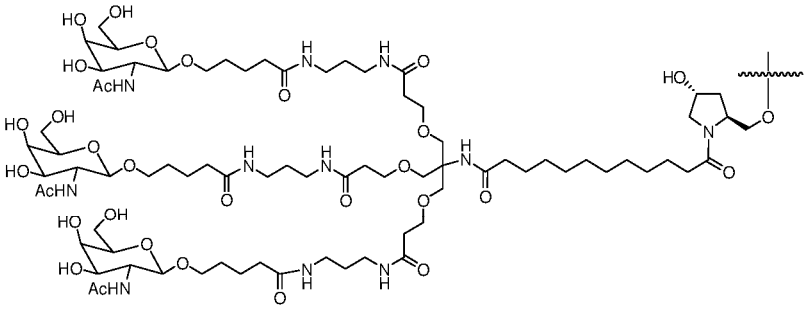
v. Peptide-based cleaving groups

In yet another embodiment, a cleavable linker comprises a peptide-based cleavable linking group. A peptide-based cleavable linking group is cleaved by enzymes such as peptidases and proteases in cells. Peptide-based cleavable linking groups are peptide bonds formed between amino acids to yield oligopeptides (*e.g.*, dipeptides, tripeptides *etc.*) and polypeptides. Peptide-based cleavable groups do not include the amide group (-C(O)NH-). The amide group can be formed between any alkylene, alkenylene or alkynelene. A peptide bond is a special type of amide bond formed between amino acids to yield peptides and proteins. The peptide based cleavage group is generally limited to the peptide bond (*i.e.*, the amide bond) formed between amino acids yielding peptides and proteins and does not include the entire amide functional group. Peptide-based cleavable linking groups have the general formula – NHCHRAC(O)NHCHRBC(O)- , where RA and RB are the R groups of the two adjacent amino acids. These candidates can be evaluated using methods analogous to those described above.

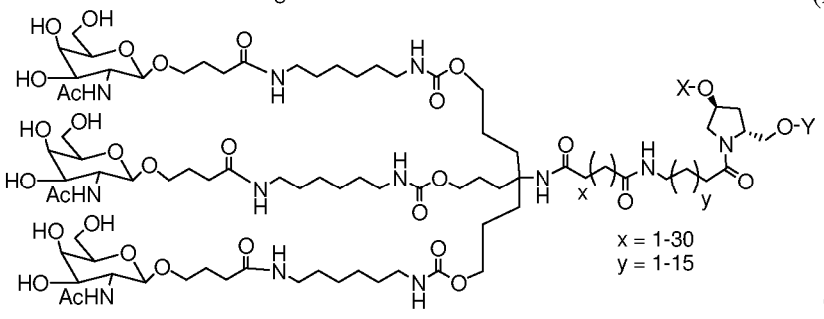
In one embodiment, an iRNA of the invention is conjugated to a carbohydrate through a linker. Non-limiting examples of iRNA carbohydrate conjugates with linkers of the compositions and methods of the invention include, but are not limited to,



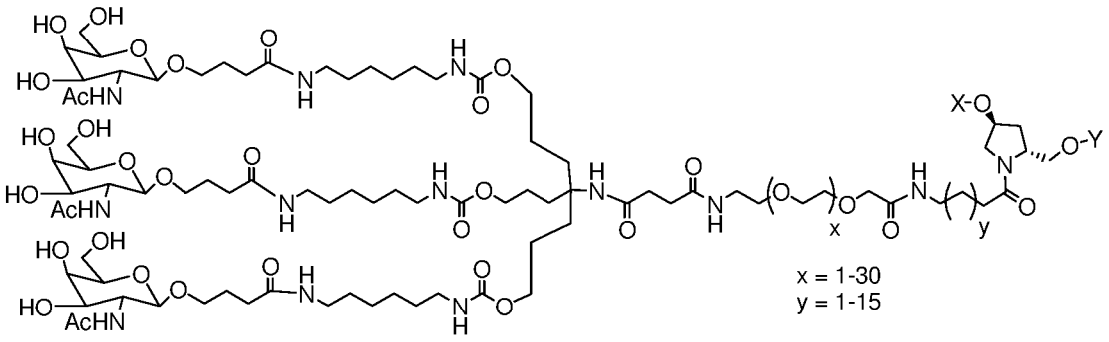
(Formula XXXVII),



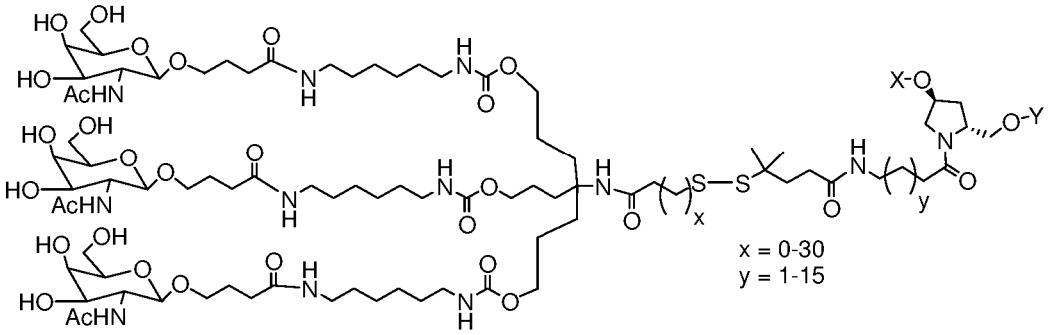
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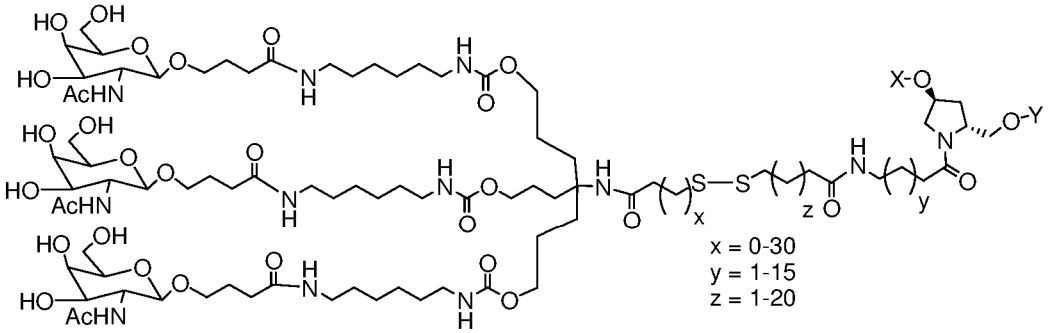
(Formula XXXIX),



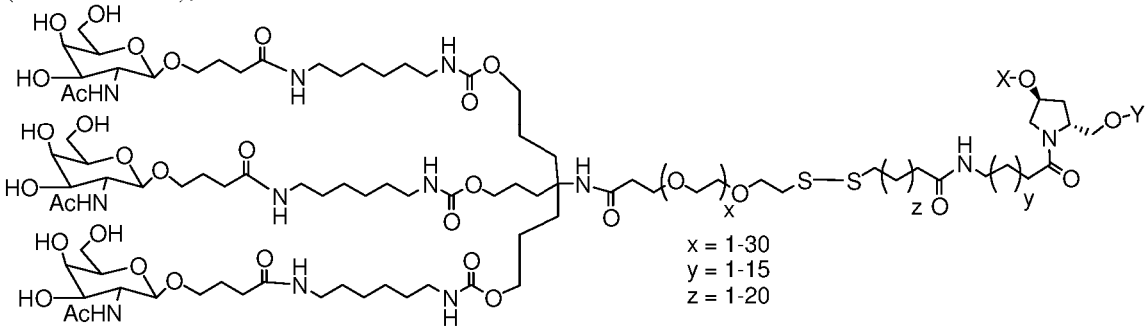
(Formula XL),



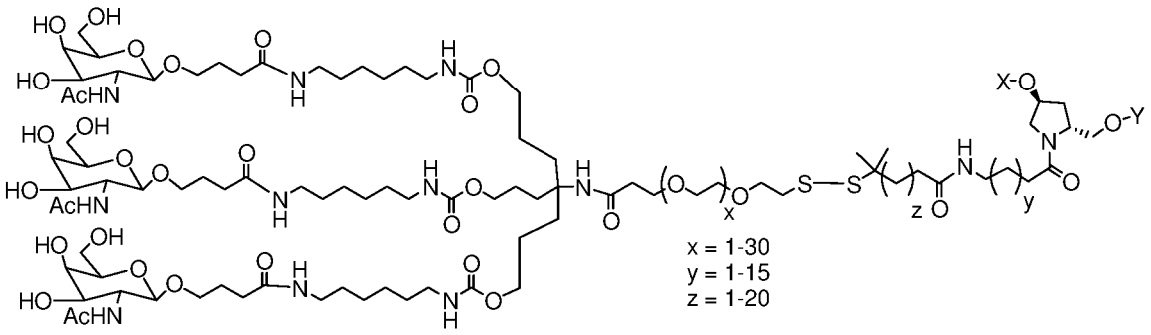
(Formula XLI),



(Formula XLII),



(Formula XLIII), and

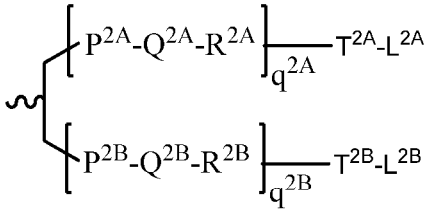


(Formula XLIV), when one of X or Y is an oligonucleotide, the other is a hydrogen.

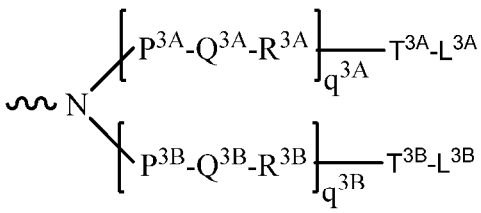
In certain embodiments of the compositions and methods of the invention, a ligand is one or more GalNAc (N-acetylgalactosamine) derivatives attached through a bivalent or trivalent branched linker.

In one embodiment, a dsRNA of the invention is conjugated to a bivalent or trivalent branched linker selected from the group of structures shown in any of formula (XLV) – (XLVI):

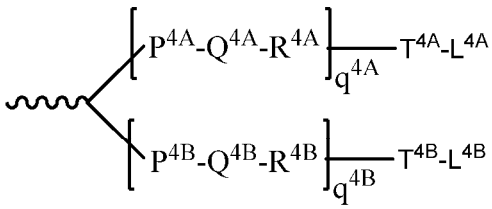
Formula XXXXV



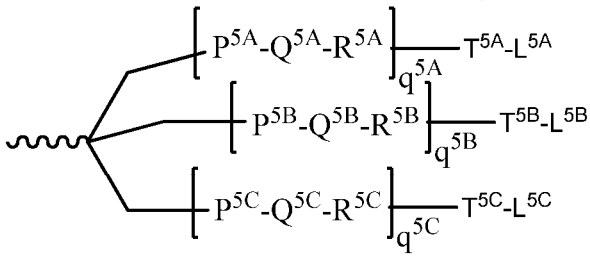
Formula XLVI



,



,



;

Formula XLVII

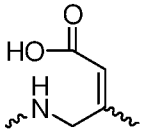
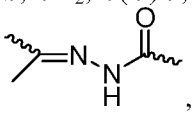
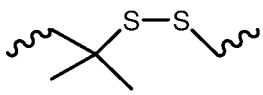
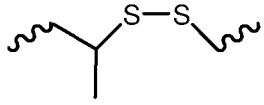
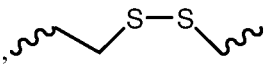
Formula XLVIII

wherein:

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

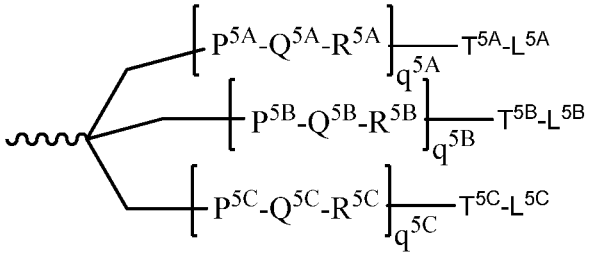
P^{2A}, P^{2B}, P^{3A}, P^{3B}, P^{4A}, P^{4B}, P^{5A}, P^{5B}, P^{5C}, T^{2A}, T^{2B}, T^{3A}, T^{3B}, T^{4A}, T^{4B}, T^{4A}, T^{5B}, T^{5C} are each independently for each occurrence absent, CO, NH, O, S, OC(O), NHC(O), CH_2, CH_2NH or CH_2O;

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

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

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

Formula XLIX



,

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

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

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

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

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

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

IV. Delivery of an iRNA of the Invention

The delivery of an iRNA of the invention 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 disorder of lipid metabolism) can be achieved in a number of different ways. For example, delivery may be performed by contacting a cell with an iRNA of the invention either *in vitro* or *in vivo*. *In vivo* delivery may also be performed directly by administering a composition comprising an iRNA, *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 iRNA. 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 an iRNA of the invention (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 iRNA molecule include, for example, biological stability of the delivered molecule, prevention of non-specific effects, and accumulation of the delivered molecule in the target tissue. The non-specific effects of an iRNA can be minimized by local administration, for example, by direct injection or implantation into a tissue 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 iRNA molecule to be administered. Several studies have shown successful knockdown of gene products when an iRNA is administered locally. For example, intraocular delivery of a 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 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 an iRNA systemically for the treatment of a disease, the RNA can be modified or alternatively delivered using a drug delivery system; both methods act to prevent the rapid degradation of the dsRNA by endo- and exo-nucleases in vivo. Modification of the RNA or the pharmaceutical carrier can also permit targeting of the iRNA composition to the target tissue and avoid undesirable off-target effects. iRNA molecules can be modified by chemical conjugation to lipophilic groups such as cholesterol to enhance cellular uptake and prevent degradation. For

example, an iRNA directed against ApoB conjugated to a lipophilic cholesterol moiety was injected systemically into mice and resulted in knockdown of apoB mRNA in both the liver and jejunum (Soutschek, J. *et al.*, (2004) *Nature* 432:173-178). Conjugation of an iRNA to an aptamer has been shown to inhibit tumor growth and mediate tumor regression in a mouse model of prostate cancer (McNamara, JO. *et al.*, (2006) *Nat. Biotechnol.* 24:1005-1015). In an alternative embodiment, the iRNA can be delivered using drug delivery systems such as a nanoparticle, a dendrimer, a polymer, liposomes, or a cationic delivery system. Positively charged cationic delivery systems facilitate binding of an iRNA molecule (negatively charged) and also enhance interactions at the negatively charged cell membrane to permit efficient uptake of an iRNA by the cell. Cationic lipids, dendrimers, or polymers can either be bound to an iRNA, or induced to form a vesicle or micelle (see *e.g.*, Kim SH. *et al.*, (2008) *Journal of Controlled Release* 129(2):107-116) that encases an iRNA. The formation of vesicles or micelles further prevents degradation of the iRNA when administered systemically. Methods for making and administering cationic- iRNA complexes are well within the abilities of one skilled in the art (see *e.g.*, Sorensen, DR., *et al.* (2003) *J. Mol. Biol* 327:761-766; Verma, UN. *et al.*, (2003) *Clin. Cancer Res.* 9:1291-1300; Arnold, AS *et al.*, (2007) *J. Hypertens.* 25:197-205, which are incorporated herein by reference in their entirety). Some non-limiting examples of drug delivery systems useful for systemic delivery of iRNAs include DOTAP (Sorensen, DR., et al (2003), supra; Verma, UN. *et al.*, (2003), supra), Oligofectamine, "solid nucleic acid lipid particles" (Zimmermann, TS. *et al.,* (2006) *Nature* 441:111-114), cardiolipin (Chien, PY. *et al.*, (2005) *Cancer Gene Ther.* 12:321-328; Pal, A. *et al.*, (2005) *Int J. Oncol.* 26:1087-1091), polyethyleneimine (Bonnet ME. *et al.*, (2008) *Pharm. Res.* Aug 16 Epub ahead of print; Aigner, A. (2006) *J. Biomed. Biotechnol.* 71659), Arg-Gly-Asp (RGD) peptides (Liu, S. (2006) *Mol. Pharm.* 3:472-487), and polyamidoamines (Tomalia, DA. *et al.*, (2007) *Biochem. Soc. Trans.* 35:61-67; Yoo, H. *et al.*, (1999) *Pharm. Res.* 16:1799-1804). In some embodiments, an iRNA forms a complex with cyclodextrin for systemic administration. Methods for administration and pharmaceutical compositions of iRNAs and cyclodextrins can be found in U.S. Patent No. 7, 427, 605, which is herein incorporated by reference in its entirety.

A. Vector encoded iRNAs of the Invention

iRNA targeting the HSD17B13 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; Skillern, A., *et al.*, International PCT Publication No. WO 00/22113, Conrad, International PCT Publication No. WO 00/22114, and Conrad, U.S. Pat. No. 6,054,299). Expression can be transient (on the order of hours to weeks) or sustained (weeks to months or longer), depending upon the specific construct used and the target tissue or cell type. These transgenes can be introduced as a linear construct, a circular plasmid, or a viral vector, which can be an integrating or non-integrating vector. The transgene can also be constructed to permit it to be inherited as an extrachromosomal plasmid (Gassmann, *et al.*, (1995) *Proc. Natl. Acad. Sci. USA* 92:1292).

The individual strand or strands of an iRNA can be transcribed from a promoter on an expression vector. Where two separate strands are to be expressed to generate, for example, a dsRNA, two separate expression vectors can be co-introduced (*e.g.*, by transfection or infection) into a target cell. Alternatively each individual strand of a dsRNA can be transcribed by promoters both of which are located on the same expression plasmid. In 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.

iRNA expression vectors are generally DNA plasmids or viral vectors. Expression vectors compatible with eukaryotic cells, preferably those compatible with vertebrate cells, can be used to produce recombinant constructs for the expression of an iRNA as described herein. Eukaryotic cell expression vectors are well known in the art and are available from a number of commercial sources. Typically, such vectors are provided containing convenient restriction sites for insertion of the desired nucleic acid segment. Delivery of iRNA expressing vectors can be systemic, such as by intravenous or intramuscular administration, by administration to target cells ex-planted from the patient followed by reintroduction into the patient, or by any other means that allows for introduction into a desired target cell.

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 an iRNA will generally require regulatory elements, *e.g.*, promoters, enhancers, *etc.*, to ensure the expression of the iRNA in target cells. Other aspects to consider for vectors and constructs are known in the art.

V. Pharmaceutical Compositions of the Invention

The present invention also includes pharmaceutical compositions and formulations which include the iRNAs of the invention. Accordingly, in one embodiment, provided herein are pharmaceutical compositions comprising a double stranded ribonucleic acid (dsRNA) agent that inhibits expression of 17β-hydroxysteroid dehydrogenases type 13 (HSD17B13) in a cell, such as a liver cell, wherein the dsRNA agent comprises a sense strand and an antisense strand, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 1, 2, or 3 nucleotides from the nucleotide sequence of SEQ ID NO:1, and said antisense strand comprises at least 15 contiguous nucleotides differing by no more than 1, 2, or 3 nucleotides from the nucleotide sequence of SEQ ID NO:7; and a pharmaceutically acceptable carrier. In some embodiments, the

dsRNA agent comprises a sense strand and an antisense strand, wherein the sense strand comprises at least 15 contiguous nucleotides from the nucleotide sequence of SEQ ID NO:1, and said antisense strand comprises at least 15 contiguous nucleotides from the nucleotide sequence of SEQ ID NO:7.

In another embodiment, provided herein are pharmaceutical compositions comprising a dsRNA agent that inhibits expression of 17β-Hydroxysteroid dehydrogenases (HSD17B13) in a cell, such as a liver cell, wherein the dsRNA agent comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity which comprises at least 15 contiguous nucleotides differing by no more than 1, 2, or 3 nucleotides from any one of the antisense sequences listed in any one of Tables 2, 3, 7, 8, 10, 11, or 13; and a pharmaceutically acceptable carrier. In some embodiments, the dsRNA agent comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity which comprises at least 15 contiguous nucleotides from any one of the antisense sequences listed in any one of Tables 2, 3, 7, 8, 10, 11, or 13.

The pharmaceutical compositions containing the iRNA of the invention are useful for treating a disease or disorder associated with the expression or activity of an HSD17B13 gene, *e.g.*, a chronic fibro-inflammatory disease.

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 delivery. Another example is compositions that are formulated for direct delivery into the liver, *e.g.*, by infusion into the liver, such as by continuous pump infusion.The pharmaceutical compositions of the invention may be administered in dosages sufficient to inhibit expression of an HSD17B13 gene. In general, a suitable dose of an iRNA of the invention will be in the range of about 0.001 to about 200.0 milligrams per kilogram body weight of the recipient per day, generally in the range of about 1 to 50 mg per kilogram body weight per day. Typically, a suitable dose of an iRNA of the invention will be in the range of about 0.1 mg/kg to about 5.0 mg/kg, preferably about 0.3 mg/kg and about 3.0 mg/kg.

A repeat-dose regimen may include administration of a therapeutic amount of iRNA on a regular basis, such as every other day to once a year. In certain embodiments, the iRNA is administered about once per week, once every 7-10 days, once every 2 weeks, once every 3 weeks, once every 4 weeks, once every 5 weeks, once every 6 weeks, once every 7 weeks, once every 8 weeks, once every 9 weeks, once every 10 weeks, once every 11 weeks, once every 12 weeks, once per month, once every 2 months, once every 3 months (once per quarter), once every 4 months, once every 5 months, or once every 6 months.

After an initial treatment regimen, the treatments can be administered on a less frequent basis.

The skilled artisan will appreciate that certain factors can influence the dosage and timing required to effectively treat a subject, including but not limited to the severity of the disease or disorder, previous treatments, the general health and/or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically effective amount of a composition can include a single treatment or a series of treatments. Estimates of effective dosages and *in vivo* half-

lives for the individual iRNAs encompassed by the invention can be made using conventional methodologies or on the basis of *in vivo* testing using an appropriate animal model, as described elsewhere herein.

Advances in mouse genetics have generated a number of mouse models for the study of various human diseases, such as an HSD17B13-associated disease, disorder, or condition that would benefit from reduction in the expression of HSD17B13. Such models can be used for *in vivo* testing of iRNA, as well as for determining a therapeutically effective dose. Such models can be used for *in vivo* testing of iRNA, as well as for determining a therapeutically effective dose. Suitable mouse models are known in the art and include, for example, mice and rats fed a high fat diet (HFD; also referred to as a Western diet), a methionine-choline deficient (MCD) diet, or a high-fat (15%), high-cholesterol (1%) diet (HFHC), an obese (ob/ob) mouse containing a mutation in the obese (ob) gene (Wiegman *et al.*, (2003) *Diabetes*, 52:1081-1089); a mouse containing homozygous knock-out of an LDL receptor (LDLR -/- mouse; Ishibashi *et al.*, (1993) *J Clin Invest* 92(2):883-893); diet-induced artherosclerosis mouse model (Ishida *et al.*, (1991) *J. Lipid. Res.*, 32:559-568); heterozygous lipoprotein lipase knockout mouse model (Weistock et al., (1995) J. Clin. Invest. 96(6):2555-2568); mice and rats fed a choline-deficient, L-amino acid-defined, high-fat diet (CDAHFD) (Matsumoto *et al.* (2013) *Int. J. Exp. Path.* 94:93-103); mice and rats fed a high-trans-fat, cholesterol diet (HTF-C) (Clapper *et al.* (2013) *Am. J. Physiol. Gastrointest. Liver Physiol.* 305:G483-G495); mice and rats fed a high-fat, high-cholesterol, bile salt diet (HF/HC/BS) (Matsuzawa *et al.* (2007) *Hepatology* 46:1392-1403); and mice and rats fed a high-fat diet + fructose (30%) water (Softic *et al.* (2018) *J. Clin. Invest.* 128(1)-85-96).

The pharmaceutical compositions of the present invention can be administered in a number of ways depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration can be topical (*e.g.*, by a transdermal patch), pulmonary, *e.g.*, by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal, intranasal, epidermal and transdermal, oral or parenteral. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal or intramuscular injection or infusion; subdermal, *e.g.*, via an implanted device; or intracranial, *e.g.*, by intraparenchymal, intrathecal or intraventricular, administration.

The iRNA can be delivered in a manner to target a particular cell or tissue, such as the liver (*e.g.*, the hepatocytes of the liver).

In some embodiments, the pharmaceutical compositions of the invention are suitable for intramuscular administration to a subject. In other embodiments, the pharmaceutical compositions of the invention are suitable for intravenous administration to a subject. In some embodiments of the invention, the pharmaceutical compositions of the invention are suitable for subcutaneous administration to a subject, *e.g.,* using a 29g or 30g needle.

The pharmaceutical compositions of the invention may include an RNAi agent of the invention in an unbuffered solution, such as saline or water, or in a buffer solution, such as a buffer solution comprising acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof.

In one embodiment, the pharmaceutical compositions of the invention, *e.g.,* such as the compositions suitable for subcutaneous administration, comprise an RNAi agent of the invention in phosphate buffered saline (PBS). Suitable concentrations of PBS include, for example, 1mM, 1.5 mM, 2 mM, 2.5 mM, 3 mM, 3.5 mM, 4 mM, 4.5 mM, 5 mM, 6.5 mM, 7 mM, 7.5.mM, 9 mM, 8.5 mM, 9 mM, 9.5 mM, or about 10 mM PBS. In one embodiment of the invention, a pharmaceutical composition of the invention comprises an RNAi agent of the inventiondissolved in a solution of about 5 mM PBS (*e.g.,* 0.64 mM NaH_2PO_4, 4.36 mM Na_2HPO_4, 85 mM NaCl). Values intermediate to the above recited ranges and values are also intended to be part of this invention. In addition, ranges of values using a combination of any of the above recited values as upper and/or lower limits are intended to be included.

The pH of the pharmaceutical compositions of the invention may be between about 5.0 to about 8.0, about 5.5 to about 8.0, about 6.0 to about 8.0, about 6.5 to about 8.0, about 7.0 to about 8.0, about 5.0 to about 7.5, about 5.5 to about 7.5, about 6.0 to about 7.5, about 6.5 to about 7.5, about 5.0 to about 7.2, about 5.25 to about 7.2, about 5.5 to about 7.2, about 5.75 to about 7.2, about 6.0 to about 7.2, about 6.5 to about 7.2, or about 6.8 to about 7.2. Ranges and values intermediate to the above recited ranges and values are also intended to be part of this invention.

The osmolality of the pharmceutical compositions of the invention may be suitable for subcutaneous administration, such as no more than about 400 mOsm/kg, *e.g.,* between 50 and 400 mOsm/kg, between 75 and 400 mOsm/kg, between 100 and 400 mOsm/kg, between 125 and 400 mOsm/kg, between 150 and 400 mOsm/kg, between 175 and 400 mOsm/kg, between 200 and 400 mOsm/kg, between 250 and 400 mOsm/kg, between 300 and 400 mOsm/kg, between 50 and 375 mOsm/kg, between 75 and 375 mOsm/kg, between 100 and 375 mOsm/kg, between 125 and 375 mOsm/kg, between 150 and 375 mOsm/kg, between 175 and 375 mOsm/kg, between 200 and 375 mOsm/kg, between 250 and 375 mOsm/kg, between 300 and 375 mOsm/kg, between 50 and 350 mOsm/kg, between 75 and 350 mOsm/kg, between 100 and 350 mOsm/kg, between 125 and 350 mOsm/kg, between 150 and 350 mOsm/kg, between 175 and 350 mOsm/kg, between 200 and 350 mOsm/kg, between 250 and 350 mOsm/kg, between 50 and 325 mOsm/kg, between 75 and 325 mOsm/kg, between 100 and 325 mOsm/kg, between 125 and 325 mOsm/kg, between 150 and 325 mOsm/kg, between 175 and 325 mOsm/kg, between 200 and 325 mOsm/kg, between 250 and 325 mOsm/kg, between 300 and 325 mOsm/kg, between 300 and 350 mOsm/kg, between 50 and 300 mOsm/kg, between 75 and 300 mOsm/kg, between 100 and 300 mOsm/kg, between 125 and 300 mOsm/kg, between 150 and 300 mOsm/kg, between 175 and 300 mOsm/kg, between 200 and 300 mOsm/kg, between 250 and 300, between 50 and 250 mOsm/kg, between 75 and 250 mOsm/kg, between 100 and 250 mOsm/kg, between 125 and 250 mOsm/kg, between 150 and 250 mOsm/kg, between 175 and 350 mOsm/kg, between 200 and 250 mOsm/kg, *e.g.,* about 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 205, 210, 215, 220, 225, 230, 235, 240, 245, 250, 255, 260, 265, 270, 275, 280, 285, 295, 300, 305, 310, 320, 325, 330, 335, 340, 345, 350, 355, 360, 365, 370, 375, 380, 385, 390, 395, or about 400 mOsm/kg. Ranges and values intermediate to the above recited ranges and values are also intended to be part of this invention.

The pharmaceutical compositions of the invention comprising the RNAi agents of the invention, may be present in a vial that contains about 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, or about 2.0 mL of the pharmaceutical composition. The concentration of the RNAi agents in the pharmaceutical compositions of the invention may be about 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 130, 125, 130, 135, 140, 145, 150, 175, 180, 185, 190, 195, 200, 205, 210, 215, 230, 225, 230, 235, 240, 245, 250, 275, 280, 285, 290, 295, 300, 305, 310, 315, 330, 325, 330, 335, 340, 345, 350, 375, 380, 385, 390, 395, 400, 405, 410, 415, 430, 425, 430, 435, 440, 445, 450, 475, 480, 485, 490, 495, or about 500 mg/mL. In one embodiment, the concentration of the RNAi agents in the pharmaceutical compositions of the invention is about 100 mg/mL. Values intermediate to the above recited ranges and values are also intended to be part of this invention.

The pharmaceutical compositions of the invention may comprise a dsRNA agent of the invention in a free acid form. In other embodiments of the invention, the pharmaceutical compositions of the invention may comprise a dsRNA agent of the invention in a salt form, such as a sodium salt form. In certain embodiments, when the dsRNA agents of the invention are in the sodium salt form, sodium ions are present in the agent as counterions for substantially all of the phosphodiester and/or phosphorothiotate groups present in the agent. Agents in which substantially all of the phosphodiester and/or phosphorothioate linkages have a sodium counterion include not more than 5, 4, 3, 2, or 1 phosphodiester and/or phosphorothioate linkages without a sodium counterion. In some embodiments, when the dsRNA agents of the invention are in the sodium salt form, sodium ions are present in the agent as counterions for all of the phosphodiester and/or phosphorothiotate groups present in the agent.

Pharmaceutical compositions and formulations for topical administration can 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 can be necessary or desirable. Coated condoms, gloves and the like can also be useful. Suitable topical formulations include those in which the iRNAs featured in the invention are in admixture with a topical delivery agent such as lipids, liposomes, fatty acids, fatty acid esters, steroids, chelating agents and surfactants. Suitable lipids and liposomes include neutral (*e.g.,* dioleoylphosphatidyl DOPE ethanolamine, dimyristoylphosphatidyl choline DMPC, distearolyphosphatidyl choline) negative (*e.g.,* dimyristoylphosphatidyl glycerol DMPG) and cationic (*e.g.,* dioleoyltetramethylaminopropyl DOTAP and dioleoylphosphatidyl ethanolamine DOTMA). iRNAs featured in the invention can be encapsulated within liposomes or can form complexes thereto, in particular to cationic liposomes. Alternatively, iRNAs can be complexed to lipids, in particular to cationic lipids. Suitable fatty acids and esters include but are not limited to arachidonic acid, oleic acid, eicosanoic acid, lauric acid, caprylic acid, capric acid, myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, dicaprate, tricaprate, monoolein, dilaurin, glyceryl 1-monocaprate, 1-dodecylazacycloheptan-2-one, an acylcarnitine, an acylcholine, or a C_{1-20} alkyl ester (*e.g.,* isopropylmyristate IPM), monoglyceride, diglyceride or pharmaceutically acceptable salt thereof. Topical formulations are described in detail in U.S. Patent No. 6,747,014, which is incorporated herein by reference.

A. iRNA Formulations Comprising Membranous Molecular Assemblies

An iRNA for use in the compositions and methods of the invention can be formulated for delivery in a membranous molecular assembly, e.g., a liposome or a micelle. There are many organized surfactant structures besides microemulsions that have been studied and used for the formulation of drugs. These include monolayers, micelles, bilayers and vesicles. Vesicles, such as liposomes, have attracted great interest because of their specificity and the duration of action they offer from the standpoint of drug delivery. As used in the present invention, the term "liposome" means a vesicle composed of amphiphilic lipids arranged in a spherical bilayer or bilayers.

Liposomes include unilamellar or multilamellar vesicles which have a membrane formed from a lipophilic material and an aqueous interior. The aqueous portion contains the composition (e.g., iRNA) to be delivered. The lipophilic material isolates the aqueous interior from an aqueous exterior, which typically does not include the iRNA composition, although in some examples, it may. Cationic liposomes possess the advantage of being able to fuse to the cell wall. Non-cationic liposomes, although not able to fuse as efficiently with the cell wall, are taken up by macrophages *in vivo*.

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

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

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

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

A liposome containing an iRNA agent can be prepared by a variety of methods. In one example, the lipid component of a liposome is dissolved in a detergent so that micelles are formed with the lipid component. For example, the lipid component can be an amphipathic cationic lipid or lipid conjugate. The detergent can have a high critical micelle concentration and may be nonionic. Exemplary detergents include cholate, CHAPS, octylglucoside, deoxycholate, and lauroyl sarcosine. The iRNA agent preparation is then added to the micelles that include the lipid component. The cationic groups on the lipid interact with the iRNA agent and condense around the iRNA agent to form a liposome. After condensation, the detergent is removed, e.g., by dialysis, to yield a liposomal preparation of iRNA agent.

If necessary a carrier compound that assists in condensation can be added during the condensation reaction, e.g., by controlled addition. For example, the carrier compound can be a polymer other than a nucleic acid (e.g., spermine or spermidine). pH can also be adjusted to favor condensation.

Methods for producing stable polynucleotide delivery vehicles, which incorporate a polynucleotide/cationic lipid complex as structural components of the delivery vehicle, are further described in, e.g., WO 96/37194, the entire contents of which are incorporated herein by reference. Liposome formation can also include one or more aspects of exemplary methods described in Felgner, P. L. et al., Proc. Natl. Acad. Sci., USA 8:7413-7417, 1987; US Patent No.4,897,355; US Patent No. 5,171,678; Bangham, et al. M. Mol. Biol.23:238, 1965; Olson, et al. Biochim. Biophys. Acta 557:9, 1979; Szoka, et al. Proc. Natl. Acad. Sci.75: 4194, 1978; Mayhew, et al. Biochim. Biophys. Acta 775:169, 1984; Kim, et al. Biochim. Biophys. Acta 728:339, 1983; and Fukunaga, et al. Endocrinol. 115:757, 1984. Commonly used techniques for preparing lipid aggregates of appropriate size for use as delivery vehicles include sonication and freeze-thaw plus extrusion (see, e.g., Mayer, et al. Biochim. Biophys. Acta 858:161, 1986). Microfluidization can be used when consistently small (50 to 200 nm) and relatively uniform aggregates are desired (Mayhew, et al. Biochim. Biophys. Acta 775:169, 1984). These methods are readily adapted to packaging iRNA agent preparations into liposomes.

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

Liposomes which are pH-sensitive or negatively-charged, entrap DNA rather than complex with it. Since both the DNA and the lipid are similarly charged, repulsion rather than complex formation occurs. Nevertheless, some DNA is entrapped within the aqueous interior of these liposomes. pH-sensitive liposomes have been used to deliver DNA encoding the thymidine

kinase gene to cell monolayers in culture. Expression of the exogenous gene was detected in the target cells (Zhou *et al.*, *Journal of Controlled Release*, 1992, 19, 269-274).

One major type of liposomal composition includes phospholipids other than naturally-derived phosphatidylcholine. Neutral liposome compositions, for example, can be formed from dimyristoyl phosphatidylcholine (DMPC) or dipalmitoyl phosphatidylcholine (DPPC). Anionic liposome compositions generally are formed from dimyristoyl phosphatidylglycerol, while anionic fusogenic liposomes are formed primarily from dioleoyl phosphatidylethanolamine (DOPE). Another type of liposomal composition is formed from phosphatidylcholine (PC) such as, for example, soybean PC, and egg PC. Another type is formed from mixtures of phospholipid and/or phosphatidylcholine and/or cholesterol.

Examples of other methods to introduce liposomes into cells in vitro and in vivo include US Patent Nos.5,283,185 and 5,171,678; WO 94/00569; WO 93/24640; WO 91/16024; Felgner, J. Biol. Chem.269:2550, 1994; Nabel, Proc. Natl. Acad. Sci.90:11307, 1993; Nabel, Human Gene Ther. 3:649, 1992; Gershon, Biochem.32:7143, 1993; and Strauss EMBO J.11:417, 1992.

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

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

Various liposomes comprising one or more glycolipids are known in the art. Papahadjopoulos *et al.* (*Ann. N.Y. Acad. Sci.*, 1987, 507, 64) reported the ability of monosialoganglioside G_{M1}, galactocerebroside sulfate and phosphatidylinositol to improve blood half-lives of liposomes. These findings were expounded upon by Gabizon *et al.* (*Proc. Natl.*

Acad. Sci. U.S.A., 1988, 85, 6949). U.S. Pat. No. 4,837,028 and WO 88/04924, both to Allen *et al.*, disclose liposomes comprising (1) sphingomyelin and (2) the ganglioside G_{M1} or a galactocerebroside sulfate ester. U.S. Pat. No. 5,543,152 (Webb *et al.*) discloses liposomes comprising sphingomyelin. Liposomes comprising 1,2-sn-dimyristoylphosphatidylcholine are disclosed in WO 97/13499 (Lim *et al*).

In some embodiments, cationic liposomes are used. Cationic liposomes possess the advantage of being able to fuse to the cell membrane. Non-cationic liposomes, although not able to fuse as efficiently with the plasma membrane, are taken up by macrophages in vivo and can be used to deliver iRNA agents to macrophages.

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

A positively charged synthetic cationic lipid, N-[1-(2,3-dioleyloxy)propyl]-N,N,N-trimethylammonium chloride (DOTMA) can be used to form small liposomes that interact spontaneously with nucleic acid to form lipid-nucleic acid complexes which are capable of fusing with the negatively charged lipids of the cell membranes of tissue culture cells, resulting in delivery of iRNA agent (see, e.g., Felgner, P. L. et al., Proc. Natl. Acad. Sci., USA 8:7413-7417, 1987 and US Patent No.4,897,355 for a description of DOTMA and its use with DNA).

A DOTMA analogue, 1,2-bis(oleoyloxy)-3-(trimethylammonia)propane (DOTAP) can be used in combination with a phospholipid to form DNA-complexing vesicles. Lipofectin™ (Bethesda Research Laboratories, Gaithersburg, Md.) is an effective agent for the delivery of highly anionic nucleic acids into living tissue culture cells that comprise positively charged DOTMA liposomes which interact spontaneously with negatively charged polynucleotides to form complexes. When enough positively charged liposomes are used, the net charge on the resulting complexes is also positive. Positively charged complexes prepared in this way spontaneously attach to negatively charged cell surfaces, fuse with the plasma membrane, and efficiently deliver functional nucleic acids into, for example, tissue culture cells. Another commercially available cationic lipid, 1,2- bis(oleoyloxy)-3,3-(trimethylammonia)propane ("DOTAP") (Boehringer Mannheim, Indianapolis, Indiana) differs from DOTMA in that the oleoyl moieties are linked by ester, rather than ether linkages.

Other reported cationic lipid compounds include those that have been conjugated to a variety of moieties including, for example, carboxyspermine which has been conjugated to one of two types of lipids and includes compounds such as 5-carboxyspermylglycine

dioctaoleoylamide ("DOGS") (Transfectam™, Promega, Madison, Wisconsin) and dipalmitoylphosphatidylcthanolaminc 5- carboxyspcrmyl-amidc ("DPPES") (scc, c.g., US Patcnt No.5,171,678).

Another cationic lipid conjugate includes derivatization of the lipid with cholesterol ("DC- Chol") which has been formulated into liposomes in combination with DOPE (See, Gao, X. and Huang, L., Biochim. Biophys. Res. Commun.179:280, 1991). Lipopolylysine, made by conjugating polylysine to DOPE, has been reported to be effective for transfection in the presence of serum (Zhou, X. et al., Biochim. Biophys. Acta 1065:8, 1991). For certain cell lines, these liposomes containing conjugated cationic lipids, are said to exhibit lower toxicity and provide more efficient transfection than the DOTMA-containing compositions. Other commercially available cationic lipid products include DMRIE and DMRIE-HP (Vical, La Jolla, California) and Lipofectamine (DOSPA) (Life Technology, Inc., Gaithersburg, Maryland). Other cationic lipids suitable for the delivery of oligonucleotides are described in WO 98/39359 and WO 96/37194.

Liposomal formulations are particularly suited for topical administration, liposomes present several advantages over other formulations. Such advantages include reduced side effects related to high systemic absorption of the administered drug, increased accumulation of the administered drug at the desired target, and the ability to administer iRNA agent into the skin. In some implementations, liposomes are used for delivering iRNA agent to epidermal cells and also to enhance the penetration of iRNA agent into dermal tissues, e.g., into skin. For example, the liposomes can be applied topically. Topical delivery of drugs formulated as liposomes to the skin has been documented (see, e.g., Weiner et al., Journal of Drug Targeting, 1992, vol.2,405-410 and du Plessis et al., Antiviral Research, 18, 1992, 259-265; Mannino, R. J. and Fould-Fogerite, S., Biotechniques 6:682-690, 1988; Itani, T. et al. Gene 56:267-276.1987; Nicolau, C. et al. Meth. Enz.149:157-176, 1987; Straubinger, R. M. and Papahadjopoulos, D. Meth. Enz.101:512-527, 1983; Wang, C. Y. and Huang, L., Proc. Natl. Acad. Sci. USA 84:7851-7855, 1987).

Non-ionic liposomal systems have also been examined to determine their utility in the delivery of drugs to the skin, in particular systems comprising non-ionic surfactant and cholesterol. Non-ionic liposomal formulations comprising Novasome™ I (glyceryl dilaurate/cholesterol/polyoxyethylene-10-stearyl ether) and Novasome™ II (glyceryl distearate/ cholesterol/polyoxyethylene-10-stearyl ether) were used to deliver a drug into the dermis of mouse skin. Such formulations with iRNA agent are useful for treating a dermatological disorder.

Liposomes that include iRNA can be made highly deformable. Such deformability can enable the liposomes to penetrate through pore that are smaller than the average radius of the liposome. For example, transfersomes are a type of deformable liposomes. Transferosomes can

be made by adding surface edge activators, usually surfactants, to a standard liposomal composition. Transfersomes that include iRNAs can be delivered, for example, subcutaneously by infection in order to deliver iRNAs to keratinocytes in the skin. In order to cross intact mammalian skin, lipid vesicles must pass through a series of fine pores, each with a diameter less than 50 nm, under the influence of a suitable transdermal gradient. In addition, due to the lipid properties, these transferosomes can be self- optimizing (adaptive to the shape of pores, e.g., in the skin), self-repairing, and can frequently reach their targets without fragmenting, and often self-loading.

Other formulations amenable to the present invention are described in WO 2008/042973.

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

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

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

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

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

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

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

The iRNA for use in the methods of the invention can also be provided as micellar formulations. "Micelles" are defined herein as a particular type of molecular assembly in which amphipathic molecules are arranged in a spherical structure such that all the hydrophobic portions of the molecules are directed inward, leaving the hydrophilic portions in contact with the surrounding aqueous phase. The converse arrangement exists if the environment is hydrophobic.

A mixed micellar formulation suitable for delivery through transdermal membranes may be prepared by mixing an aqueous solution of iRNA, an alkali metal C_8 to C_{22} alkyl sulphate, and a micelle forming compounds. Exemplary micelle forming compounds include lecithin, hyaluronic acid, pharmaceutically acceptable salts of hyaluronic acid, glycolic acid, lactic acid, chamomile extract, cucumber extract, oleic acid, linoleic acid, linolenic acid, monoolein, monooleates, monolaurates, borage oil, evening of primrose oil, menthol, trihydroxy oxo cholanyl glycine and pharmaceutically acceptable salts thereof, glycerin, polyglycerin, lysine, polylysine, triolein, polyoxyethylene ethers and analogues thereof, polidocanol alkyl ethers and analogues thereof, chenodeoxycholate, deoxycholate, and mixtures thereof. The micelle forming compounds may be added at the same time or after addition of the alkali metal alkyl sulphate. Mixed micelles will form with substantially any kind of mixing of the ingredients but vigorous mixing in order to provide smaller size micelles.

In one method a first micellar composition is prepared which contains the RNAi and at least the alkali metal alkyl sulphate. The first micellar composition is then mixed with at least three micelle forming compounds to form a mixed micellar composition. In another method, the

micellar composition is prepared by mixing the RNAi, the alkali metal alkyl sulphate and at least one of the micelle forming compounds, followed by addition of the remaining micelle forming compounds, with vigorous mixing.

Phenol or m-cresol may be added to the mixed micellar composition to stabilize the formulation and protect against bacterial growth. Alternatively, phenol or m-cresol may be added with the micelle forming ingredients. An isotonic agent such as glycerin may also be added after formation of the mixed micellar composition.

For delivery of the micellar formulation as a spray, the formulation can be put into an aerosol dispenser and the dispenser is charged with a propellant. The propellant, which is under pressure, is in liquid form in the dispenser. The ratios of the ingredients are adjusted so that the aqueous and propellant phases become one, i.e., there is one phase. If there are two phases, it is necessary to shake the dispenser prior to dispensing a portion of the contents, e.g., through a metered valve. The dispensed dose of pharmaceutical agent is propelled from the metered valve in a fine spray.

Propellants may include hydrogen-containing chlorofluorocarbons, hydrogen-containing fluorocarbons, dimethyl ether and diethyl ether. In certain embodiments, HFA 134a (1,1,1,2 tetrafluoroethane) may be used.

The specific concentrations of the essential ingredients can be determined by relatively straightforward experimentation. For absorption through the oral cavities, it is often desirable to increase, e.g., at least double or triple, the dosage for through injection or administration through the gastrointestinal tract.

B. Lipid particles

iRNAs, e.g., dsRNA agents of in the invention may be fully encapsulated in a lipid formulation, e.g., an LNP, or other nucleic acid-lipid particle.

As used herein, the term "LNP" refers to a stable nucleic acid-lipid particle. LNPs typically contain a cationic lipid, a non-cationic lipid, and a lipid that prevents aggregation of the particle (*e.g.*, a PEG-lipid conjugate). LNPs are extremely useful for systemic applications, as they exhibit extended circulation lifetimes following intravenous (i.v.) injection and accumulate at distal sites (*e.g.*, sites physically separated from the administration site). As used herein, the term "SPLP" refers to a nucleic acid-lipid particle comprising plasmid DNA encapsulated within a lipid vesicle. LNPs include "pSPLP," which include an encapsulated condensing agent-nucleic acid complex as set forth in PCT Publication No. WO 00/03683. The particles of the present invention typically have a mean diameter of about 50 nm to about 150 nm, more typically about 60 nm to about 130 nm, more typically about 70 nm to about 110 nm, most typically about 70 nm to about 90 nm, and are substantially nontoxic. In addition, the nucleic acids when present in the nucleic acid- lipid particles of the present invention are resistant in aqueous solution to degradation with a nuclease. Nucleic acid-lipid particles and their method of preparation are

disclosed in, *e.g.*, U.S. Patent Nos. 5,976,567; 5,981,501; 6,534,484; 6,586,410; 6,815,432; and PCT Publication No. WO 96/40964.

In certain embodiments, the lipid to drug ratio (mass/mass ratio) (*e.g.*, lipid to dsRNA ratio) will be in the range of from about 1:1 to about 50:1, from about 1:1 to about 25:1, from about 3:1 to about 15:1, from about 4:1 to about 10:1, from about 5:1 to about 9:1, or about 6:1 to about 9:1. Ranges intermediate to the above recited ranges are also contemplated to be part of the invention.

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

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

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

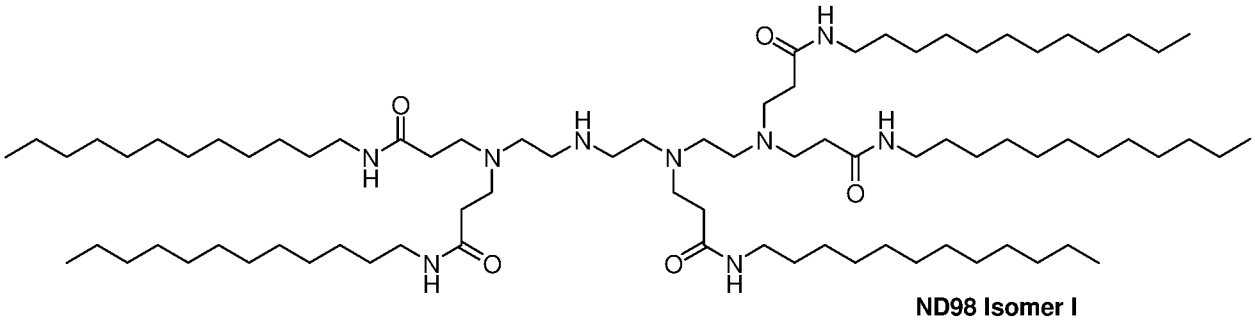
The non-cationic lipid may be an anionic lipid or a neutral lipid including, but not limited to, distearoylphosphatidylcholine (DSPC), dioleoylphosphatidylcholine (DOPC), dipalmitoylphosphatidylcholine (DPPC), dioleoylphosphatidylglycerol (DOPG), dipalmitoylphosphatidylglycerol (DPPG), dioleoyl-phosphatidylethanolamine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

The conjugated lipid that inhibits aggregation of particles may be, for example, a polyethyleneglycol (PEG)-lipid including, without limitation, a PEG-diacylglycerol (DAG), a PEG-dialkyloxypropyl (DAA), a PEG-phospholipid, a PEG-ceramide (Cer), or a mixture thereof. The PEG-DAA conjugate may be, for example, a PEG-dilauryloxypropyl (Ci_2), a PEG-dimyristyloxypropyl (Ci_4), a PEG-dipalmityloxypropyl (Ci_6), or a PEG- distearyloxypropyl ($C]_8$). The conjugated lipid that prevents aggregation of particles may be from 0 mol % to about 20 mol % or about 2 mol % of the total lipid present in the particle.

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

LNP01

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



Formula 1

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

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

Table A: Exemplary lipid formulations

	Cationic Lipid	**cationic lipid/non-cationic lipid/cholesterol/PEG-lipid conjugate Lipid:siRNA ratio**
SNALP	l,2-Dilinolenyloxy-N,N-dimethylaminopropane (DLinDMA)	DLinDMA/DPPC/Cholesterol/PEG-cDMA (57.1/7.1/34.4/1.4) lipid:siRNA ~ 7:1
S-XTC	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DPPC/Cholesterol/PEG-cDMA 57.1/7.1/34.4/1.4 lipid:siRNA ~ 7:1
LNP05	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DSPC/Cholesterol/PEG-DMG 57.5/7.5/31.5/3.5 lipid:siRNA ~ 6:1
LNP06	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DSPC/Cholesterol/PEG-DMG 57.5/7.5/31.5/3.5 lipid:siRNA ~ 11:1
LNP07	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DSPC/Cholesterol/PEG-DMG 60/7.5/31/1.5, lipid:siRNA ~ 6:1
LNP08	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DSPC/Cholesterol/PEG-DMG 60/7.5/31/1.5, lipid:siRNA ~ 11:1
LNP09	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DSPC/Cholesterol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA 10:1
LNP10	(3aR,5s,6aS)-N,N-dimethyl-2,2-di((9Z,12Z)-octadeca-9,12-dienyl)tetrahydro-3aH-cyclopenta[d][1,3]dioxol-5-amine (ALN100)	ALN100/DSPC/Cholesterol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA 10:1
LNP11	(6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate (MC3)	MC-3/DSPC/Cholesterol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA 10:1
LNP12	1,1'-(2-(4-(2-((2-(bis(2-hydroxydodecyl)amino)ethyl)(2-hydroxydodecyl)amino)ethyl)piperazin-	C12-200/DSPC/Cholesterol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA 10:1

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

DSPC: distearoylphosphatidylcholine

DPPC: dipalmitoylphosphatidylcholine

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

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

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

SNALP (1,2-Dilinolenyloxy-N,N-dimethylaminopropane (DLinDMA)) comprising formulations are described in International Publication No. WO2009/127060, filed April 15, 2009, which is hereby incorporated by reference.

XTC comprising formulations are described, e.g., in U.S. Provisional Serial No. 61/148,366, filed January 29, 2009; U.S. Provisional Serial No. 61/156,851, filed March 2, 2009; U.S. Provisional Serial No. 61/185,712, filed June 10, 2009; U.S. Provisional Serial No. 61/228,373, filed July 24, 2009; U.S. Provisional Serial No. 61/239,686, filed September 3,

2009, and International Application No. PCT/US2010/022614, filed January 29, 2010, which are hereby incorporated by reference.

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

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

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

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

poly(isobutylcyanoacrylate), poly(isohexylcynaoacrylate), DEAE-methacrylate, DEAE-hexylacrylate, DEAE-acrylamide, DEAE-albumin and DEAE-dextran, polymethylacrylate, polyhexylacrylate, poly(D,L-lactic acid), poly(DL-lactic-co-glycolic acid (PLGA), alginate, and polyethyleneglycol (PEG). Oral formulations for dsRNAs and their preparation are described in detail in U.S. Patent 6,887,906, US Publication. No. 20030027780, and U.S. Patent No. 6,747,014, each of which is incorporated herein by reference.

Compositions and formulations for parenteral, intraparenchymal (into the brain), intrathecal, intraventricular or intrahepatic administration can include sterile aqueous solutions which can also contain buffers, diluents and other suitable additives such as, but not limited to, penetration enhancers, carrier compounds and other pharmaceutically acceptable carriers or excipients.

Pharmaceutical compositions of the present invention include, but are not limited to, solutions, emulsions, and liposome-containing formulations. These compositions can be generated from a variety of components that include, but are not limited to, preformed liquids, self-emulsifying solids and self-emulsifying semisolids. Particularly preferred are formulations that target the liver when treating hepatic disorders such as hepatic carcinoma.

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

The compositions of the present invention can be formulated into any of many possible dosage forms such as, but not limited to, tablets, capsules, gel capsules, liquid syrups, soft gels, suppositories, and enemas. The compositions of the present invention can also be formulated as suspensions in aqueous, non-aqueous or mixed media. Aqueous suspensions can further contain substances which increase the viscosity of the suspension including, for example, sodium carboxymethylcellulose, sorbitol and/or dextran. The suspension can also contain stabilizers.

Many liposomes comprising lipids derivatized with one or more hydrophilic polymers, and methods of preparation thereof, are known in the art. Sunamoto *et al.* (Bull. *Chem. Soc. Jpn.*, 1980, 53, 2778) described liposomes comprising a nonionic detergent, $2C_{1215G}$, that contains a PEG moiety. Illum *et al.* (*FEBS Lett.*, 1984, 167, 79) noted that hydrophilic coating of polystyrene particles with polymeric glycols results in significantly enhanced blood half-lives. Synthetic phospholipids modified by the attachment of carboxylic groups of polyalkylene glycols (*e.g.*, PEG) are described by Sears (U.S. Pat. Nos. 4,426,330 and 4,534,899). Klibanov *et al.* (*FEBS Lett.*, 1990, 268, 235) described experiments demonstrating that liposomes comprising phosphatidylethanolamine (PE) derivatized with PEG or PEG stearate have significant increases in blood circulation half-lives. Blume *et al.* (*Biochimica et Biophysica Acta*, 1990, 1029, 91) extended such observations to other PEG-derivatized phospholipids, *e.g.*,

DSPE-PEG, formed from the combination of distearoylphosphatidylethanolamine (DSPE) and PEG. Liposomes having covalently bound PEG moieties on their external surface are described in European Patent No. EP 0 445 131 B1 and WO 90/04384 to Fisher. Liposome compositions containing 1-20 mole percent of PE derivatized with PEG, and methods of use thereof, are described by Woodle *et al.* (U.S. Pat. Nos. 5,013,556 and 5,356,633) and Martin *et al.* (U.S. Pat. No. 5,213,804 and European Patent No. EP 0 496 813 B1). Liposomes comprising a number of other lipid-polymer conjugates are disclosed in WO 91/05545 and U.S. Pat. No. 5,225,212 (both to Martin *et al.*) and in WO 94/20073 (Zalipsky *et al.*). Liposomes comprising PEG-modified ceramide lipids are described in WO 96/10391 (Choi *et al*). U.S. Pat. No. 5,540,935 (Miyazaki *et al.*) and U.S. Pat. No. 5,556,948 (Tagawa *et al.*) describe PEG-containing liposomes that can be further derivatized with functional moieties on their surfaces.

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

i. Emulsions

The compositions of the present invention can be prepared and formulated as emulsions. Emulsions are typically heterogeneous systems of one liquid dispersed in another in the form of droplets usually exceeding 0.1μm in diameter (see *e.g.*, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Idson, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199; Rosoff, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., Volume 1, p. 245; Block in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 2, p. 335; Higuchi *et al.*, in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa., 1985, p. 301). Emulsions are often biphasic systems comprising two immiscible liquid phases intimately mixed and dispersed with each other. In general, emulsions can be of either the water-in-oil (w/o) or the oil-in-water (o/w) variety. When an aqueous phase is finely divided into and dispersed as minute droplets into a bulk oily phase, the resulting composition is called a water-in-oil (w/o) emulsion. Alternatively, when an oily phase is finely divided into and dispersed as minute droplets into a bulk aqueous phase, the resulting composition is called an oil-in-water (o/w) emulsion. Emulsions can contain additional components in addition to the dispersed phases, and the active drug which can be present as a solution in either aqueous phase, oily phase or itself as a separate phase. Pharmaceutical excipients such as emulsifiers, stabilizers, dyes, and anti-oxidants can also be present in emulsions as needed.

Pharmaceutical emulsions can also be multiple emulsions that are comprised of more than two phases such as, for example, in the case of oil-in-water-in-oil (o/w/o) and water-in-oil-in-water (w/o/w) emulsions. Such complex formulations often provide certain advantages that simple binary emulsions do not. Multiple emulsions in which individual oil droplets of an o/w emulsion enclose small water droplets constitute a w/o/w emulsion. Likewise a system of oil droplets enclosed in globules of water stabilized in an oily continuous phase provides an o/w/o emulsion.

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

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

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

hectorite, kaolin, montmorillonite, colloidal aluminum silicate and colloidal magnesium aluminum silicate, pigments and nonpolar solids such as carbon or glyceryl tristearate.

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

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

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

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

ii. Microemulsions

In one embodiment of the present invention, the compositions of iRNAs and nucleic acids are formulated as microemulsions. A microemulsion can be defined as a system of water, oil and amphiphile which is a single optically isotropic and thermodynamically stable liquid solution (see *e.g.*, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Rosoff, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 245). Typically microemulsions are systems that are prepared by first dispersing an oil in an aqueous surfactant solution and then adding a sufficient amount of a fourth component, generally an intermediate chain-length alcohol to form a transparent system. Therefore, microemulsions have also been described as thermodynamically stable, isotropically clear dispersions of two immiscible liquids that are stabilized by interfacial films of surface-active molecules (Leung and Shah, in: Controlled Release of Drugs: Polymers and Aggregate Systems, Rosoff, M., Ed., 1989, VCH Publishers, New York, pages 185-215). Microemulsions commonly are prepared via a combination of three to five components that include oil, water, surfactant, cosurfactant and electrolyte. Whether the microemulsion is of the water-in-oil (w/o) or an oil-in-water (o/w) type is dependent on the properties of the oil and surfactant used and on the structure and geometric packing of the polar heads and hydrocarbon tails of the surfactant molecules (Schott, in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa., 1985, p. 271).

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

Surfactants used in the preparation of microemulsions include, but are not limited to, ionic surfactants, non-ionic surfactants, Brij 96, polyoxyethylene oleyl ethers, polyglycerol fatty acid esters, tetraglycerol monolaurate (ML310), tetraglycerol monooleate (MO310), hexaglycerol monooleate (PO310), hexaglycerol pentaoleate (PO500), decaglycerol monocaprate (MCA750), decaglycerol monooleate (MO750), decaglycerol sequioleate (SO750), decaglycerol decaoleate (DAO750), alone or in combination with cosurfactants. The cosurfactant, usually a short-chain alcohol such as ethanol, 1-propanol, and 1-butanol, serves to increase the interfacial fluidity by penetrating into the surfactant film and consequently creating a disordered film because of the void space generated among surfactant molecules. Microemulsions can, however, be prepared without the use of cosurfactants and alcohol-free self-emulsifying microemulsion systems are known in the art.

The aqueous phase can typically be, but is not limited to, water, an aqueous solution of the drug, glycerol, PEG300, PEG400, polyglycerols, propylene glycols, and derivatives of ethylene glycol. The oil phase can include, but is not limited to, materials such as Captex 300, Captex 355, Capmul MCM, fatty acid esters, medium chain (C8-C12) mono, di, and tri-glycerides, polyoxyethylated glyceryl fatty acid esters, fatty alcohols, polyglycolized glycerides, saturated polyglycolized C8-C10 glycerides, vegetable oils and silicone oil.

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

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

iii. Microparticles

An RNAi agent of the invention may be incorporated into a particle, *e.g.*, a microparticle. Microparticles can be produced by spray-drying, but may also be produced by other methods including lyophilization, evaporation, fluid bed drying, vacuum drying, or a combination of these techniques.

iv. Penetration Enhancers

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

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

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

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

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

The physiological role of bile includes the facilitation of dispersion and absorption of lipids and fat-soluble vitamins (see *e.g.*, Malmsten, M. Surfactants and polymers in drug delivery, Informa Health Care, New York, NY, 2002; Brunton, Chapter 38 in: Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th Ed., Hardman *et al.* Eds., McGraw-Hill, New York, 1996, pp. 934-935). Various natural bile salts, and their synthetic derivatives, act as penetration enhancers. Thus the term "bile salts" includes any of the naturally occurring components of bile as well as any of their synthetic derivatives. Suitable bile salts include, for example, cholic acid (or its pharmaceutically acceptable sodium salt, sodium cholate), dehydrocholic acid (sodium dehydrocholate), deoxycholic acid (sodium deoxycholate), glucholic acid (sodium glucholate), glycholic acid (sodium glycocholate), glycodeoxycholic acid (sodium glycodeoxycholate), taurocholic acid (sodium taurocholate), taurodeoxycholic acid (sodium taurodeoxycholate), chenodeoxycholic acid (sodium chenodeoxycholate), ursodeoxycholic acid (UDCA), sodium tauro-

24,25-dihydro-fusidate (STDHF), sodium glycodihydrofusidate and polyoxyethylene-9-lauryl ether (POE) (see *e.g.*, Malmsten, M. Surfactants and polymers in drug delivery, Informa Health Care, New York, NY, 2002; Lee *et al.*, Critical Reviews in Therapeutic Drug Carrier Systems, 1991, page 92; Swinyard, Chapter 39 In: Remington's Pharmaceutical Sciences, 18th Ed., Gennaro, ed., Mack Publishing Co., Easton, Pa., 1990, pages 782-783; Muranishi, Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7, 1-33; Yamamoto *et al.*, J. Pharm. Exp. Ther., 1992, 263, 25; Yamashita *et al.*, J. Pharm. Sci., 1990, 79, 579-583).

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

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

Agents that enhance uptake of iRNAs at the cellular level can also be added to the pharmaceutical and other compositions of the present invention. For example, cationic lipids, such as lipofectin (Junichi *et al*, U.S. Pat. No. 5,705,188), cationic glycerol derivatives, and polycationic molecules, such as polylysine (Lollo *et al.*, PCT Application WO 97/30731), are also known to enhance the cellular uptake of dsRNAs. Examples of commercially available transfection reagents include, for example Lipofectamine™ (Invitrogen; Carlsbad, CA), Lipofectamine 2000™ (Invitrogen; Carlsbad, CA), 293fectin™ (Invitrogen; Carlsbad, CA), Cellfectin™ (Invitrogen; Carlsbad, CA), DMRIE-C™ (Invitrogen; Carlsbad, CA), FreeStyle™ MAX (Invitrogen; Carlsbad, CA), Lipofectamine™ 2000 CD (Invitrogen; Carlsbad, CA), Lipofectamine™ (Invitrogen; Carlsbad, CA), RNAiMAX (Invitrogen; Carlsbad, CA), Oligofectamine™ (Invitrogen; Carlsbad, CA), Optifect™ (Invitrogen; Carlsbad, CA), X-tremeGENE Q2 Transfection Reagent (Roche;

Grenzacherstrasse, Switzerland), DOTAP Liposomal Transfection Reagent (Grenzacherstrasse, Switzerland), DOSPER Liposomal Transfection Reagent (Grenzacherstrasse, Switzerland), or Fugene (Grenzacherstrasse, Switzerland), Transfectam® Reagent (Promega; Madison, WI), TransFast™ Transfection Reagent (Promega; Madison, WI), Tfx™-20 Reagent (Promega; Madison, WI), Tfx™-50 Reagent (Promega; Madison, WI), DreamFect™ (OZ Biosciences; Marseille, France), EcoTransfect (OZ Biosciences; Marseille, France), TransPass[a] D1 Transfection Reagent (New England Biolabs; Ipswich, MA, USA), LyoVec™/LipoGen™ (Invitrogen; San Diego, CA, USA), PerFectin Transfection Reagent (Genlantis; San Diego, CA, USA), NeuroPORTER Transfection Reagent (Genlantis; San Diego, CA, USA), GenePORTER Transfection reagent (Genlantis; San Diego, CA, USA), GenePORTER 2 Transfection reagent (Genlantis; San Diego, CA, USA), Cytofectin Transfection Reagent (Genlantis; San Diego, CA, USA), BaculoPORTER Transfection Reagent (Genlantis; San Diego, CA, USA), TroganPORTER™ transfection Reagent (Genlantis; San Diego, CA, USA), RiboFect (Bioline; Taunton, MA, USA), PlasFect (Bioline; Taunton, MA, USA), UniFECTOR (B-Bridge International; Mountain View, CA, USA), SureFECTOR (B-Bridge International; Mountain View, CA, USA), or HiFect™ (B-Bridge International, Mountain View, CA, USA), among others.

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

v. Carriers

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

vi. Excipients

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

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

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

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

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

vii. Other Components

The compositions of the present invention can additionally contain other adjunct components conventionally found in pharmaceutical compositions, at their art-established usage levels. Thus, for example, the compositions can contain additional, compatible, pharmaceutically-active materials such as, for example, antipruritics, astringents, local anesthetics or anti-inflammatory agents, or can contain additional materials useful in physically formulating various dosage forms of the compositions of the present invention, such as dyes, flavoring agents, preservatives, antioxidants, opacifiers, thickening agents and stabilizers. However, such materials, when added, should not unduly interfere with the biological activities of the components of the compositions of the present invention. The formulations can be sterilized and, if desired, mixed with auxiliary agents, *e.g.*, lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, colorings, flavorings and/or aromatic substances and the like which do not deleteriously interact with the nucleic acid(s) of the formulation.

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

In some embodiments, pharmaceutical compositions featured in the invention include (a) one or more iRNA compounds and (b) one or more agents which function by a non-RNAi mechanism and which are useful in treating an HSD17B13-associated disease, disorder, or condition. Examples of such agents include, but are not lmited to

pyridoxine, an ACE inhibitor (angiotensin converting enzyme inhibitors), *e.g.*, benazepril (Lotensin); an angiotensin II receptor antagonist (ARB) (*e.g.*, losartan potassium, such as Merck & Co. 's Cozaar®), *e.g.*, Candesartan (Atacand); an HMG-CoA reductase inhibitor (*e.g.*, a statin); calcium binding agents, *e.g.*, Sodium cellulose phosphate (Calcibind); diuretics, *e.g.*, thiazide diuretics, such as hydrochlorothiazide (Microzide); an insulin sensitizer, such as the PPARγ agonist pioglitazone, a glp-1r agonist, such as liraglutatide, vitamin E, an SGLT2 inhibitor, a DPPIV inhibitor, and kidney/liver transplant; or a combination of any of the foregoing.

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

The data obtained from cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of compositions featured herein in the invention lies generally within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage can vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the methods featured in the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose can be formulated in animal models to achieve a circulating plasma concentration range of the compound or, when appropriate, of the polypeptide product of a target sequence (*e.g.*, achieving a decreased concentration of the polypeptide) that includes the IC_{50} (*i.e.*, the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma can be measured, for example, by high performance liquid chromatography.

In addition to their administration, as discussed above, the iRNAs featured in the invention can be administered in combination with other known agents effective in treatment of pathological processes mediated by HSD17B13 expression. In any event, the administering physician can adjust the amount and timing of iRNA administration on the basis of results observed using standard measures of efficacy known in the art or described herein.

Synthesis of cationic lipids:

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

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

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

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

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

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

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

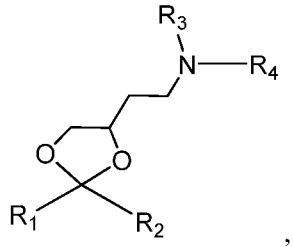
heterocycle substituents may be further substituted with one or more of oxo, halogen, -OH, -CN, alkyl, $-OR^x$, heterocycle, $-NR^xR^y$, $-NR^xC(=O)R^y$, $-NR^xSO_2R^y$, $-C(=O)R^x$, $-C(=O)OR^x$, $-C(=O)NR^xR^y$, $-SO_nR^x$ and $-SO_nNR^xR^y$.

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

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

Synthesis of Formula A:

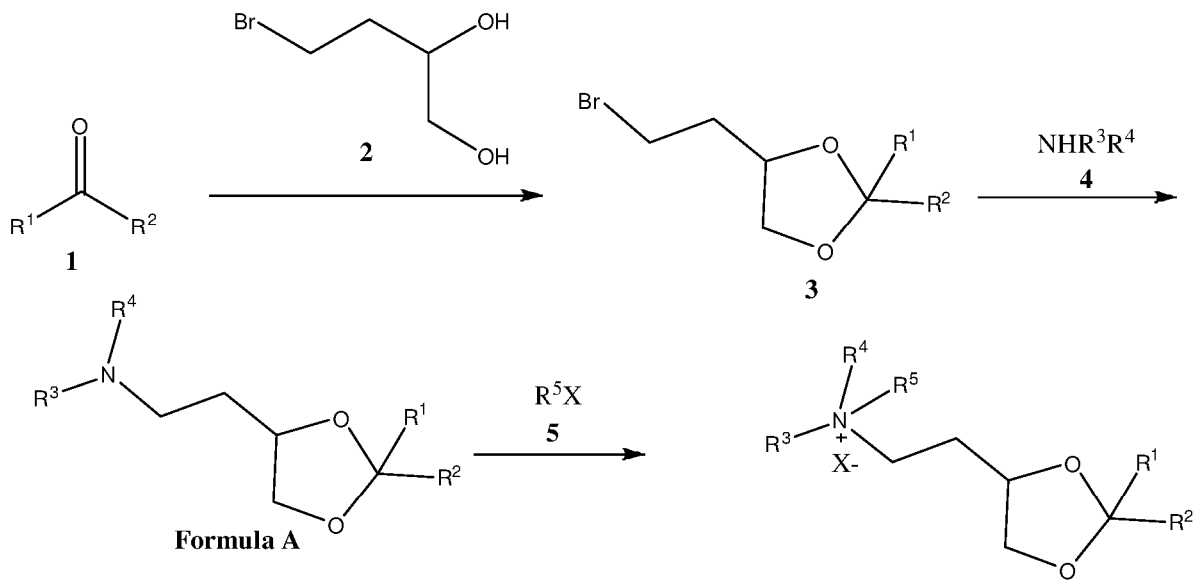
In certain embodiments, nucleic acid-lipid particles featured in the invention are formulated using a cationic lipid of formula A:



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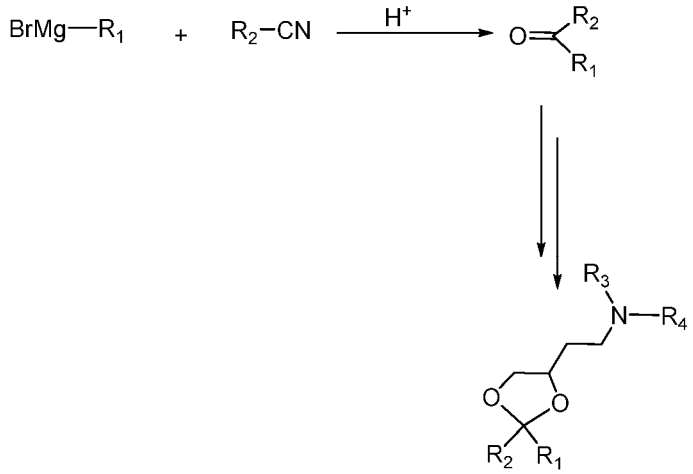
where R1 and R2 are independently alkyl, alkenyl or alkynyl, each can be optionally substituted, and R3 and R4 are independently lower alkyl or R3 and R4 can be taken together to form an optionally substituted heterocyclic ring. In some embodiments, the cationic lipid is XTC (2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane).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

Scheme 1



Lipid A, where R_1 and R_2 are independently alkyl, alkenyl or alkynyl, each can be optionally substituted, and R_3 and R_4 are independently lower alkyl or R_3 and R_4 can be taken together to form an optionally substituted heterocyclic ring, can be prepared according to Scheme 1. Ketone 1 and bromide 2 can be purchased or prepared according to methods known to those of ordinary skill in the art. Reaction of 1 and 2 yields ketal 3. Treatment of ketal 3 with amine 4 yields lipids of formula A. The lipids of formula A can be converted to the corresponding ammonium salt with an organic salt of formula 5, where X is anion counter ion selected from halogen, hydroxide, phosphate, sulfate, or the like.

Scheme 2



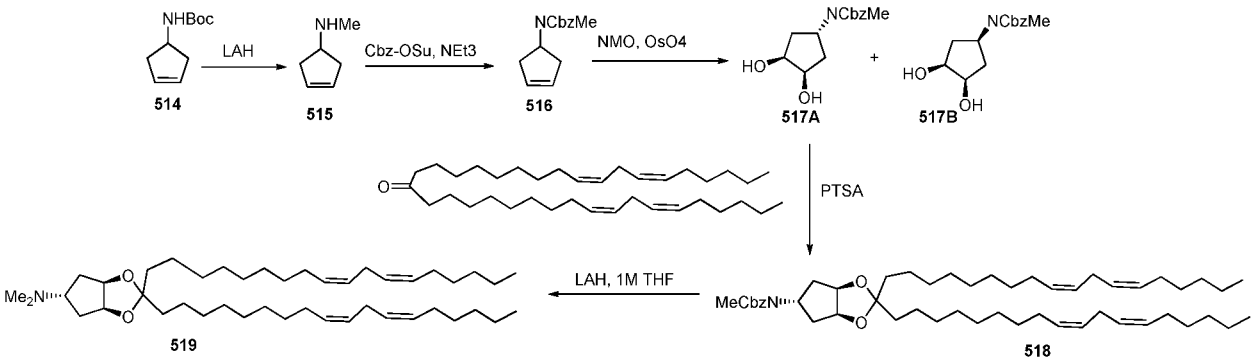
Alternatively, the ketone 1 starting material can be prepared according to Scheme 2. Grignard reagent 6 and cyanide 7 can be purchased or prepared according to methods known to those of ordinary skill in the art. Reaction of 6 and 7 yields ketone 1. Conversion of ketone 1 to the corresponding lipids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

Synthesis of MC3:

Preparation of DLin-M-C3-DMA (*i.e.*, (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate) was as follows. A solution of (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-ol (0.53 g), 4-N,N-dimethylaminobutyric acid hydrochloride (0.51 g), 4-N,N-dimethylaminopyridine (0.61g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.53 g) in dichloromethane (5 mL) was stirred at room temperature overnight. The solution was washed with dilute hydrochloric acid followed by dilute aqueous sodium bicarbonate. The organic fractions were dried over anhydrous magnesium sulphate, filtered and the solvent removed on a rotovap. The residue was passed down a silica gel column (20 g) using a 1-5% methanol/dichloromethane elution gradient. Fractions containing the purified product were combined and the solvent removed, yielding a colorless oil (0.54 g).

Synthesis of ALNY-100:

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



Synthesis of 515:

To a stirred suspension of LiAlH4 (3.74 g, 0.09852 mol) in 200 ml anhydrous THF in a two neck RBF (1L), was added a solution of 514 (10g, 0.04926mol) in 70 mL of THF slowly at 0 0C under nitrogen atmosphere. After complete addition, reaction mixture was warmed to room temperature and then heated to reflux for 4 h. Progress of the reaction was monitored by TLC. After completion of reaction (by TLC) the mixture was cooled to 0 0C and quenched with careful addition of saturated Na2SO4 solution. Reaction mixture was stirred for 4 h at room temperature and filtered off. Residue was washed well with THF. The filtrate and washings were mixed and diluted with 400 mL dioxane and 26 mL conc. HCl and stirred for 20 minutes at room temperature. The volatilities were stripped off under vacuum to furnish the hydrochloride salt of 515 as a white solid. Yield: 7.12 g 1H-NMR (DMSO, 400MHz): δ= 9.34 (broad, 2H), 5.68 (s, 2H), 3.74 (m, 1H), 2.66-2.60 (m, 2H), 2.50-2.45 (m, 5H).

Synthesis of 516:

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

Synthesis of 517A and 517B:

The cyclopentene 516 (5 g, 0.02164 mol) was dissolved in a solution of 220 mL acetone and water (10:1) in a single neck 500 mL RBF and to it was added N-methyl morpholine-N-oxide (7.6 g, 0.06492 mol) followed by 4.2 mL of 7.6% solution of OsO4 (0.275 g, 0.00108 mol) in tert-butanol at room temperature. After completion of the reaction (~ 3 h), the mixture was quenched with addition of solid Na2SO3 and resulting mixture was stirred for 1.5 h at room temperature. Reaction mixture was diluted with DCM (300 mL) and washed with water (2 x 100 mL) followed by saturated NaHCO3 (1 x 50 mL) solution, water (1 x 30 mL) and finally with brine (1x 50 mL). Organic phase was dried over Na_2SO_4 and solvent was removed in vacuum. Silica gel column chromatographic purification of the crude material was afforded a mixture of diastereomers, which were separated by prep HPLC. Yield: - 6 g crude 517A - Peak-1 (white solid), 5.13 g (96%). 1H-NMR (DMSO, 400MHz): δ= 7.39-7.31(m, 5H), 5.04(s, 2H), 4.78-4.73 (m, 1H), 4.48-4.47(d, 2H), 3.94-3.93(m, 2H), 2.71(s, 3H), 1.72- 1.67(m, 4H). LC-MS - [M+H]-266.3, [M+NH4 +]-283.5 present, HPLC-97.86%. Stereochemistry confirmed by X-ray.

Synthesis of 518:

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

General Procedure for the Synthesis of Compound 519:

A solution of compound 518 (1 eq) in hexane (15 mL) was added in a drop-wise fashion to an ice-cold solution of LAH in THF (1 M, 2 eq). After complete addition, the mixture was heated at 40°C over 0.5 h then cooled again on an ice bath. The mixture was carefully hydrolyzed with saturated aqueous Na_2SO_4 then filtered through Celite® and reduced to an oil. Column chromatography provided the pure 519 (1.3 g, 68%) which was obtained as a colorless oil. 13C NMR = 130.2, 130.1 (x2), 127.9 (x3), 112.3, 79.3, 64.4, 44.7, 38.3, 35.4, 31.5, 29.9 (x2), 29.7, 29.6 (x2), 29.5 (x3), 29.3 (x2), 27.2 (x3), 25.6, 24.5, 23.3, 226, 14.1; Electrospray MS (+ve): Molecular weight for C44H80NO2 (M + H)+ Calc. 654.6, Found 654.6.

Formulations prepared by either the standard or extrusion-free method can be characterized in similar manners. For example, formulations are typically characterized by visual inspection. They should be whitish translucent solutions free from aggregates or sediment. Particle size and particle size distribution of lipid-nanoparticles can be measured by light scattering using, for example, a Malvern Zetasizer Nano ZS (Malvern, USA). Particles should be about 20-300 nm, such as 40-100 nm in size. The particle size distribution should be unimodal. The total dsRNA concentration in the formulation, as well as the entrapped fraction, is estimated using a dye exclusion assay. A sample of the formulated dsRNA can be incubated with an RNA-binding dye, such as RiboGreen® (Molecular Probes) in the presence or absence of a formulation disrupting surfactant, *e.g.*, 0.5% Triton-X100. The total dsRNA in the formulation can be determined by the signal from the sample containing the surfactant, relative to a standard curve. The entrapped fraction is determined by subtracting the "free" dsRNA content (as measured by the signal in the absence of surfactant) from the total dsRNA content. Percent entrapped dsRNA is typically >85%. For SNALP formulation, the particle size is at least 30 nm, at least 40 nm, at least 50 nm, at least 60 nm, at least 70 nm, at least 80 nm, at least 90 nm, at least 100 nm, at least 110 nm, and at least 120 nm. The suitable range is typically about at least 50 nm to about at least 110 nm, about at least 60 nm to about at least 100 nm, or about at least 80 nm to about at least 90 nm.

VI. Methods of the Invention

The present invention also provides methods of using an iRNA of the invention and/or a composition of the invention to reduce and/or inhibit HSD17B13 expression in a cell, such as a cell in a subject, *e.g.*, a hepatocyte. The methods include contacting the cell with an RNAi agent or pharmaceutical composition comprising an iRNA agent of the invention. In some embodiments, the cell is maintained for a time sufficient to obtain degradation of the mRNA transcript of an HSD17B13 gene.

The present invention also provides methods of using an iRNA of the invention and/or a composition of the invention and an iRNA agent targeting a Patatin-like Phospholipase Domain Containing 3 (PNPLA3) gene and/or pharmaceutical composition comprising an iRNA agent targeting PNPLA3 to reduce and/or inhibit HSD17B13 expression in a cell, such as a cell in a subject, *e.g.,* a hepatocyte.

In addition, the present invention provides methods of inhibiting the accumulation and/or expansion of lipid droplets in a cell, such as a cell in a subject, *e.g.,* a hepatocyte. The methods include contacting the cell with an RNAi agent or pharmaceutical composition comprising an iRNA agent of the invention and an iRNA agent targeting a PNPLA3 gene and/or pharmaceutical composition comprising an iRNA agent targeting PNPLA3. In some embodiments, the cell is maintained for a time sufficient to obtain degradation of the mRNA transcript of an HSD17B13 gene and a PNPLA3 gene.

Reduction in gene expression can be assessed by any methods known in the art. For example, a reduction in the expression of HSD17B13 may be determined by determining the mRNA expression level of HSD17B13 using methods routine to one of ordinary skill in the art, *e.g.,* Northern blotting, qRT-PCR; by determining the protein level of HSD17B13 using methods routine to one of ordinary skill in the art, such as Western blotting, immunological techniques. A reduction in the expression of HSD17B13 may also be assessed indirectly by measuring a decrease in biological activity of HSD17B13, *e.g.*, a decrease in the enzymatic activity of HSD17B13 and/or a decrease in one or more of a lipid, a triglyceride, cholesterol (including LDL-C, HDL-C, VLDL-C, IDL-C and total cholesterol), or free fatty acids in a plasma, or a tissue sample, and/or a reduction in accumulation of fat and/or expansion of lipid droplets in the liver.

Suitable agents targeting a PNPLA3 gene are described in, for example, U.S. Patent Publication No.: 2017/0340661, the entire contents of which are incorporated herein by reference.

In the methods of the invention the cell may be contacted *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 an HSD17B13 gene (and, in some embodiments, a PNPLA3 gene). 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 or a non-human primate cell, *e.g.*, a monkey cell or a chimpanzee cell), a non-primate cell (such as a cow cell, a pig cell, a camel cell, a llama cell, a horse cell, a goat cell, a rabbit cell, a sheep cell, a hamster, a guinea pig cell, a cat cell, a dog cell, a rat cell, a mouse cell, a lion cell, a tiger cell, a bear cell, or a buffalo cell), a bird cell (*e.g.*, a duck cell or a goose cell), or a whale cell. In one embodiment, the cell is a human cell, *e.g.,* a human liver cell.

HSD17B13 expression is inhibited in the cell by at least about 5, 6, 7, 8, 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, 36, 37, 38, 39, 40, 41, 42, 43, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96,

97, 98, 99, or about 100%. In preferred embodiments, HSD17B13 expression is inhibited by at least 20%.

In some embodiment, PNPLA3 expression is also inhibited in the cell by at least about 5, 6, 7, 8, 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, 36, 37, 38, 39, 40, 41, 42, 43, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or about 100%. In preferred embodiments, PNPLA3 expression is inhibited by at least 20%.

In one embodiment, 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 HSD17B13 gene of the mammal to be treated.

In another embodiment, the *in vivo* methods of the invention may include administering to a subject a composition containing a first iRNA agent and a second iRNA agent, where the first iRNA includes a nucleotide sequence that is complementary to at least a part of an RNA transcript of the HSD17B13 gene of the mammal to be treated and and the second iRNA includes a nucleotide sequence that is complementary to at least a part of an RNA transcript of the PNPLA3 gene of the mammal to be treated.

When the organism to be treated is a mammal such as a human, 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, 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 some embodiments, the administration is *via* a depot injection. A depot injection may release the iRNA in a consistent way over a prolonged time period. Thus, a depot injection may reduce the frequency of dosing needed to obtain a desired effect, *e.g.*, a desired inhibition of HSD17B13, or a therapeutic or prophylactic effect. A depot injection may also provide more consistent serum concentrations. Depot injections may include subcutaneous injections or intramuscular injections. In preferred embodiments, the depot injection is a subcutaneous injection.

In some embodiments, the administration is *via* a pump. The pump may be an external pump or a surgically implanted pump. In certain embodiments, the pump is a subcutaneously implanted osmotic pump. In other embodiments, the pump is an infusion pump. An infusion pump may be used for intravenous, subcutaneous, arterial, or epidural infusions. In preferred embodiments, the infusion pump is a subcutaneous infusion pump. In other embodiments, the pump is a surgically implanted pump that delivers the iRNA to the liver.

An iRNA of the invention may be present in a pharmaceutical composition, such as 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.

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 an HSD17B13 gene in a mammal. The methods include administering to the mammal a composition comprising a dsRNA that targets an HSD17B13 gene in a cell of the mammal, thereby inhibiting expression of the HSD17B13 gene in the cell.

In some embodiment, the methods include administering to the mammal a composition comprising a dsRNA that targets an HSD17B13 gene in a cell of the mammal, thereby inhibiting expression of the HSD17B13 gene in the cell. In another embodiment, the methods include administering to the mammal a pharmaceutical composition comprising a dsRNA agent that targets an HSD17B13 gene in a cell of the mammal.

In another aspect, the present invention provides use of an iRNA agent or a pharmaceutical composition of the invention for inhibiting the expression of an HSD17B13 gene in a mammal.

In yet another aspect, the present invention provides use of an iRNA agent of the invention targeting a HSD17B13gene or a pharmaceutical composition comprising such an agent in the manufacture of a medicament for inhibiting expression of a HSD17B13 gene in a mammal.

In another aspect, the present invention also provides methods for inhibiting the expression of an HSD17B13 gene and a PNPLA3 gene in a mammal. The methods include administering to the mammal a composition comprising a dsRNA that targets an HSD17B13 gene in a cell of the mammal and a composition comprising a dsRNA that targets an PNPLA3 gene in a cell of the mammal, thereby inhibiting expression of the HSD17B13 gene and the PNPLA3 gene in the cell. In one embodiment, the methods include administering to the mammal a pharmaceutical composition comprising a dsRNA agent that targets an HSD17B13 gene and a PNPLA3 gene in a cell of the mammal.

In one aspect, the present invention provides use of an iRNA agent or a pharmaceutical composition of the invention, and a dsRNA that targets a PNPLA3 gene or a pharmaceutical composition comprising such an agent for inhibiting the expression of an HSD17B13 gene and a PNPLA3 gene in a mammal.

In yet another aspect, the present invention provides use of an iRNA agent of the invention targeting a HSD17B13gene or a pharmaceutical composition comprising such an agent, and a dsRNA that targets an PNPLA3 gene or a pharmaceutical composition comprising such an agent in

the manufacture of a medicament for inhibiting expression of a HSD17B13 gene and a PNPLA3 gene in a mammal.

Reduction in gene expression can be assessed by any methods known it the art and by methods, *e.g.* qRT-PCR, described herein. Reduction in protein production can be assessed by any methods known it the art and by methods, *e.g.* ELISA, enzymatic activity, described herein.

The present invention also provides therapeutic and prophylactic methods which include administering to a subject having, or prone to developing a fatty liver-associated disease, disorder, or condition, the iRNA agents, pharmaceutical compositions comprising an iRNA agent, or vectors comprising an iRNA of the invention.

In one aspect, the present invention provides methods of treating a subject having a disorder that would benefit from reduction in HSD17B13 expression, *e.g.,* an HSD17B13-associated disease.

The treatment methods (and uses) of the invention include administering to the subject, *e.g.,* a human, a therapeutically effective amount of a dsRNA agent that inhibits expression of HSD17B13 or a pharmaceutical composition comprising a dsRNA that inhibits expression of HSD17B13, thereby treating the subject.

In one aspect, the invention provides methods of preventing at least one symptom in a subject having a disorder that would benefit from reduction in HSD17B13 expression, *e.g.,*a chronic fibro-inflammatory disease. The methods include administering to the subject a prophylactically effective amount of dsRNA agent or a pharmaceutical composition comprising a dsRNA, thereby preventing at least one symptom in the subject.

In one embodiment, an HSD17B13-associated disease, disorder, or condition is a chronic fibro-inflammatory liver disease. Non-limiting examples of chronic fibro-inflammatory liver diseases include cancer, *e.g.,* cancer, *e.g.,* hepatocellular carcinoma, nonalcoholic steatohepatitis (NASH), cirrhosis of the liver, inflammation of the liver, hepatocellular necrosis, liver fibrosis, and nonalcoholic fatty liver disease (NAFLD).

The present invention also provides therapeutic and prophylactic methods which include administering to a subject having, or prone to developing a fatty liver-associated disease, disorder, or condition, the iRNA agents, pharmaceutical compositions comprising an iRNA agent, or vectors comprising an iRNA of the invention and and iRNA agent targeting PNPLA3, pharmaceutical compositions comprising such an iRNA agent, or vectors comprising such an iRNA.

The present invention also provides use of a therapeutically effective amount of an iRNA agent of the invention or a pharmaceutical composition comprising a dsRNA that inhibits expression of HSD17B13 for treating a subject, *e.g.*, a subject that would benefit from a reduction and/or inhibition of HSD17B13 expression, *e.g.,* an HSD17B13-associated disease, *e.g.,*a chronic fibro-inflammatory disease.

In another aspect, the present invention provides use of an iRNA agent, *e.g.,* a dsRNA, of the invention targeting a HSD17B13 for gene or a pharmaceutical composition comprising an iRNA agent targeting a HSD17B13 for gene in the manufacture of a medicament for treating a subject, *e.g.,*

a subject that would benefit from a reduction and/or inhibition of HSD17B13for expression, *e.g.,* a HSD17B13-associated disease.

The present invention also provides use of a prophylactically effective amount of an iRNA agent of the invention or a pharmaceutical composition comprising a dsRNA that inhibits expression of HSD17B13 for preventing at least one symptom in a subject having a disorder that would benefit from reduction in HSD17B13 expression, *e.g.,*a chronic fibro-inflammatory disease.

In another aspect, the present invention provides use of an iRNA agent, *e.g.,* a dsRNA, of the invention targeting a HSD17B13 gene or a pharmaceutical composition comprising an iRNA agent targeting a HSD17B13 gene in the manufacture of a medicament for preventing at least one symptom in a subject having a disorder that would benefit from reduction in HSD17B13 expression, *e.g.,*a chronic fibro-inflammatory disease.

In one aspect, the present invention also provides use of a therapeutically effective amount of an iRNA agent of the invention or a pharmaceutical composition comprising a dsRNA that inhibits expression of HSD17B13 in combination with a dsRNA that targets a PNPLA3 gene or a pharmaceutical composition comprising such an agent for treating a subject, *e.g.*, a subject that would benefit from a reduction and/or inhibition of HSD17B13 expression, *e.g.,* an HSD17B13-associated disease, *e.g.,*a chronic fibro-inflammatory disease.

In one aspect, the present invention also provides use of an iRNA agent, *e.g.,* a dsRNA, of the invention targeting a HSD17B13 gene or a pharmaceutical composition comprising an iRNA agent targeting a HSD17B13 gene in combination with a dsRNA that targets a PNPLA3 gene or a pharmaceutical composition comprising such an agent for preventing at least one symptom in a subject having a disorder that would benefit from reduction in HSD17B13 expression, *e.g.,*a chronic fibro-inflammatory disease.

The combination methods of the invention for treating a subject, *e.g.,* a human subject, having a HSD17B13-associated disease, disorder, or condition, such as a chronic fibro-inflammatory liver disease, *e.g.,* NASH, are useful for treating such subjects as silencing of PNPLA3 decreases steatosis (*i.e.* liver fat) while silencing HSD17B13 decreases inflammation and fibrosis. For example, genome wide association studies have demonstrated that silencing PNPLA3 and HSD17B13 have an additive effect to decrease NASH pathology. Indeed, a protective loss-of-function HSD17B13 allele was found to be associated with lower prevalence of NASH in subjects with pathogenic PNPLA3 alleles. In subjects having wild-type PNPLA3 alleles which have lower risk of NASH, the added presence of loss-of-function HSD17B13 alleles conferred even greater protection.

Accordingly, in one aspect, the present invention provides methods of treating a subject having a disorder that would benefit from reduction in HSD17B13 expression, *e.g.,* an HSD17B13-associated disease, such as a chronic fibro-inflammatory liver disease (*e.g.,* cancer, *e.g.,* hepatocellular carcinoma, nonalcoholic steatohepatitis (NASH), cirrhosis of the liver, inflammation of the liver, hepatocellular necrosis, liver fibrosis, and nonalcoholic fatty liver disease (NAFLD). In one embodiment, the chronic fibro-inflammatory liver disease is NASH.

The combination treatment methods (and uses) of the invention include administering to the subject, *e.g.,* a human subject, a therapeutically effective amount of a dsRNA agent that inhibits expression of HSD17B13 or a pharmaceutical composition comprising a dsRNA that inhibits expression of HSD17B13, and a dsRNA agent that inhibits expression of PNPLA3 or a pharmaceutical composition comprising a dsRNA that inhibits expression of PNPLA3, thereby treating the subject.

In one aspect, the invention provides methods of preventing at least one symptom in a subject having a disorder that would benefit from reduction in HSD17B13 expression, *e.g.,*a chronic fibro-inflammatory disease, *e.g.,* NASH. The methods include administering to the subject a prophylactically effective amount of dsRNA agent or a pharmaceutical composition comprising a dsRNA that inhibits expression of HSD17B13, and a dsRNA agent that inhibits expression of PNPLA3 or a pharmaceutical composition comprising a dsRNA that inhibits expression of PNPLA3, thereby preventing at least one symptom in the subject.

In one embodiment, the subject is heterozygous for the gene encoding the patatin like phospholipase domain containg 3 (PNPLA3) I148M variation. In another embodiment, the subject is homozygous for the gene encoding the PNPLA3 I148M variation. In one embodiment, the subject is heterozygous for the gene encoding the patatin like phospholipase domain containg 3 (PNPLA3) I144M variation. In another embodiment, the subject is homozygous for the gene encoding the PNPLA3 I144M variation. In one embodiment, the subject is homozygous for the gene encoding a functional HSD17B13 protein. In another embodiment, the subject is heterozygous for the gene encoding a functional HSD17B13 protein. In yet another embodiment, the subject is heterozygous for the gene encoding a functional HSD17B13 protein and a gene encoding a loss of function variant of HSD17B13. In another embodiment, the subject is not a carrier of the *HSD17B13* rs72613567 variant.

In certain embodiments of the invention the methods may include identifying a subject that would benefit from reduction in HSD17B13 expression. The methods generally include determining whether or not a sample from the subject comprises a nucleic acid encoding a PNPLA3Ile148Met variant or a PNPLA3Ile144Met variant. The methods may also include classifying a subject as a candidate for treating or inhibiting a liver disease by inhibiting the expression of aHSD17B13, by determining whether or not a sample from the subject comprises a first nucleic acid encoding a PNPLA3 protein comprising an I148M variation and a second nucleic acid encoding a functional HSD17B13 protein, and/or a PNPLA3 protein comprising an I148M variation and a functional HSD17B13 protein, and classifying the subject as a candidate for treating or inhibiting a liver disease by inhibiting HSD17B13 when both the first and second nucleic acids are detected and/or when both proteins are detected.

The variant PNPLA3 Ile148Met variant or PNPLA3 Ile144Met variant can be any of the PNPLA3 Ile148Met variants and PNPLA3 Ile144Met variants described herein. The PNPLA3 Ile148Met variant or PNPLA3 Ile144Met variant can be detected by any suitable means, such as ELISA assay, RT-PCR, sequencing.

In some embodiments, the methods further comprise determining whether the subject is homozygous or heterozygous for the PNPLA3 Ile148Met variant or the PNPLA3 Ile144Met variant. In some embodiments, the subject is homozygous for the PNPLA3 Ile148Met variant or the PNPLA3 Ile144Met variant. In some embodiments, the subject is heterozygous for the PNPLA3 Ile148Met variant or the PNPLA3 Ile144Met variant. In some embodiments, the subject is homozygous for the PNPLA3 Ile148Met variant. In some embodiments, the subject is heterozygous for the PNPLA3 Ile148Met variant. In some embodiments, the subject is homozygous for the PNPLA3 Ile144Met variant. In some embodiments, the subject is heterozygous for the PNPLA3 Ile144Met variant.

In some embodiments, the subject does not comprise any genes encoding loss of function variations in the HSD17B13 protein. It is believed that loss of function variations in the HSD17B13 protein, including those described herein and in U.S. Provisional Application Serial No. 62/570,985, filed on October 11, 2017, confer a liver disease-protective effect and it is further believed that this protective effect is enhanced in the presence of the variant PNPLA3 Ile148M variation.

In some embodiments, the methods further comprise determining whether the subject is obese. In some embodiments, a subject is obese if their body mass index (BMI) is over 30 kg/m^2 . Obesity can be a characteristic of a subject having, or at risk of developing, a liver disease. In some embodiments, the methods further comprise determining whether the subject has a fatty liver. A fatty liver can be a characteristic of a subject having, or at risk of developing, a liver disease. In some embodiments, the methods further comprise determining whether the subject is obese and has a fatty liver.

As used herein, "nonalcoholic fatty liver disease," used interchangeably with the term "NAFLD," refers to a disease defined by the presence of macrovascular steatosis in the presence of less than 20 gm of alcohol ingestion per day. NAFLD is the most common liver disease in the United States, and is commonly associated with insulin resistance/type 2 diabetes mellitus and obesity. NAFLD is manifested by steatosis, steatohepatitis, cirrhosis, and sometimes hepatocellaular carcinoma. For a review of NAFLD, see Tolman and Dalpiaz (2007) Ther. Clin. Risk. Manag., 3(6):1153-1163 the entire contents of which are incorporated herein by reference.

As used herein, the terms "steatosis," "hepatic steatosis," and "fatty liver disease" refer to the accumulation of triglycerides and other fats in the liver cells.

As used herein, ther term "Nonalcoholic steatohepatitis" or "NASH" refers to liver inflammation and damage caused by a buildup of fat in the liver. NASH is part of a group of conditions called nonalcoholic fatty liver disease (NAFLD). NASH resembles alcoholic liver disease, but occurs in people who drink little or no alcohol. The major feature in NASH is fat in the liver, along with inflammation and damage. Most people with NASH feel well and are not aware that they have a liver problem. Nevertheless, NASH can be severe and can lead to cirrhosis, in which the liver is permanently damaged and scarred and no longer able to work properly. NASH is usually first suspected in a person who is found to have elevations in liver tests that are included in routine blood test panels, such as alanine aminotransferase (ALT) or aspartate aminotransferase (AST). When further evaluation shows no apparent reason for liver disease (such as medications, viral hepatitis, or

excessive use of alcohol) and when x rays or imaging studies of the liver show fat, NASH is suspected. The only means of proving a diagnosis of NASH and separating it from simple fatty liver is a liver biopsy.

As used herein, the term "cirrhosis," defined histologically, is a diffuse hepatic process characterized by fibrosis and conversion of the normal liver architecture into structurally abnormal nodules.

As used herein, the term "serum lipid" refers to any major lipid present in the blood. Serum lipids may be present in the blood either in free form or as a part of a protein complex, *e.g.*, a lipoprotein complex. Non-limiting examples of serum lipids may include triglycerides (TG), cholesterol, such as total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), very low density lipoprotein cholesterol (VLDL-C) and intermediate-density lipoprotein cholesterol (IDL-C).

In one embodiment, a subject that would benefit from the reduction of the expression of HSD17B13 (and, in some embodiments, PNPLA3) is, for example, a subject that has type 2 diabetes and prediabetes, or obesity; a subject that has high levels of fats in the blood, such as cholesterol, or has high blood pressure; a subject that has certain metabolic disorders, including metabolic syndrome; a subject that has rapid weight loss; a subject that has certain infections, such as hepatitis C infection, or a subject that has been exposed to some toxins. In one embodiment, a subject that would benefit from the reduction of the expression of HSD17B13 (and, in some embodiments, PNPLA3) is, for example, a subject that is middle-aged or older; a subject that is Hispanic, non-Hispanic whites, or African Americans; a subject that takes certain drugs, such as corticosteroids and cancer drugs.

In the methods (and uses) of the invention which comprise administering to a subject a first dsRNA agent targeting HSD17B13 and a second dsRNA agent targeting PNPLA3, the first and second dsRNA agents may be formulated in the same composition or different compositions and may administered to the subject in the same composition or in separate compositions.

In one embodiment, an "iRNA" for use in the methods of the invention is a "dual targeting RNAi agent." The term "dual targeting RNAi agent" refers to a molecule comprising a first dsRNA agent comprising 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 first target RNA, *i.e.,* an HSD17B13 gene, covalently attached to a molecule comprising a second dsRNA agent comprising 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 second target RNA, *i.e.,* a PNPLA3 gene. In some embodiments of the invention, a dual targeting RNAi agent triggers the degradation of the first and the second target RNAs, *e.g.*, mRNAs, through a post-transcriptional gene-silencing mechanism referred to herein as RNA interference or RNAi.

The dsRNA agent may be administered to the subject at a dose of about 0.1 mg/kg to about 50 mg/kg. Typically, a suitable dose will be in the range of about 0.1 mg/kg to about 5.0 mg/kg, preferably about 0.3 mg/kg and about 3.0 mg/kg.

The iRNA can be administered by intravenous infusion over a period of time, on a regular basis. In certain embodiments, after an initial treatment regimen, the treatments can be administered on a less frequent basis.

Administration of the iRNA can reduce HSD17B13 levels, *e.g.*, in a cell, tissue, blood, urine or other compartment of the patient by at least about 5%, 6, 7, 8, 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, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 39, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or at least about 99% or more. In a preferred embodiment, administration of the iRNA can reduce HSD17B13 levels, *e.g.*, in a cell, tissue, blood, urine or other compartment of the patient by at least 20%.

Administration of the iRNA can reduce PNPLA3 levels, *e.g.*, in a cell, tissue, blood, urine or other compartment of the patient by at least about 5%, 6, 7, 8, 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, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 39, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or at least about 99% or more. In a preferred embodiment, administration of the iRNA can reduce PNPLA3 levels, *e.g.*, in a cell, tissue, blood, urine or other compartment of the patient by at least 20%.

Before administration of a full dose of the iRNA, patients can be administered a smaller dose, such as a 5% infusion reaction, and monitored for adverse effects, such as an allergic reaction. In another example, the patient can be monitored for unwanted immunostimulatory effects, such as increased cytokine (*e.g.*, TNF-alpha or INF-alpha) levels.

Alternatively, the iRNA can be administered subcutaneously, *i.e.*, by subcutaneous injection. One or more injections may be used to deliver the desired daily 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 every other day or to once a year. In certain embodiments, the iRNA is administered about once per week, once every 7-10 days, once every 2 weeks, once every 3 weeks, once every 4 weeks, once every 5 weeks, once every 6 weeks, once every 7 weeks, once every 8 weeks, once every 9 weeks, once every 10 weeks, once every 11 weeks, once every 12 weeks, once per month, once every 2 months, once every 3 months once per quarter), once every 4 months, once every 5 months, or once every 6 months.

In one embodiment, the method includes administering a composition featured herein such that expression of the target HSD17B13 gene is decreased, such as for about 1, 2, 3, 4, 5, 6, 7, 8, 12, 16, 18, 24 hours, 28, 32, or abour 36 hours. In one embodiment, expression of the target HSD17B13 gene is decreased for an extended duration, *e.g.*, at least about two, three, four days or more, *e.g.*, about one week, two weeks, three weeks, or four weeks or longer.

In another embodiment, the method includes administering a composition featured herein such that expression of the target PNPLA3 gene is decreased, such as for about 1, 2, 3, 4, 5, 6, 7, 8, 12, 16, 18, 24 hours, 28, 32, or abour 36 hours. In one embodiment, expression of the target PNPLA3 gene is decreased for an extended duration, *e.g.*, at least about two, three, four days or more, *e.g.*, about one week, two weeks, three weeks, or four weeks or longer.

Preferably, the iRNAs useful for the methods and compositions featured herein specifically target RNAs (primary or processed) of the target HSD17B13 gene (and, in some embodiments, a PNPLA3 gene). Compositions and methods for inhibiting the expression of these genes using iRNAs can be prepared and performed as described herein.

Administration of the dsRNA according to the methods of the invention may result in a reduction of the severity, signs, symptoms, and/or markers of such diseases or disorders in a patient with a disorder of lipid metabolism. By "reduction" in this context is meant a statistically significant decrease in such level. The reduction can be, for example, at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or about 100%.

Efficacy of treatment or prevention of disease can be assessed, for example by measuring disease progression, disease remission, symptom severity, reduction in pain, quality of life, dose of a medication required to sustain a treatment effect, level of a disease marker or any other measurable parameter appropriate for a given disease being treated or targeted for prevention. It is well within the ability of one skilled in the art to monitor efficacy of treatment or prevention by measuring any one of such parameters, or any combination of parameters. For example, efficacy of treatment of a disorder of lipid metabolism may be assessed, for example, by periodic monitoring of one or more serum lipid levels, *e.g.,* triglyceride levels. Comparisons of the later readings with the initial readings provide a physician an indication of whether the treatment is effective. It is well within the ability of one skilled in the art to monitor efficacy of treatment or prevention by measuring any one of such parameters, or any combination of parameters. In connection with the administration of an iRNA or pharmaceutical composition thereof, "effective against" a disorder of lipid metabolism indicates that administration in a clinically appropriate manner results in a beneficial effect for at least a statistically significant fraction of patients, such as a improvement of symptoms, a cure, a reduction in disease, extension of life, improvement in quality of life, or other effect generally recognized as positive by medical doctors familiar with treating disorder of lipid metabolisms and the related causes.

A treatment or preventive effect is evident when there is a statistically significant improvement in one or more parameters of disease status, or by a failure to worsen or to develop symptoms where they would otherwise be anticipated. As an example, a favorable change of at least

10% in a measurable parameter of disease, and preferably at least 20%, 30%, 40%, 50% or more can be indicative of effective treatment. Efficacy for a given iRNA drug or formulation of that drug can also be judged using an experimental animal model for the given disease as known in the art.

The invention further provides methods for the use of a iRNA agent or a pharmaceutical composition of the invention, *e.g.*, for treating a subject that would benefit from reduction and/or inhibition of HSD17B13 expression or HSD17B13, *e.g.,* a subject having an HSD17B13-associated disease disorder, or condition, 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. In some embodiments, the invention provides methods for the use of a iRNA agent or a pharmaceutical composition of the invention and an iRNA agent targeting PNPLA3, *e.g.*, for treating a subject that would benefit from reduction and/or inhibition of HSD17B13 expression and PNPLA3 expression, *e.g.,* a subject having an HSD17B13-associated disease disorder, or condition (*e.g.,* NASH), 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. For example, in certain embodiments, an iRNA agent or pharmaceutical composition of the invention is administered in combination with, *e.g.*, pyridoxine, an ACE inhibitor (angiotensin converting enzyme inhibitors), *e.g.*, benazepril agents to decrease blood pressure, e.g., diuretics, beta-blockers, ACE inhibitors, angiotensin II receptor blockers, calcium channel blockers, alpha blockers, alpha-2 receptor antagonists, combined alpha- and beta-blockers, central agonists, peripheral adrenergic inhibitors, and blood vessel dialators; or agents to decrease cholesterol, e.g., statins, selective cholesterol absorption inhibitors, resins; lipid lowering therapies; insulin sensitizers, such as the PPARγ agonist pioglitazone; glp-1r agonists, such as liraglutatide; vitamin E; SGLT2 inhibitors; or DPPIV inhibitors; or a combination of any of the foregoing. In one embodiment, an iRNA agent or pharmaceutical composition of the invention is administered in combination with an agent that inhibits the expression and/or activity of a transmembrane 6 superfamily member 2 (TM6SF2) gene, *e.g.,* an RNAi agent that inhibits the expression of a TM6SF2 gene.

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.*, subcutaneously, 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.

VII. Kits

The present invention also provides kits for performing any of the methods of the invention. Such kits include one or more RNAi agent(s) and instructions for use, *e.g.*, instructions for inhibiting expression of a HSD17B13 in a cell by contacting the cell with an RNAi agent or pharmaceutical composition of the invention in an amount effective to inhibit expression of the HSD17B13. The kits may optionally further comprise means for contacting the cell with the RNAi agent (*e.g.*, an injection device), or means for measuring the inhibition of HSD17B13 (*e.g.*, means for measuring the

inhibition of HSD17B13 mRNA and/or HSD17B13 protein). Such means for measuring the inhibition of HSD17B13 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 administering the RNAi agent(s) to a subject or means for determining the therapeutically effective or prophylactically effective amount.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the iRNAs and methods featured in the invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

EXAMPLES

Example 1. iRNA Design, Synthesis, and Selection

This Example describes methods for the design, synthesis, and selection of HSD17B13 iRNA agents.

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.

Bioinformatics

A set of siRNAs targeting the human hydroxysteroid 17-beta dehydrogenase 13 gene (HSD17B13; human NCBI refseqID NM_178135.4; NCBI GeneID: 345275) as well the toxicology-species HSD17B13 ortholog from cynomolgus monkey: XM_005555367.2 was designed using custom R and Python scripts. All the siRNA designs have a perfect match to the human HSD17B13 transcript and a subset either perfect or near-perfect matches to the cynomolgus monkey ortholog. The human NM_178135 REFSEQ mRNA, version 4, has a length of 2397 bases. The rationale and method for the set of siRNA designs is as follows: the predicted efficacy for every potential 23mer siRNA from position 10 through the end was determined with a random forest model derived from the direct measure of mRNA knockdown from several thousand distinct siRNA designs targeting a diverse set of vertebrate genes. For each strand of the siRNA, a custom Python script was used in a brute force search to measure the number and positions of mismatches between the siRNA and all potential alignments in the human transcriptome. Extra weight was given to mismatches in the seed region, defined here as positions 2-9 of the antisense oligonucleotide, as well the cleavage site of the siRNA, defined here as positions 10-11 of the antisense oligonucleotide. The relative weight of the mismatches was 2.8, 1.2, 1 for seed mismatches, cleavage site, and other positions up through antisense position 19. Mismatches in the first position were ignored. A specificity score was calculated for each strand by summing the value of each weighted mismatch. Preference was given to siRNAs whose antisense score in human and cynomolgus monkey was >= 2 and predicted efficacy was >= 50% knockdown.

A detailed list of the unmodified nucleotide sequences of the sense strand and antisense strand sequences is shown in Table 2.

A detailed list of the modified nucleotide sequences of the sense strand and antisense strand sequences is shown in Table 3.

In vitro Cos-7 (Dual-Luciferase psiCHECK2 vector), Primary Human Hepatocytes, and Primary Cynomolgus Hepatocytes screening

Cell culture and transfections:

Cos-7 (ATCC) were transfected by adding 5µl of 1 ng/ul, diluted in Opti-MEM, HSD17B13 psiCHECK2 vector (Blue Heron Biotechnology), 4.9µl of Opti-MEM plus 0.1µl of Lipofectamine 2000 per well (Invitrogen, Carlsbad CA. cat #11668-019) to 5µl of siRNA duplexes per well, with 4 replicates of each siRNA duplex, into a 384-well plate, and incubated at room temperature for 15

minutes. Thirty-five µl of Dulbecco's Modified Eagle Medium (ThermoFisher) containing ~5 $x10^3$ cells were then added to the siRNA mixture. Cells were incubated for 48 hours followed by Firefly (transfection control) and Renilla (fused to target sequence) luciferase measurements. Single dose experiments were performed at 50nM.

Primary Human Hepatocytes (BioIVT) were transfected by adding 4.9µl of Opti-MEM plus 0.1µl of RNAiMAX per well (Invitrogen, Carlsbad CA. cat # 13778-150) to 5µl of siRNA duplexes per well, with 4 replicates of each siRNA duplex, into a 384-well plate, and incubated at room temperature for 15 minutes. Firthy µl of InVitroGRO CP plating media (BioIVT) containing ~15 $x10^3$ cells were then added to the siRNA mixture. Cells were incubated for 48 hours prior to RNA purification. Single dose experiments were performed at 50nM.

Primary Cynomolgus Hepatocytes (BioIVT) were transfected by adding 4.9µl of Opti-MEM plus 0.1µl of RNAiMAX per well (Invitrogen, Carlsbad CA. cat # 13778-150) to 5µl of siRNA duplexes per well, with 4 replicates of each siRNA duplex, into a 384-well plate, and incubated at room temperature for 15 minutes. Firthy µl of InVitroGRO CP plating media (BioIVT) containing ~5 $x10^3$ cells were then added to the siRNA mixture. Cells were incubated for 48 hours prior to RNA purification. Single dose experiments were performed at 50nM.

Total RNA isolation using DYNABEADS mRNA Isolation Kit:

RNA was isolated using an automated protocol on a BioTek-EL406 platform using DYNABEADs (Invitrogen, cat#61012). Briefly, 70ul of Lysis/Binding Buffer and 10ul of lysis buffer containing 3ul of magnetic beads were added to the plate with cells. Plates were incubated on an electromagnetic shaker for 10 minutes at room temperature and then magnetic beads were captured and the supernatant was removed. Bead-bound RNA was then washed 2 times with 150ul Wash Buffer A and once with Wash Buffer B. Beads were then washed with 150ul Elution Buffer, re-captured and supernatant removed.

cDNA synthesis using ABI High capacity cDNA reverse transcription kit (Applied Biosystems, Foster City, CA, Cat #4368813):

Ten µl of a master mix containing 1µl 10X Buffer, 0.4ul 25X dNTPs, 1µl 10x Random primers, 0.5µl Reverse Transcriptase, 0.5µl RNase inhibitor and 6.6µl of H2O per reaction was added to RNA isolated above. Plates were sealed, mixed, and incubated on an electromagnetic shaker for 10 minutes at room temperature, followed by 2h 37°C.

Real time PCR:

Two µl of cDNA and 5µl Lightcycler 480 probe master mix (Roche Cat # 04887301001) were added to either 0.5µl of Human GAPDH TaqMan Probe (4326317E) and 0.5µl HSD17B13 Human probe (Hs01068199_m1, Thermo) or 0.5µl Cyno GAPDH (custom) and 0.5µl HSD17B13 Cyno probe (Mf02888851_m1, Thermo) per well in a 384 well plates (Roche cat # 04887301001). Real time PCR was done in a LightCycler480 Real Time PCR system (Roche). Each duplex was tested at least two times and data were normalized to cells transfected with a non-targeting control siRNA. To calculate relative fold change, real time data were analyzed using the ΔΔCt method and normalized to assays performed with cells transfected with a non-targeting control siRNA.

Table 4 shows the results of a 50 nM single dose screen in Cos-7 (Dual-Luciferase psiCHECK2 vector) cells transfected with the indicate iRNA agents. Data are expressed as percent of message remaining relative to untreated cells.

Table 5 shows the results of a 50 nM single dose screen in Primary Human Hepatocytes transfected with the indicate iRNA agents. Data are expressed as percent of message remaining relative to untreated cells.

Table 6 shows the results of a 50 nM single dose screen in Primary Cynomolgus Hepatocytes transfected with the indicate iRNA agents. Data are expressed as percent of message remaining relative to untreated cells.

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.

Abbreviation	**Nucleotide(s)**
A	Adenosine-3'-phosphate
Ab	beta-L-adenosine-3`-phosphate
Abs	beta-L-adenosine-3`-phosphorothioate
Af	2'-fluoroadenosine-3'-phosphate
Afs	2'-fluoroadenosine-3'-phosphorothioate
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

Abbreviation	Nucleotide(s)
Us	uridine -3'-phosphorothioate
N	any nucleotide (G, A, C, T or U)
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
L96	N-[tris(GalNAc-alkyl)-amidodecanoyl)]-4-hydroxyprolinol
P	Phosphate
VP	Vinyl-phosphate
dA	2`-deoxyadenosine-3`-phosphate
dAs	2`-deoxyadenosine-3`-phosphorothioate
dC	2`-deoxycytidine-3`-phosphate
dCs	2`-deoxycytidine-3`-phosphorothioate
dG	2`-deoxyguanosine-3`-phosphate
dGs	2`-deoxyguanosine-3`-phosphorothioate
dT	2`-deoxythymidine-3`-phosphate
dTs	2`-deoxythymidine-3`-phosphorothioate
dU	2`-deoxyuridine
dUs	2`-deoxyuridine-3`-phosphorothioate
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
(Aam)	2`-O-(N-methylacetamide)adenosine-3`-phosphate
(Aams)	2`-O-(N-methylacetamide)adenosine-3`-phosphorothioate
(Gam)	2`-O-(N-methylacetamide)guanosine-3`-phosphate

Abbreviation	Nucleotide(s)
(Gams)	2`-O-(N-methylacetamide)guanosine-3`-phosphorothioate
(Tam)	2`-O-(N-methylacetamide)thymidine-3`-phosphate
(Tams)	2`-O-(N-methylacetamide)thymidine-3`-phosphorothioate
(Aeo)	2`-O-methoxyethyladenosine-3`-phosphate
(Aeos)	2`-O-methoxyethyladenosine-3`-phosphorothioate
(Geo)	2`-O-methoxyethylguanosine-3`-phosphate
(Geos)	2`-O-methoxyethylguanosine-3`-phosphorothioate
(Teo)	2`-O-methoxyethyl-5-methyluridine-3`-phosphate
(Teos)	2`-O-methoxyethyl-5-methyluridine-3`-phosphorothioate
(m5Ceo)	2`-O-methoxyethyl-5-methylcytidine-3`-phosphate
(m5Ceos)	2`-O-methoxyethyl-5-methylcytidine-3`-phosphorothioate
(A3m)	3`-O-methyladenosine-2`-phosphate
(A3mx)	3`-O-methyl-xylofuranosyladenosine-2`-phosphate
(G3m)	3`-O-methylguanosine-2`-phosphate
(G3mx)	3`-O-methyl-xylofuranosylguanosine-2`-phosphate
(C3m)	3`-O-methylcytidine-2`-phosphate
(C3mx)	3`-O-methyl-xylofuranosylcytidine-2`-phosphate
(U3m)	3`-O-methyluridine-2`-phosphate
U3mx)	3`-O-methyl-xylofuranosyluridine-2`-phosphate
(m5Cam)	2`-O-(N-methylacetamide)-5-methylcytidine-3`-phosphate
(m5Cams)	2`-O-(N-methylacetamide)-5-methylcytidine-3`-phosphorothioate
(Chd)	2'-O-hexadecyl-cytidine-3'-phosphate
(Chds)	2'-O-hexadecyl-cytidine-3'-phosphorothioate
(Uhd)	2'-O-hexadecyl-uridine-3'-phosphate
(Uhds)	2'-O-hexadecyl-uridine-3'-phosphorothioate
(pshe)	Hydroxyethylphosphorothioate

[1]The chemical structure of L96 is as follows:

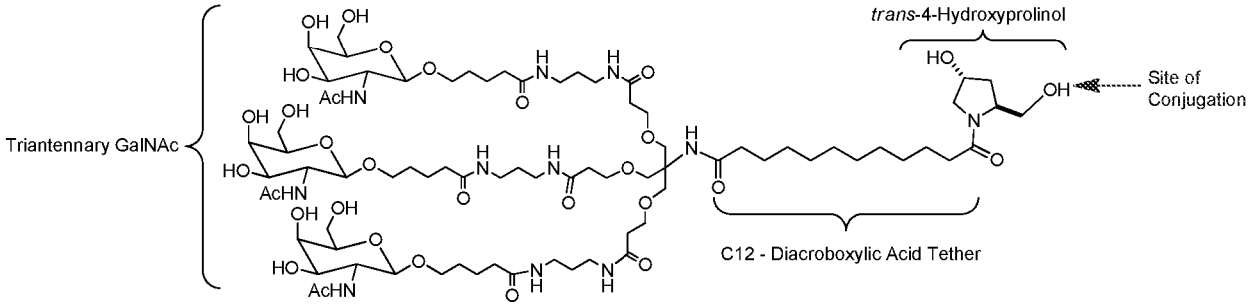

Triantennary GalNAc
trans-4-Hydroxyprolinol
Site of Conjugation
C12 - Diacroboxylic Acid Tether

TABLE 2. HSD17B13 Unmodified Sequences

Duplex Name	SEQ ID NO:	Sense Strand Sequence 5' to 3'	Range in NM_178135.4	SEQ ID N(	Antisense Strand Sequence 5' to 3'	Range in NM_178135.4
AD-238911.1	3003	CAGUACCUCCUCCCUAGGACU	4-24	3299	AGUCCUAGGGAGGAGGUACUGUC	2-24
AD-238912.1	3004	AGUACCUCCUCCCUAGGACUA	5-25	3300	UAGUCCUAGGGAGGAGGUACUGU	3-25
AD-238913.1	3005	GUACCUCCUCCCUAGGACUAA	6-26	3301	UUAGUCCUAGGGAGGAGGUACUG	4-26
AD-238929.1	3006	ACUACACAAGGACUGAACCAA	22-42	3302	UUGGUUCAGUCCUUGUGUAGUCC	20-42
AD-238930.1	3007	CUACACAAGGACUGAACCAGA	23-43	3303	UCUGGUUCAGUCCUUGUGUAGUC	21-43
AD-238932.1	3008	ACACAAGGACUGAACCAGAAA	25-45	3304	UUUCUGGUUCAGUCCUUGUGUAG	23-45
AD-238960.1	3009	CAGAGCAAAGCCAUGAACAUA	54-74	3305	UAUGUUCAUGGCUUUGCUCUGUC	52-74
AD-238979.1	3010	UCAUCCUAGAAAUCCUUCUGA	73-93	3306	UCAGAAGGAUUUCUAGGAUGAUG	71-93
AD-238991.1	3011	UCCUUCUGCUUCUGAUCACCA	85-105	3307	UGGUGAUCAGAAGCAGAAGGAUU	83-105
AD-239009.1	3012	CCAUCAUCUACUCCUACUUGA	103-123	3308	UCAAGUAGGAGUAGAUGAUGGUG	101-123
AD-239015.1	3013	UCUACUCCUACUUGGAGUCGU	109-129	3309	ACGACUCCAAGUAGGAGUAGAUG	107-129
AD-239016.1	3014	CUACUCCUACUUGGAGUCGUU	110-130	3310	AACGACUCCAAGUAGGAGUAGAU	108-130
AD-239017.1	3015	UACUCCUACUUGGAGUCGUUA	111-131	3311	UAACGACUCCAAGUAGGAGUAGA	109-131
AD-239018.1	3016	ACUCCUACUUGGAGUCGUUGA	112-132	3312	UCAACGACUCCAAGUAGGAGUAG	110-132
AD-239019.1	3017	CUCCUACUUGGAGUCGUUGGU	113-133	3313	ACCAACGACUCCAAGUAGGAGUA	111-133
AD-239020.1	3018	UCCUACUUGGAGUCGUUGGUA	114-134	3314	UACCAACGACUCCAAGUAGGAGU	112-134
AD-239031.1	3019	GUCGUUGGUGAAGUUUUUCAU	125-145	3315	AUGAAAAACUUCACCAACGACUC	123-145
AD-239062.1	3020	GAGAUUGUUCUCAUUACUGGA	174-194	3316	UCCAGUAAUGAGAACAAUCUCCC	172-194
AD-239066.1	3021	UUGUUCUCAUUACUGGAGCUA	178-198	3317	UAGCUCCAGUAAUGAGAACAAUC	176-198
AD-239103.1	3022	GCAGACUACUUAUGAAUUUGA	215-235	3318	UCAAAUUCAUAAGUAGUCUGCCU	213-235
AD-239110.1	3023	ACUUAUGAAUUUGCAAAACGA	222-242	3319	UCGUUUUGCAAAUUCAUAAGUAG	220-242
AD-239118.1	3024	AUUUGCAAAACGACAGAGCAU	230-250	3320	AUGCUCUGUCGUUUUGCAAAUUC	228-250
AD-239119.1	3025	UUUGCAAAACGACAGAGCAUA	231-251	3321	UAUGCUCUGUCGUUUUGCAAAUU	229-251
AD-239131.1	3026	CAGAGCAUAUUGGUUCUGUGA	243-263	3322	UCACAGAACCAAUAUGCUCUGUC	241-263

AD-239132.1	3027	AGAGCAUAUUGGUUCUGUGGA	244-264	3323	UCCACAGAACCAAUAUGCUCUGU	242-264
AD-239133.1	3028	GAGCAUAUUGGUUCUGUGGGA	245-265	3324	UCCCACAGAACCAAUAUGCUCUG	243-265
AD-239146.1	3029	CUGUGGGAUAUUAAUAAGCGA	258-278	3325	UCGCUUAUUAAUAUCCCACAGAA	256-278
AD-239155.1	3030	AUUAAUAAGCGCGGUGUGGAA	267-287	3326	UUCCACACCGCGCUUAUUAAUAU	265-287
AD-239156.1	3031	UUAAUAAGCGCGGUGUGGAGA	268-288	3327	UCUCCACACCGCGCUUAUUAAUA	266-288
AD-239177.1	3032	AAACUGCAGCUGAGUGCCGAA	289-309	3328	UUCGGCACUCAGCUGCAGUUUCC	287-309
AD-239178.1	3033	AACUGCAGCUGAGUGCCGAAA	290-310	3329	UUUCGGCACUCAGCUGCAGUUUC	288-310
AD-239179.1	3034	ACUGCAGCUGAGUGCCGAAAA	291-311	3330	UUUUCGGCACUCAGCUGCAGUUU	289-311
AD-239180.1	3035	CUGCAGCUGAGUGCCGAAAAC	292-312	3331	GUUUUCGGCACUCAGCUGCAGUU	290-312
AD-239181.1	3036	UGCAGCUGAGUGCCGAAAACU	293-313	3332	AGUUUUCGGCACUCAGCUGCAGU	291-313
AD-239182.1	3037	GCAGCUGAGUGCCGAAAACUA	294-314	3333	UAGUUUUCGGCACUCAGCUGCAG	292-314
AD-239183.1	3038	CAGCUGAGUGCCGAAAACUAA	295-315	3334	UUAGUUUUCGGCACUCAGCUGCA	293-315
AD-239185.1	3039	GCUGAGUGCCGAAAACUAGGA	297-317	3335	UCCUAGUUUUCGGCACUCAGCUG	295-317
AD-239186.1	3040	CUGAGUGCCGAAAACUAGGCA	298-318	3336	UGCCUAGUUUUCGGCACUCAGCU	296-318
AD-239187.1	3041	UGAGUGCCGAAAACUAGGCGU	299-319	3337	ACGCCUAGUUUUCGGCACUCAGC	297-319
AD-239188.1	3042	GAGUGCCGAAAACUAGGCGUA	300-320	3338	UACGCCUAGUUUUCGGCACUCAG	298-320
AD-239189.1	3043	AGUGCCGAAAACUAGGCGUCA	301-321	3339	UGACGCCUAGUUUUCGGCACUCA	299-321
AD-239190.1	3044	GUGCCGAAAACUAGGCGUCAA	302-322	3340	UUGACGCCUAGUUUUCGGCACUC	300-322
AD-239191.1	3045	UGCCGAAAACUAGGCGUCACU	303-323	3341	AGUGACGCCUAGUUUUCGGCACU	301-323
AD-239192.1	3046	GCCGAAAACUAGGCGUCACUA	304-324	3342	UAGUGACGCCUAGUUUUCGGCAC	302-324
AD-239193.1	3047	CCGAAAACUAGGCGUCACUGA	305-325	3343	UCAGUGACGCCUAGUUUUCGGCA	303-325
AD-239194.1	3048	CGAAAACUAGGCGUCACUGCA	306-326	3344	UGCAGUGACGCCUAGUUUUCGGC	304-326
AD-239196.1	3049	AAAACUAGGCGUCACUGCGCA	308-328	3345	UGCGCAGUGACGCCUAGUUUUCG	306-328
AD-239198.1	3050	AACUAGGCGUCACUGCGCAUA	310-330	3346	UAUGCGCAGUGACGCCUAGUUUU	308-330
AD-239199.1	3051	ACUAGGCGUCACUGCGCAUGA	311-331	3347	UCAUGCGCAGUGACGCCUAGUUU	309-331
AD-239203.1	3052	GGCGUCACUGCGCAUGCGUAU	315-335	3348	AUACGCAUGCGCAGUGACGCCUA	313-335
AD-239214.1	3053	GCAUGCGUAUGUGGUAGACUA	326-346	3349	UAGUCUACCACAUACGCAUGCGC	324-346
AD-239215.1	3054	CAUGCGUAUGUGGUAGACUGA	327-347	3350	UCAGUCUACCACAUACGCAUGCG	325-347

AD-239239.1	3055	AACAGAGAAGAGAUCUAUCGA	351-371	3351	UCGAUAGAUCUCUUCUCUGUUGC	349-371
AD-239240.1	3056	ACAGAGAAGAGAUCUAUCGCU	352-372	3352	AGCGAUAGAUCUCUUCUCUGUUG	350-372
AD-239241.1	3057	CAGAGAAGAGAUCUAUCGCUA	353-373	3353	UAGCGAUAGAUCUCUUCUCUGUU	351-373
AD-239242.1	3058	AGAGAAGAGAUCUAUCGCUCU	354-374	3354	AGAGCGAUAGAUCUCUUCUCUGU	352-374
AD-239243.1	3059	GAGAAGAGAUCUAUCGCUCUA	355-375	3355	UAGAGCGAUAGAUCUCUUCUCUG	353-375
AD-239245.1	3060	GAAGAGAUCUAUCGCUCUCUA	357-377	3356	UAGAGAGCGAUAGAUCUCUUCUC	355-377
AD-239246.1	3061	AAGAGAUCUAUCGCUCUCUAA	358-378	3357	UUAGAGAGCGAUAGAUCUCUUCU	356-378
AD-239247.1	3062	AGAGAUCUAUCGCUCUCUAAA	359-379	3358	UUUAGAGAGCGAUAGAUCUCUUC	357-379
AD-239250.1	3063	GAUCUAUCGCUCUCUAAAUCA	362-382	3359	UGAUUUAGAGAGCGAUAGAUCUC	360-382
AD-239251.1	3064	AUCUAUCGCUCUCUAAAUCAA	363-383	3360	UUGAUUUAGAGAGCGAUAGAUCU	361-383
AD-239253.1	3065	CUAUCGCUCUCUAAAUCAGGU	365-385	3361	ACCUGAUUUAGAGAGCGAUAGAU	363-385
AD-239254.1	3066	UAUCGCUCUCUAAAUCAGGUA	366-386	3362	UACCUGAUUUAGAGAGCGAUAGA	364-386
AD-239255.1	3067	AUCGCUCUCUAAAUCAGGUGA	367-387	3363	UCACCUGAUUUAGAGAGCGAUAG	365-387
AD-239290.1	3068	GAUGUAACAAUCGUGGUGAAU	402-422	3364	AUUCACCACGAUUGUUACAUCAC	400-422
AD-239291.1	3069	AUGUAACAAUCGUGGUGAAUA	403-423	3365	UAUUCACCACGAUUGUUACAUCA	401-423
AD-239292.1	3070	UGUAACAAUCGUGGUGAAUAA	404-424	3366	UUAUUCACCACGAUUGUUACAUC	402-424
AD-239293.1	3071	GUAACAAUCGUGGUGAAUAAU	405-425	3367	AUUAUUCACCACGAUUGUUACAU	403-425
AD-239304.1	3072	GGUGAAUAAUGCUGGGACAGU	416-436	3368	ACUGUCCCAGCAUUAUUCACCAC	414-436
AD-239312.1	3073	AUGCUGGGACAGUAUAUCCAA	424-444	3369	UUGGAUAUACUGUCCCAGCAUUA	422-444
AD-239313.1	3074	UGCUGGGACAGUAUAUCCAGA	425-445	3370	UCUGGAUAUACUGUCCCAGCAUU	423-445
AD-239314.1	3075	GCUGGGACAGUAUAUCCAGCA	426-446	3371	UGCUGGAUAUACUGUCCCAGCAU	424-446
AD-239316.1	3076	UGGGACAGUAUAUCCAGCCGA	428-448	3372	UCGGCUGGAUAUACUGUCCCAGC	426-448
AD-239317.1	3077	GGGACAGUAUAUCCAGCCGAU	429-449	3373	AUCGGCUGGAUAUACUGUCCCAG	427-449
AD-239318.1	3078	GGACAGUAUAUCCAGCCGAUA	430-450	3374	UAUCGGCUGGAUAUACUGUCCCA	428-450
AD-239321.1	3079	CAGUAUAUCCAGCCGAUCUUA	433-453	3375	UAAGAUCGGCUGGAUAUACUGUC	431-453
AD-239332.1	3080	GCCGAUCUUCUCAGCACCAAA	444-464	3376	UUUGGUGCUGAGAAGAUCGGCUG	442-464
AD-239337.1	3081	UCUUCUCAGCACCAAGGAUGA	449-469	3377	UCAUCCUUGGUGCUGAGAAGAUC	447-469
AD-239348.1	3082	CCAAGGAUGAAGAGAUUACCA	460-480	3378	UGGUAAUCUCUUCAUCCUUGGUG	458-480

AD-239362.1	3083	AUUACCAAGACAUUUGAGGUA	474-494	3379	UACCUCAAAUGUCUUGGUAAUCU	472-494
AD-239366.1	3084	CCAAGACAUUUGAGGUCAACA	478-498	3380	UGUUGACCUCAAAUGUCUUGGUA	476-498
AD-239368.1	3085	AAGACAUUUGAGGUCAACAUA	480-500	3381	UAUGUUGACCUCAAAUGUCUUGG	478-500
AD-239372.1	3086	CAUUUGAGGUCAACAUCCUAA	484-504	3382	UUAGGAUGUUGACCUCAAAUGUC	482-504
AD-239373.1	3087	AUUUGAGGUCAACAUCCUAGA	485-505	3383	UCUAGGAUGUUGACCUCAAAUGU	483-505
AD-239379.1	3088	GGUCAACAUCCUAGGACAUUU	491-511	3384	AAAUGUCCUAGGAUGUUGACCUC	489-511
AD-239380.1	3089	GUCAACAUCCUAGGACAUUUU	492-512	3385	AAAAUGUCCUAGGAUGUUGACCU	490-512
AD-239387.1	3090	UCCUAGGACAUUUUUGGAUCA	499-519	3386	UGAUCCAAAAAUGUCCUAGGAUG	497-519
AD-239397.1	3091	UUUUUGGAUCACAAAAGCACU	509-529	3387	AGUGCUUUUGUGAUCCAAAAAUG	507-529
AD-239411.1	3092	AAGCACUUCUUCCAUCGAUGA	523-543	3388	UCAUCGAUGGAAGAAGUGCUUUU	521-543
AD-239412.1	3093	AGCACUUCUUCCAUCGAUGAU	524-544	3389	AUCAUCGAUGGAAGAAGUGCUUU	522-544
AD-239431.1	3094	AUGGAGAGAAAUCAUGGCCAA	543-563	3390	UUGGCCAUGAUUUCUCUCCAUCA	541-563
AD-239433.1	3095	GGAGAGAAAUCAUGGCCACAU	545-565	3391	AUGUGGCCAUGAUUUCUCUCCAU	543-565
AD-239436.1	3096	GAGAAAUCAUGGCCACAUCGU	548-568	3392	ACGAUGUGGCCAUGAUUUCUCUC	546-568
AD-239437.1	3097	AGAAAUCAUGGCCACAUCGUA	549-569	3393	UACGAUGUGGCCAUGAUUUCUCU	547-569
AD-239438.1	3098	GAAAUCAUGGCCACAUCGUCA	550-570	3394	UGACGAUGUGGCCAUGAUUUCUC	548-570
AD-239439.1	3099	AAAUCAUGGCCACAUCGUCAA	551-571	3395	UUGACGAUGUGGCCAUGAUUUCU	549-571
AD-239450.1	3100	ACAUCGUCACAGUGGCUUCAA	562-582	3396	UUGAAGCCACUGUGACGAUGUGG	560-582
AD-239451.1	3101	CAUCGUCACAGUGGCUUCAGU	563-583	3397	ACUGAAGCCACUGUGACGAUGUG	561-583
AD-239452.1	3102	AUCGUCACAGUGGCUUCAGUA	564-584	3398	UACUGAAGCCACUGUGACGAUGU	562-584
AD-239453.1	3103	UCGUCACAGUGGCUUCAGUGU	565-585	3399	ACACUGAAGCCACUGUGACGAUG	563-585
AD-239475.1	3104	CGGCCACGAAGGGAUUCCUUA	587-607	3400	UAAGGAAUCCCUUCGUGGCCGCA	585-607
AD-239476.1	3105	GGCCACGAAGGGAUUCCUUAA	588-608	3401	UUAAGGAAUCCCUUCGUGGCCGC	586-608
AD-239478.1	3106	CCACGAAGGGAUUCCUUACCU	590-610	3402	AGGUAAGGAAUCCCUUCGUGGCC	588-610
AD-239479.1	3107	CACGAAGGGAUUCCUUACCUA	591-611	3403	UAGGUAAGGAAUCCCUUCGUGGC	589-611
AD-239480.1	3108	ACGAAGGGAUUCCUUACCUCA	592-612	3404	UGAGGUAAGGAAUCCCUUCGUGG	590-612
AD-239482.1	3109	GAAGGGAUUCCUUACCUCAUA	594-614	3405	UAUGAGGUAAGGAAUCCCUUCGU	592-614
AD-239483.1	3110	AAGGGAUUCCUUACCUCAUCA	595-615	3406	UGAUGAGGUAAGGAAUCCCUUCG	593-615

AD-239499.1	3111	CAUCCCAUAUUGUUCCAGCAA	611-631	3407	UUGCUGGAACAAUAUGGGAUGAG	609-631
AD-239510.1	3112	GUUCCAGCAAAUUUGCCGCUA	622-642	3408	UAGCGGCAAAUUUGCUGGAACAA	620-642
AD-239520.1	3113	AUUUGCCGCUGUUGGCUUUCA	632-652	3409	UGAAAGCCAACAGCGGCAAAUUU	630-652
AD-239521.1	3114	UUUGCCGCUGUUGGCUUUCAA	633-653	3410	UUGAAAGCCAACAGCGGCAAAUU	631-653
AD-239522.1	3115	UUGCCGCUGUUGGCUUUCACA	634-654	3411	UGUGAAAGCCAACAGCGGCAAAU	632-654
AD-239534.1	3116	GCUUUCACAGAGGUCUGACAU	646-666	3412	AUGUCAGACCUCUGUGAAAGCCA	644-666
AD-239539.1	3117	CACAGAGGUCUGACAUCAGAA	651-671	3413	UUCUGAUGUCAGACCUCUGUGAA	649-671
AD-239544.1	3118	AGGUCUGACAUCAGAACUUCA	656-676	3414	UGAAGUUCUGAUGUCAGACCUCU	654-676
AD-239566.1	3119	GCCUUGGGAAAAACUGGUAUA	678-698	3415	UAUACCAGUUUUUCCCAAGGCCU	676-698
AD-239578.1	3120	ACUGGUAUCAAAACCUCAUGU	690-710	3416	ACAUGAGGUUUUGAUACCAGUUU	688-710
AD-239579.1	3121	CUGGUAUCAAAACCUCAUGUA	691-711	3417	UACAUGAGGUUUUGAUACCAGUU	689-711
AD-239611.1	3122	UUUGUGAAUACUGGGUUCACA	723-743	3418	UGUGAACCCAGUAUUCACAAAAA	721-743
AD-239612.1	3123	UUGUGAAUACUGGGUUCACCA	724-744	3419	UGGUGAACCCAGUAUUCACAAAA	722-744
AD-239613.1	3124	UGUGAAUACUGGGUUCACCAA	725-745	3420	UUGGUGAACCCAGUAUUCACAAA	723-745
AD-239617.1	3125	AAUACUGGGUUCACCAAAAAU	729-749	3421	AUUUUUGGUGAACCCAGUAUUCA	727-749
AD-239618.1	3126	AUACUGGGUUCACCAAAAAUA	730-750	3422	UAUUUUUGGUGAACCCAGUAUUC	728-750
AD-239637.1	3127	UCCAAGCACAAGAUUAUGGCA	749-769	3423	UGCCAUAAUCUUGUGCUUGGAUU	747-769
AD-239641.1	3128	AGCACAAGAUUAUGGCCUGUA	753-773	3424	UACAGGCCAUAAUCUUGUGCUUG	751-773
AD-239642.1	3129	GCACAAGAUUAUGGCCUGUAU	754-774	3425	AUACAGGCCAUAAUCUUGUGCUU	752-774
AD-239643.1	3130	CACAAGAUUAUGGCCUGUAUU	755-775	3426	AAUACAGGCCAUAAUCUUGUGCU	753-775
AD-239645.1	3131	CAAGAUUAUGGCCUGUAUUGA	757-777	3427	UCAAUACAGGCCAUAAUCUUGUG	755-777
AD-239647.1	3132	AGAUUAUGGCCUGUAUUGGAA	759-779	3428	UUCCAAUACAGGCCAUAAUCUUG	757-779
AD-239649.1	3133	AUUAUGGCCUGUAUUGGAGAA	761-781	3429	UUCUCCAAUACAGGCCAUAAUCU	759-781
AD-239650.1	3134	UUAUGGCCUGUAUUGGAGACA	762-782	3430	UGUCUCCAAUACAGGCCAUAAUC	760-782
AD-239653.1	3135	UGGCCUGUAUUGGAGACAGAU	765-785	3431	AUCUGUCUCCAAUACAGGCCAUA	763-785
AD-239654.1	3136	GGCCUGUAUUGGAGACAGAUA	766-786	3432	UAUCUGUCUCCAAUACAGGCCAU	764-786
AD-239662.1	3137	UUGGAGACAGAUGAAGUCGUA	774-794	3433	UACGACUUCAUCUGUCUCCAAUA	772-794
AD-239668.1	3138	ACAGAUGAAGUCGUAAGAAGU	780-800	3434	ACUUCUUACGACUUCAUCUGUCU	778-800

AD-239669.1	3139	CAGAUGAAGUCGUAAGAAGUA	781-801	3435	UACUUCUUACGACUUCAUCUGUC	779-801
AD-239670.1	3140	AGAUGAAGUCGUAAGAAGUCU	782-802	3436	AGACUUCUUACGACUUCAUCUGU	780-802
AD-239671.1	3141	GAUGAAGUCGUAAGAAGUCUA	783-803	3437	UAGACUUCUUACGACUUCAUCUG	781-803
AD-239674.1	3142	GAAGUCGUAAGAAGUCUGAUA	786-806	3438	UAUCAGACUUCUUACGACUUCAU	784-806
AD-239676.1	3143	AGUCGUAAGAAGUCUGAUAGA	788-808	3439	UCUAUCAGACUUCUUACGACUUC	786-808
AD-239681.1	3144	UAAGAAGUCUGAUAGAUGGAA	793-813	3440	UUCCAUCUAUCAGACUUCUUACG	791-813
AD-239682.1	3145	AAGAAGUCUGAUAGAUGGAAU	794-814	3441	AUUCCAUCUAUCAGACUUCUUAC	792-814
AD-239684.1	3146	GAAGUCUGAUAGAUGGAAUAA	796-816	3442	UUAUUCCAUCUAUCAGACUUCUU	794-816
AD-239685.1	3147	AAGUCUGAUAGAUGGAAUACU	797-817	3443	AGUAUUCCAUCUAUCAGACUUCU	795-817
AD-239697.1	3148	UGGAAUACUUACCAAUAAGAA	809-829	3444	UUCUUAUUGGUAAGUAUUCCAUC	807-829
AD-239713.1	3149	AAUGAUUUUUGUUCCAUCGUA	830-850	3445	UACGAUGGAACAAAAAUCAUUUU	828-850
AD-239714.1	3150	AUGAUUUUUGUUCCAUCGUAU	831-851	3446	AUACGAUGGAACAAAAAUCAUUU	829-851
AD-239717.1	3151	AUUUUUGUUCCAUCGUAUAUA	834-854	3447	UAUAUACGAUGGAACAAAAAUCA	832-854
AD-239721.1	3152	UUGUUCCAUCGUAUAUCAAUA	838-858	3448	UAUUGAUAUACGAUGGAACAAAA	836-858
AD-239723.1	3153	GUUCCAUCGUAUAUCAAUAUA	840-860	3449	UAUAUUGAUAUACGAUGGAACAA	838-860
AD-239724.1	3154	UUCCAUCGUAUAUCAAUAUCU	841-861	3450	AGAUAUUGAUAUACGAUGGAACA	839-861
AD-239725.1	3155	UCCAUCGUAUAUCAAUAUCUU	842-862	3451	AAGAUAUUGAUAUACGAUGGAAC	840-862
AD-239726.1	3156	CCAUCGUAUAUCAAUAUCUUU	843-863	3452	AAAGAUAUUGAUAUACGAUGGAA	841-863
AD-239755.1	3157	ACAGAAGUUUCUUCCUGAACA	872-892	3453	UGUUCAGGAAGAAACUUCUGUAG	870-892
AD-239757.1	3158	AGAAGUUUCUUCCUGAACGCA	874-894	3454	UGCGUUCAGGAAGAAACUUCUGU	872-894
AD-239759.1	3159	AAGUUUCUUCCUGAACGCGCA	876-896	3455	UGCGCGUUCAGGAAGAAACUUCU	874-896
AD-239761.1	3160	GUUUCUUCCUGAACGCGCCUA	878-898	3456	UAGGCGCGUUCAGGAAGAAACUU	876-898
AD-239764.1	3161	UCUUCCUGAACGCGCCUCAGA	881-901	3457	UCUGAGGCGCGUUCAGGAAGAAA	879-901
AD-239778.1	3162	CCUCAGCGAUUUUAAAUCGUA	895-915	3458	UACGAUUUAAAAUCGCUGAGGCG	893-915
AD-239779.1	3163	CUCAGCGAUUUUAAAUCGUAU	896-916	3459	AUACGAUUUAAAAUCGCUGAGGC	894-916
AD-239780.1	3164	UCAGCGAUUUUAAAUCGUAUA	897-917	3460	UAUACGAUUUAAAAUCGCUGAGG	895-917
AD-239781.1	3165	CAGCGAUUUUAAAUCGUAUGA	898-918	3461	UCAUACGAUUUAAAAUCGCUGAG	896-918
AD-239782.1	3166	AGCGAUUUUAAAUCGUAUGCA	899-919	3462	UGCAUACGAUUUAAAAUCGCUGA	897-919

AD-239783.1	3167	GCGAUUUUAAAUCGUAUGCAA	900-920	3463	UUGCAUACGAUUUAAAAUCGCUG	898-920
AD-239784.1	3168	CGAUUUUAAAUCGUAUGCAGA	901-921	3464	UCUGCAUACGAUUUAAAAUCGCU	899-921
AD-239785.1	3169	GAUUUUAAAUCGUAUGCAGAA	902-922	3465	UUCUGCAUACGAUUUAAAAUCGC	900-922
AD-239786.1	3170	AUUUUAAAUCGUAUGCAGAAU	903-923	3466	AUUCUGCAUACGAUUUAAAAUCG	901-923
AD-239787.1	3171	UUUUAAAUCGUAUGCAGAAUA	904-924	3467	UAUUCUGCAUACGAUUUAAAAUC	902-924
AD-239791.1	3172	AAAUCGUAUGCAGAAUAUUCA	908-928	3468	UGAAUAUUCUGCAUACGAUUUAA	906-928
AD-239793.1	3173	AUCGUAUGCAGAAUAUUCAAU	910-930	3469	AUUGAAUAUUCUGCAUACGAUUU	908-930
AD-239806.1	3174	UAUUCAAUUUGAAGCAGUGGU	923-943	3470	ACCACUGCUUCAAAUUGAAUAUU	921-943
AD-239839.1	3175	GAAUAAAUAAGCUCCAGCCAA	967-987	3471	UUGGCUGGAGCUUAUUUAUUCAU	965-987
AD-239840.1	3176	AAUAAAUAAGCUCCAGCCAGA	968-988	3472	UCUGGCUGGAGCUUAUUUAUUCA	966-988
AD-239854.1	3177	AGCCAGAGAUGUAUGCAUGAU	982-1002	3473	AUCAUGCAUACAUCUCUGGCUGG	980-1002
AD-239855.1	3178	GCCAGAGAUGUAUGCAUGAUA	983-1003	3474	UAUCAUGCAUACAUCUCUGGCUG	981-1003
AD-239876.1	3179	AUAUGAAUAGUUUCGAAUCAA	1007-1027	3475	UUGAUUCGAAACUAUUCAUAUCA	1005-1027
AD-239877.1	3180	UAUGAAUAGUUUCGAAUCAAU	1008-1028	3476	AUUGAUUCGAAACUAUUCAUAUC	1006-1028
AD-239881.1	3181	AAUAGUUUCGAAUCAAUGCUA	1012-1032	3477	UAGCAUUGAUUCGAAACUAUUCA	1010-1032
AD-239905.1	3182	UUCAGUCCUGAUAAUAUUAAA	1054-1074	3478	UUUAAUAUUAUCAGGACUGAAAA	1052-1074
AD-239914.1	3183	AAAAACAUUGGUUUGGCACUA	1072-1092	3479	UAGUGCCAAACCAAUGUUUUUAA	1070-1092
AD-239915.1	3184	AAAACAUUGGUUUGGCACUAA	1073-1093	3480	UUAGUGCCAAACCAAUGUUUUUA	1071-1093
AD-239941.1	3185	GUCAAACGAACAAGAUUAAUU	1099-1119	3481	AAUUAAUCUUGUUCGUUUGACUG	1097-1119
AD-239944.1	3186	AAACGAACAAGAUUAAUUACA	1102-1122	3482	UGUAAUUAAUCUUGUUCGUUUGA	1100-1122
AD-239945.1	3187	AACGAACAAGAUUAAUUACCU	1103-1123	3483	AGGUAAUUAAUCUUGUUCGUUUG	1101-1123
AD-239946.1	3188	ACGAACAAGAUUAAUUACCUA	1104-1124	3484	UAGGUAAUUAAUCUUGUUCGUUU	1102-1124
AD-239947.1	3189	CGAACAAGAUUAAUUACCUGU	1105-1125	3485	ACAGGUAAUUAAUCUUGUUCGUU	1103-1125
AD-239977.1	3190	UCUCAAGAAUAUUUACGUAGU	1135-1155	3486	ACUACGUAAAUAUUCUUGAGAAA	1133-1155
AD-239979.1	3191	UCAAGAAUAUUUACGUAGUUU	1137-1157	3487	AAACUACGUAAAUAUUCUUGAGA	1135-1157
AD-239980.1	3192	CAAGAAUAUUUACGUAGUUUU	1138-1158	3488	AAAACUACGUAAAUAUUCUUGAG	1136-1158
AD-239998.1	3193	UUUCAUAGGUCUGUUUUUCCU	1157-1177	3489	AGGAAAAACAGACCUAUGAAAAA	1155-1177
AD-240019.1	3194	UUCAUGCCUCUUAAAAACUUA	1178-1198	3490	UAAGUUUUUAAGAGGCAUGAAAG	1176-1198

AD-240031.1	3195	AAAAACUUCUGUGCUUACAUA	1190-1210	3491	UAUGUAAGCACAGAAGUUUUUAA	1188-1210
AD-240032.1	3196	AAAACUUCUGUGCUUACAUAA	1191-1211	3492	UUAUGUAAGCACAGAAGUUUUUA	1189-1211
AD-240033.1	3197	AAACUUCUGUGCUUACAUAAA	1192-1212	3493	UUUAUGUAAGCACAGAAGUUUUU	1190-1212
AD-240064.1	3198	UUUUUCCAUUUAAAGGUGGAA	1245-1265	3494	UUCCACCUUUAAAUGGAAAAAUA	1243-1265
AD-240090.1	3199	CUACCUCCCUAAAAGUAAAUA	1271-1291	3495	UAUUUACUUUUAGGGAGGUAGCU	1269-1291
AD-240091.1	3200	UACCUCCCUAAAAGUAAAUAA	1272-1292	3496	UUAUUUACUUUUAGGGAGGUAGC	1270-1292
AD-240108.1	3201	UACAAAGAGAACUUAUUUACA	1290-1310	3497	UGUAAAUAAGUUCUCUUUGUAUU	1288-1310
AD-240117.1	3202	AACUUAUUUACACAGGGAAGA	1299-1319	3498	UCUUCCCUGUGUAAAUAAGUUCU	1297-1319
AD-240124.1	3203	UUACACAGGGAAGGUUUAAGA	1306-1326	3499	UCUUAAACCUUCCCUGUGUAAAU	1304-1326
AD-240125.1	3204	UACACAGGGAAGGUUUAAGAA	1307-1327	3500	UUCUUAAACCUUCCCUGUGUAAA	1305-1327
AD-240126.1	3205	ACACAGGGAAGGUUUAAGACU	1308-1328	3501	AGUCUUAAACCUUCCCUGUGUAA	1306-1328
AD-240135.1	3206	AGGUUUAAGACUGUUCAAGUA	1317-1337	3502	UACUUGAACAGUCUUAAACCUUC	1315-1337
AD-240138.1	3207	UUUAAGACUGUUCAAGUAGCA	1320-1340	3503	UGCUACUUGAACAGUCUUAAACC	1318-1340
AD-240140.1	3208	UAAGACUGUUCAAGUAGCAUU	1322-1342	3504	AAUGCUACUUGAACAGUCUUAAA	1320-1342
AD-240142.1	3209	AGACUGUUCAAGUAGCAUUCA	1324-1344	3505	UGAAUGCUACUUGAACAGUCUUA	1322-1344
AD-240145.1	3210	CUGUUCAAGUAGCAUUCCAAU	1327-1347	3506	AUUGGAAUGCUACUUGAACAGUC	1325-1347
AD-240147.1	3211	GUUCAAGUAGCAUUCCAAUCU	1329-1349	3507	AGAUUGGAAUGCUACUUGAACAG	1327-1349
AD-240148.1	3212	UUCAAGUAGCAUUCCAAUCUA	1330-1350	3508	UAGAUUGGAAUGCUACUUGAACA	1328-1350
AD-240154.1	3213	UAGCAUUCCAAUCUGUAGCCA	1336-1356	3509	UGGCUACAGAUUGGAAUGCUACU	1334-1356
AD-240155.1	3214	AGCAUUCCAAUCUGUAGCCAU	1337-1357	3510	AUGGCUACAGAUUGGAAUGCUAC	1335-1357
AD-240156.1	3215	GCAUUCCAAUCUGUAGCCAUA	1338-1358	3511	UAUGGCUACAGAUUGGAAUGCUA	1336-1358
AD-240171.1	3216	GCCAUGCCACAGAAUAUCAAA	1353-1373	3512	UUUGAUAUUCUGUGGCAUGGCUA	1351-1373
AD-240172.1	3217	CCAUGCCACAGAAUAUCAACA	1354-1374	3513	UGUUGAUAUUCUGUGGCAUGGCU	1352-1374
AD-240192.1	3218	AAGAACACAGAAUGAGUGCAA	1374-1394	3514	UUGCACUCAUUCUGUGUUCUUGU	1372-1394
AD-240227.1	3219	GUUUCAGCAGGCAGCUUUAUA	1409-1429	3515	UAUAAAGCUGCCUGCUGAAACUU	1407-1429
AD-240228.1	3220	UUUCAGCAGGCAGCUUUAUCU	1410-1430	3516	AGAUAAAGCUGCCUGCUGAAACU	1408-1430
AD-240237.1	3221	GCAGCUUUAUCUCAACCUGGA	1419-1439	3517	UCCAGGUUGAGAUAAAGCUGCCU	1417-1439
AD-240245.1	3222	AUCUCAACCUGGACAUAUUUU	1427-1447	3518	AAAAUAUGUCCAGGUUGAGAUAA	1425-1447

AD-240276.1	3223	AUUUGAAAGAUUUCCCUAGCA	1458-1478	3519	UGCUAGGGAAAUCUUUCAAAUGC	1456-1478
AD-240278.1	3224	UUGAAAGAUUUCCCUAGCCUA	1460-1480	3520	UAGGCUAGGGAAAUCUUUCAAAU	1458-1480
AD-240279.1	3225	UGAAAGAUUUCCCUAGCCUCU	1461-1481	3521	AGAGGCUAGGGAAAUCUUUCAAA	1459-1481
AD-240280.1	3226	GAAAGAUUUCCCUAGCCUCUU	1462-1482	3522	AAGAGGCUAGGGAAAUCUUUCAA	1460-1482
AD-240308.1	3227	CAUUAGCCCAAAACGGUGCAA	1490-1510	3523	UUGCACCGUUUUGGGCUAAUGAA	1488-1510
AD-240309.1	3228	AUUAGCCCAAAACGGUGCAAA	1491-1511	3524	UUUGCACCGUUUUGGGCUAAUGA	1489-1511
AD-240310.1	3229	UUAGCCCAAAACGGUGCAACU	1492-1512	3525	AGUUGCACCGUUUUGGGCUAAUG	1490-1512
AD-240311.1	3230	UAGCCCAAAACGGUGCAACUA	1493-1513	3526	UAGUUGCACCGUUUUGGGCUAAU	1491-1513
AD-240312.1	3231	AGCCCAAAACGGUGCAACUCU	1494-1514	3527	AGAGUUGCACCGUUUUGGGCUAA	1492-1514
AD-240313.1	3232	GCCCAAAACGGUGCAACUCUA	1495-1515	3528	UAGAGUUGCACCGUUUUGGGCUA	1493-1515
AD-240315.1	3233	CCAAAACGGUGCAACUCUAUU	1497-1517	3529	AAUAGAGUUGCACCGUUUUGGGC	1495-1517
AD-240317.1	3234	AAAACGGUGCAACUCUAUUCU	1499-1519	3530	AGAAUAGAGUUGCACCGUUUUGG	1497-1519
AD-240318.1	3235	AAACGGUGCAACUCUAUUCUA	1500-1520	3531	UAGAAUAGAGUUGCACCGUUUUG	1498-1520
AD-240319.1	3236	AACGGUGCAACUCUAUUCUGA	1501-1521	3532	UCAGAAUAGAGUUGCACCGUUUU	1499-1521
AD-240322.1	3237	GGUGCAACUCUAUUCUGGACU	1504-1524	3533	AGUCCAGAAUAGAGUUGCACCGU	1502-1524
AD-240324.1	3238	UGCAACUCUAUUCUGGACUUU	1506-1526	3534	AAAGUCCAGAAUAGAGUUGCACC	1504-1526
AD-240326.1	3239	CAACUCUAUUCUGGACUUUAU	1508-1528	3535	AUAAAGUCCAGAAUAGAGUUGCA	1506-1528
AD-240327.1	3240	AACUCUAUUCUGGACUUUAUU	1509-1529	3536	AAUAAAGUCCAGAAUAGAGUUGC	1507-1529
AD-240333.1	3241	AUUCUGGACUUUAUUACUUGA	1515-1535	3537	UCAAGUAAUAAAGUCCAGAAUAG	1513-1535
AD-240364.1	3242	UGUAUAACUCUGAAGUCCACA	1546-1566	3538	UGUGGACUUCAGAGUUAUACAGA	1544-1566
AD-240365.1	3243	GUAUAACUCUGAAGUCCACCA	1547-1567	3539	UGGUGGACUUCAGAGUUAUACAG	1545-1567
AD-240375.1	3244	GAAGUCCACCAAAAGUGGACA	1557-1577	3540	UGUCCACUUUUGGUGGACUUCAG	1555-1577
AD-240378.1	3245	GUCCACCAAAAGUGGACCCUA	1560-1580	3541	UAGGGUCCACUUUUGGUGGACUU	1558-1580
AD-240381.1	3246	CACCAAAAGUGGACCCUCUAU	1563-1583	3542	AUAGAGGGUCCACUUUUGGUGGA	1561-1583
AD-240382.1	3247	ACCAAAAGUGGACCCUCUAUA	1564-1584	3543	UAUAGAGGGUCCACUUUUGGUGG	1562-1584
AD-240383.1	3248	CCAAAAGUGGACCCUCUAUAU	1565-1585	3544	AUAUAGAGGGUCCACUUUUGGUG	1563-1585
AD-240385.1	3249	AAAAGUGGACCCUCUAUAUUU	1567-1587	3545	AAAUAUAGAGGGUCCACUUUUGG	1565-1587
AD-240386.1	3250	AAAGUGGACCCUCUAUAUUUA	1568-1588	3546	UAAAUAUAGAGGGUCCACUUUUG	1566-1588

AD-240387.1	3251	AAGUGGACCCUCUAUAUUUCA	1569-1589	3547	UGAAAUAUAGAGGGUCCACUUUU	1567-1589
AD-240419.1	3252	AUACAUUAUGAAAGGUGACCA	1612-1632	3548	UGGUCACCUUUCAUAAUGUAUCU	1610-1632
AD-240420.1	3253	UACAUUAUGAAAGGUGACCGA	1613-1633	3549	UCGGUCACCUUUCAUAAUGUAUC	1611-1633
AD-240421.1	3254	ACAUUAUGAAAGGUGACCGAA	1614-1634	3550	UUCGGUCACCUUUCAUAAUGUAU	1612-1634
AD-240422.1	3255	CAUUAUGAAAGGUGACCGACU	1615-1635	3551	AGUCGGUCACCUUUCAUAAUGUA	1613-1635
AD-240423.1	3256	AUUAUGAAAGGUGACCGACUA	1616-1636	3552	UAGUCGGUCACCUUUCAUAAUGU	1614-1636
AD-240431.1	3257	AGGUGACCGACUCUAUUUUAA	1624-1644	3553	UUAAAAUAGAGUCGGUCACCUUU	1622-1644
AD-240446.1	3258	AUCUCAGAAUUUUAAGUUCUA	1645-1665	3554	UAGAACUUAAAAUUCUGAGAUUU	1643-1665
AD-240474.1	3259	CUUUCAUAUAUCCUUGGUCCA	1699-1719	3555	UGGACCAAGGAUAUAUGAAAGCA	1697-1719
AD-240475.1	3260	UUUCAUAUAUCCUUGGUCCCA	1700-1720	3556	UGGGACCAAGGAUAUAUGAAAGC	1698-1720
AD-240476.1	3261	UUCAUAUAUCCUUGGUCCCAA	1701-1721	3557	UUGGGACCAAGGAUAUAUGAAAG	1699-1721
AD-240490.1	3262	GUCCCAGAGAUGUUUAGACAA	1715-1735	3558	UUGUCUAAACAUCUCUGGGACCA	1713-1735
AD-240494.1	3263	CAGAGAUGUUUAGACAAUUUU	1719-1739	3559	AAAAUUGUCUAAACAUCUCUGGG	1717-1739
AD-240495.1	3264	AGAGAUGUUUAGACAAUUUUA	1720-1740	3560	UAAAAUUGUCUAAACAUCUCUGG	1718-1740
AD-240501.1	3265	GUUUAGACAAUUUUAGGCUCA	1726-1746	3561	UGAGCCUAAAAUUGUCUAAACAU	1724-1746
AD-240502.1	3266	UUUAGACAAUUUUAGGCUCAA	1727-1747	3562	UUGAGCCUAAAAUUGUCUAAACA	1725-1747
AD-240503.1	3267	UUAGACAAUUUUAGGCUCAAA	1728-1748	3563	UUUGAGCCUAAAAUUGUCUAAAC	1726-1748
AD-240504.1	3268	UAGACAAUUUUAGGCUCAAAA	1729-1749	3564	UUUUGAGCCUAAAAUUGUCUAAA	1727-1749
AD-240505.1	3269	AGACAAUUUUAGGCUCAAAAA	1730-1750	3565	UUUUUGAGCCUAAAAUUGUCUAA	1728-1750
AD-240507.1	3270	ACAAUUUUAGGCUCAAAAAUU	1732-1752	3566	AAUUUUUGAGCCUAAAAUUGUCU	1730-1752
AD-240512.1	3271	UUUAGGCUCAAAAAUUAAAGA	1737-1757	3567	UCUUUAAUUUUUGAGCCUAAAAU	1735-1757
AD-240513.1	3272	UUAGGCUCAAAAAUUAAAGCU	1738-1758	3568	AGCUUUAAUUUUUGAGCCUAAAA	1736-1758
AD-240514.1	3273	UAGGCUCAAAAAUUAAAGCUA	1739-1759	3569	UAGCUUUAAUUUUUGAGCCUAAA	1737-1759
AD-240538.1	3274	CAGGAAAAGGAACUGUACUGA	1763-1783	3570	UCAGUACAGUUCCUUUUCCUGUG	1761-1783
AD-240540.1	3275	GGAAAAGGAACUGUACUGGCU	1765-1785	3571	AGCCAGUACAGUUCCUUUUCCUG	1763-1785
AD-240542.1	3276	AAAAGGAACUGUACUGGCUAU	1767-1787	3572	AUAGCCAGUACAGUUCCUUUUCC	1765-1787
AD-240545.1	3277	AGGAACUGUACUGGCUAUUAA	1770-1790	3573	UUAAUAGCCAGUACAGUUCCUUU	1768-1790
AD-240546.1	3278	GGAACUGUACUGGCUAUUACA	1771-1791	3574	UGUAAUAGCCAGUACAGUUCCUU	1769-1791

AD-240779.1	3279	UAAUCCGACUCCCACUACAUA	2181-2201	3575	UAUGUAGUGGGAGUCGGAUUAUU	2179-2201
AD-240782.1	3280	UCCGACUCCCACUACAUCAAA	2184-2204	3576	UUUGAUGUAGUGGGAGUCGGAUU	2182-2204
AD-240787.1	3281	CUCCCACUACAUCAAGACUAA	2189-2209	3577	UUAGUCUUGAUGUAGUGGGAGUC	2187-2209
AD-240788.1	3282	UCCCACUACAUCAAGACUAAU	2190-2210	3578	AUUAGUCUUGAUGUAGUGGGAGU	2188-2210
AD-240789.1	3283	CCCACUACAUCAAGACUAAUA	2191-2211	3579	UAUUAGUCUUGAUGUAGUGGGAG	2189-2211
AD-240790.1	3284	CCACUACAUCAAGACUAAUCU	2192-2212	3580	AGAUUAGUCUUGAUGUAGUGGGA	2190-2212
AD-240792.1	3285	ACUACAUCAAGACUAAUCUUA	2194-2214	3581	UAAGAUUAGUCUUGAUGUAGUGG	2192-2214
AD-240793.1	3286	CUACAUCAAGACUAAUCUUGU	2195-2215	3582	ACAAGAUUAGUCUUGAUGUAGUG	2193-2215
AD-240794.1	3287	UACAUCAAGACUAAUCUUGUU	2196-2216	3583	AACAAGAUUAGUCUUGAUGUAGU	2194-2216
AD-240795.1	3288	ACAUCAAGACUAAUCUUGUUU	2197-2217	3584	AAACAAGAUUAGUCUUGAUGUAG	2195-2217
AD-240826.1	3289	GUAUUAUAGAAUGCUUUUGCA	2234-2254	3585	UGCAAAAGCAUUCUAUAAUACAU	2232-2254
AD-240830.1	3290	UAUAGAAUGCUUUUGCAUGGA	2238-2258	3586	UCCAUGCAAAAGCAUUCUAUAAU	2236-2258
AD-240833.1	3291	AGAAUGCUUUUGCAUGGACUA	2241-2261	3587	UAGUCCAUGCAAAAGCAUUCUAU	2239-2261
AD-240834.1	3292	GAAUGCUUUUGCAUGGACUAU	2242-2262	3588	AUAGUCCAUGCAAAAGCAUUCUA	2240-2262
AD-240837.1	3293	UGCUUUUGCAUGGACUAUCCU	2245-2265	3589	AGGAUAGUCCAUGCAAAAGCAUU	2243-2265
AD-240839.1	3294	CUUUUGCAUGGACUAUCCUCU	2247-2267	3590	AGAGGAUAGUCCAUGCAAAAGCA	2245-2267
AD-240843.1	3295	UGCAUGGACUAUCCUCUUGUU	2251-2271	3591	AACAAGAGGAUAGUCCAUGCAAA	2249-2271
AD-240844.1	3296	GCAUGGACUAUCCUCUUGUUU	2252-2272	3592	AAACAAGAGGAUAGUCCAUGCAA	2250-2272
AD-240871.1	3297	AAAUAACCUCUUGUAGUUAUA	2349-2369	3593	UAUAACUACAAGAGGUUAUUUUU	2347-2369
AD-240875.1	3298	AACCUCUUGUAGUUAUAAAAU	2353-2373	3594	AUUUUAUAACUACAAGAGGUUAU	2351-2373

TABLE 3. HSD17B13 Modified Sequences

Duplex Name	SEQ ID NO:	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Strand Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence
AD-238911.1	3595	csasguacCfuCfCfUfcccuaggacuL96	3891	asGfsuccUfaGfGfgaggAfgGfuacugsusc	4187	GACAGUACCUCCUCCCUAGGACU
AD-238912.1	3596	asgsuaccUfcCfUfCfccuaggacuaL96	3892	usAfsgucCfuAfGfggagGfaGfguacusgsu	4188	ACAGUACCUCCUCCCUAGGACUA
AD-238913.1	3597	gsusaccuCfcUfCfCfcuaggacuaaL96	3893	usUfsaguCfcUfAfgggaGfgAfgguacsusg	4189	CAGUACCUCCUCCCUAGGACUAC
AD-238929.1	3598	ascsuacaCfaAfGfGfacugaaccaaL96	3894	usUfsgguUfcAfGfuccuUfgUfguaguscsc	4190	GGACUACACAAGGACUGAACCAG
AD-238930.1	3599	csusacacAfaGfGfAfcugaaccagaL96	3895	usCfsuggUfuCfAfguccUfuGfuguagsusc	4191	GACUACACAAGGACUGAACCAGA
AD-238932.1	3600	ascsacaaGfgAfCfUfgaaccagaaaL96	3896	usUfsucuGfgUfUfcaguCfcUfugugusasg	4192	CUACACAAGGACUGAACCAGAAG
AD-238960.1	3601	csasgagcAfaAfGfCfcaugaacauaL96	3897	usAfsuguUfcAfUfggcuUfuGfcucugsusc	4193	GACAGAGCAAAGCCAUGAACAUC
AD-238979.1	3602	uscsauccUfaGfAfAfauccuucugaL96	3898	usCfsagaAfgGfAfuuucUfaGfgaugasusg	4194	CAUCAUCCUAGAAAUCCUUCUGC
AD-238991.1	3603	uscscuucUfgCfUfUfcugaucaccaL96	3899	usGfsgugAfuCfAfgaagCfaGfaaggasusu	4195	AAUCCUUCUGCUUCUGAUCACCA
AD-239009.1	3604	cscsaucaUfcUfAfCfuccuacuugaL96	3900	usCfsaagUfaGfGfaguaGfaUfgauggsusg	4196	CACCAUCAUCUACUCCUACUUGG
AD-239015.1	3605	uscsuacuCfcUfAfCfuuggagucguL96	3901	asCfsgacUfcCfAfaguaGfgAfguagasusg	4197	CAUCUACUCCUACUUGGAGUCGU
AD-239016.1	3606	csusacucCfuAfCfUfuggagucguuL96	3902	asAfscgaCfuCfCfaaguAfgGfaguagsasu	4198	AUCUACUCCUACUUGGAGUCGUU
AD-239017.1	3607	usascuccUfaCfUfUfggagucguuaL96	3903	usAfsacgAfcUfCfcaagUfaGfgaguasgsa	4199	UCUACUCCUACUUGGAGUCGUUG
AD-239018.1	3608	ascsuccuAfcUfUfGfgagucguugaL96	3904	usCfsaacGfaCfUfccaaGfuAfggagusasg	4200	CUACUCCUACUUGGAGUCGUUGG
AD-239019.1	3609	csusccuaCfuUfGfGfagucguugguL96	3905	asCfscaaCfgAfCfuccaAfgUfaggagsusa	4201	UACUCCUACUUGGAGUCGUUGGU
AD-239020.1	3610	uscscuacUfuGfGfAfgucguugguaL96	3906	usAfsccaAfcGfAfcuccAfaGfuaggasgsu	4202	ACUCCUACUUGGAGUCGUUGGUG
AD-239031.1	3611	gsuscguuGfgUfGfAfaguuuuucauL96	3907	asUfsgaaAfaAfCfuucaCfcAfacgacsusc	4203	GAGUCGUUGGUGAAGUUUUUCAU
AD-239062.1	3612	gsasgauuGfuUfCfUfcauuacuggaL96	3908	usCfscagUfaAfUfgagaAfcAfaucucscsc	4204	GGGAGAUUGUUCUCAUUACUGGA
AD-239066.1	3613	ususguucUfcAfUfUfacuggagcuaL96	3909	usAfsgcuCfcAfGfuaauGfaGfaacaasusc	4205	GAUUGUUCUCAUUACUGGAGCUG
AD-239103.1	3614	gscsagacUfaCfUfUfaugaauuugaL96	3910	usCfsaaaUfuCfAfuaagUfaGfucugcscsu	4206	AGGCAGACUACUUAUGAAUUUGC
AD-239110.1	3615	ascsuuauGfaAfUfUfugcaaaacgaL96	3911	usCfsguuUfuGfCfaaauUfcAfuaagusasg	4207	CUACUUAUGAAUUUGCAAAACGA
AD-239118.1	3616	asususugcAfaAfAfCfgacagagcauL96	3912	asUfsgcuCfuGfUfcguuUfuGfcaaaususc	4208	GAAUUUGCAAAACGACAGAGCAU
AD-239119.1	3617	ususugcaAfaAfCfGfacagagcauaL96	3913	usAfsugcUfcUfGfucguUfuUfgcaaasusu	4209	AAUUUGCAAAACGACAGAGCAUA
AD-239131.1	3618	csasgagcAfuAfUfUfgguucugugaL96	3914	usCfsacaGfaAfCfcaauAfuGfcucugsusc	4210	GACAGAGCAUAUUGGUUCUGUGG
AD-239132.1	3619	asgsagcaUfaUfUfGfguucuguggaL96	3915	usCfscacAfgAfAfccaaUfaUfgcucusgsu	4211	ACAGAGCAUAUUGGUUCUGUGGG
AD-239133.1	3620	gsasgcauAfuUfGfGfuucugugggaL96	3916	usCfsccaCfaGfAfaccaAfuAfugcucsusg	4212	CAGAGCAUAUUGGUUCUGUGGGA
AD-239146.1	3621	csusguggGfaUfAfUfuaauaagcgaL96	3917	usCfsgcuUfaUfUfaauaUfcCfcacagsasa	4213	UUCUGUGGGAUAUUAAUAAGCGC
AD-239155.1	3622	asusuaauAfaGfCfCfgcgguguggaaL96	3918	usUfsccaCfaCfCfgcgcUfuAfuuaausasu	4214	AUAUUAAUAAGCGCGGUGUGGAG
AD-239156.1	3623	ususaauaAfgCfGfCfgguguggagaL96	3919	usCfsuccAfcAfCfcgcgCfuUfauuaasusa	4215	UAUUAAUAAGCGCGGUGUGGAGG

AD-239177.1	3624	asasacugCfaGfCfUfgagugccgaaL96	3920	usUfscggCfaCfUfcagcUfgCfaguuuscsc	4216	GGAAACUGCAGCUGAGUGCCGAA
AD-239178.1	3625	asascugcAfgCfUfGfagugccgaaaL96	3921	usUfsucgGfcAfCfucagCfuGfcaguususc	4217	GAAACUGCAGCUGAGUGCCGAAA
AD-239179.1	3626	ascsugcaGfcUfGfAfgugccgaaaaL96	3922	usUfsuucGfgCfAfcucaGfcUfgcagususu	4218	AAACUGCAGCUGAGUGCCGAAAA
AD-239180.1	3627	csusgcagCfuGfAfGfugccgaaaacL96	3923	gsUfsuuuCfgGfCfacucAfgCfugcagsusu	4219	AACUGCAGCUGAGUGCCGAAAAC
AD-239181.1	3628	usgscagcUfgAfGfUfgccgaaaacuL96	3924	asGfsuuuUfcGfGfcacuCfaGfcugcasgsu	4220	ACUGCAGCUGAGUGCCGAAAACU
AD-239182.1	3629	gscsagcuGfaGfUfGfccgaaaacuaL96	3925	usAfsguuUfuCfGfgcacUfcAfgcugcsasg	4221	CUGCAGCUGAGUGCCGAAAACUA
AD-239183.1	3630	csasgcugAfgUfGfCfcgaaaacuaaL96	3926	usUfsaguUfuUfCfggcaCfuCfagcugscsa	4222	UGCAGCUGAGUGCCGAAAACUAG
AD-239185.1	3631	gscsugagUfgCfCfGfaaaacuaggaL96	3927	usCfscuaGfuUfUfucggCfaCfucagcsusg	4223	CAGCUGAGUGCCGAAAACUAGGC
AD-239186.1	3632	csusgaguGfcCfGfAfaaacuaggcaL96	3928	usGfsccuAfgUfUfuucgGfcAfcucagscsu	4224	AGCUGAGUGCCGAAAACUAGGCG
AD-239187.1	3633	usgsagugCfcGfAfAfaacuaggcguL96	3929	asCfsgccUfaGfUfuuucGfgCfacucasgsc	4225	GCUGAGUGCCGAAAACUAGGCGU
AD-239188.1	3634	gsasgugcCfgAfAfAfacuaggcguaL96	3930	usAfscgcCfuAfGfuuuuCfgGfcacucsasg	4226	CUGAGUGCCGAAAACUAGGCGUC
AD-239189.1	3635	asgsugccGfaAfAfAfcuaggcgucaL96	3931	usGfsacgCfcUfAfguuuUfcGfgcacuscsa	4227	UGAGUGCCGAAAACUAGGCGUCA
AD-239190.1	3636	gsusgccgAfaAfAfCfuaggcgucaaL96	3932	usUfsgacGfcCfUfaguuUfuCfggcacsusc	4228	GAGUGCCGAAAACUAGGCGUCAC
AD-239191.1	3637	usgsccgaAfaAfCfUfaggcgucacuL96	3933	asGfsugaCfgCfCfuaguUfuUfcggcascsu	4229	AGUGCCGAAAACUAGGCGUCACU
AD-239192.1	3638	gscscgaaAfaCfUfAfggcgucacuaL96	3934	usAfsgugAfcGfCfcuagUfuUfucggcsasc	4230	GUGCCGAAAACUAGGCGUCACUG
AD-239193.1	3639	cscsgaaaAfcUfAfGfgcgucacugaL96	3935	usCfsaguGfaCfGfccuaGfuUfuucggscsa	4231	UGCCGAAAACUAGGCGUCACUGC
AD-239194.1	3640	csgsaaaaCfuAfGfGfcgucacugcaL96	3936	usGfscagUfgAfCfgccuAfgUfuuucgsgsc	4232	GCCGAAAACUAGGCGUCACUGCG
AD-239196.1	3641	asasaacuAfgGfCfGfucacugcgcaL96	3937	usGfscgcAfgUfGfacgcCfuAfguuuuscsg	4233	CGAAAACUAGGCGUCACUGCGCA
AD-239198.1	3642	asascuagGfcGfUfCfacugcgcauaL96	3938	usAfsugcGfcAfGfugacGfcCfuaguususu	4234	AAAACUAGGCGUCACUGCGCAUG
AD-239199.1	3643	ascsuaggCfgUfCfAfcugcgcaugaL96	3939	usCfsaugCfgCfAfgugaCfgCfcuagususu	4235	AAACUAGGCGUCACUGCGCAUGC
AD-239203.1	3644	gsgscgucAfcUfGfCfgcaugcguauL96	3940	asUfsacgCfaUfGfcgcaGfuGfacgccsusa	4236	UAGGCGUCACUGCGCAUGCGUAU
AD-239214.1	3645	gscsaugcGfuAfUfGfugguagacuaL96	3941	usAfsgucUfaCfCfacauAfcGfcaugcsgsc	4237	GCGCAUGCGUAUGUGGUAGACUG
AD-239215.1	3646	csasugcgUfaUfGfUfgguagacugaL96	3942	usCfsaguCfuAfCfcacaUfaCfgcaugscsg	4238	CGCAUGCGUAUGUGGUAGACUGC
AD-239239.1	3647	asascagaGfaAfGfAfgaucuaucgaL96	3943	usCfsgauAfgAfUfcucuUfcUfcuguusgsc	4239	GCAACAGAGAAGAGAUCUAUCGC
AD-239240.1	3648	ascsagagAfaGfAfGfaucuaucgcuL96	3944	asGfscgaUfaGfAfucucUfuCfucugususg	4240	CAACAGAGAAGAGAUCUAUCGCU
AD-239241.1	3649	csasgagaAfgAfGfAfucuaucgcuaL96	3945	usAfsgcgAfuAfGfaucuCfuUfcucugsusu	4241	AACAGAGAAGAGAUCUAUCGCUC
AD-239242.1	3650	asgsagaaGfaGfAfUfcuaucgcucuL96	3946	asGfsagcGfaUfAfgaucUfcUfucucusgsu	4242	ACAGAGAAGAGAUCUAUCGCUCU
AD-239243.1	3651	gsasgaagAfgAfUfCfuaucgcucuaL96	3947	usAfsgagCfgAfUfagauCfuCfuucucsusg	4243	CAGAGAAGAGAUCUAUCGCUCUC
AD-239245.1	3652	gsasagagAfuCfUfAfucgcucucuaL96	3948	usAfsgagAfgCfGfauagAfuCfucuucsusc	4244	GAGAAGAGAUCUAUCGCUCUCUA
AD-239246.1	3653	asasgagaUfcUfAfUfcgcucucuaaL96	3949	usUfsagaGfaGfCfgauaGfaUfcucuuscsu	4245	AGAAGAGAUCUAUCGCUCUCUAA
AD-239247.1	3654	asgsagauCfuAfUfCfgcucucuaaaL96	3950	usUfsuagAfgAfGfcgauAfgAfucucususc	4246	GAAGAGAUCUAUCGCUCUCUAAA
AD-239250.1	3655	gsasucuaUfcGfCfUfcucuaaaucaL96	3951	usGfsauuUfaGfAfgagcGfaUfagaucsusc	4247	GAGAUCUAUCGCUCUCUAAAUCA
AD-239251.1	3656	asuscuauCfgCfUfCfucuaaaucaaL96	3952	usUfsgauUfuAfGfagagCfgAfuagauscsu	4248	AGAUCUAUCGCUCUCUAAAUCAG
AD-239253.1	3657	csusaucgCfuCfUfCfuaaaucagguL96	3953	asCfscugAfuUfUfagagAfgCfgauagsasu	4249	AUCUAUCGCUCUCUAAAUCAGGU
AD-239254.1	3658	usasucgcUfcUfCfUfaaaucagguaL96	3954	usAfsccuGfaUfUfuagaGfaGfcgauasgsa	4250	UCUAUCGCUCUCUAAAUCAGGUG

AD-239255.1	3659	asuscgcuCfuCfUfAfaaucaggugaL96	3955	usCfsaccUfgAfUfuuagAfgAfgcgausasg	4251	CUAUCGCUCUCUAAAUCAGGUGA
AD-239290.1	3660	gsasuguaAfcAfAfUfcguggugaauL96	3956	asUfsucaCfcAfCfgauuGfuUfacaucsasc	4252	GUGAUGUAACAAUCGUGGUGAAU
AD-239291.1	3661	asusguaaCfaAfUfCfguggugaauaL96	3957	usAfsuucAfcCfAfcgauUfgUfuacauscsa	4253	UGAUGUAACAAUCGUGGUGAAUA
AD-239292.1	3662	usgsuaacAfaUfCfGfuggugaauaaL96	3958	usUfsauuCfaCfCfacgaUfuGfuuacasusc	4254	GAUGUAACAAUCGUGGUGAAUAA
AD-239293.1	3663	gsusaacaAfuCfGfUfggugaauaauL96	3959	asUfsuauUfcAfCfcacgAfuUfguuacsasu	4255	AUGUAACAAUCGUGGUGAAUAAU
AD-239304.1	3664	gsgsugaaUfaAfUfGfcugggacaguL96	3960	asCfsuguCfcCfAfgcauUfaUfucaccsasc	4256	GUGGUGAAUAAUGCUGGGACAGU
AD-239312.1	3665	asusgcugGfgAfCfAfguauauccaaL96	3961	usUfsggaUfaUfAfcuguCfcCfagcaususa	4257	UAAUGCUGGGACAGUAUAUCCAG
AD-239313.1	3666	usgscuggGfaCfAfGfuauauccagaL96	3962	usCfsuggAfuAfUfacugUfcCfcagcasusu	4258	AAUGCUGGGACAGUAUAUCCAGC
AD-239314.1	3667	gscsugggAfcAfGfUfauauccagcaL96	3963	usGfscugGfaUfAfuacuGfuCfccagcsasu	4259	AUGCUGGGACAGUAUAUCCAGCC
AD-239316.1	3668	usgsggacAfgUfAfUfauccagccgaL96	3964	usCfsggcUfgGfAfuauaCfuGfucccasgsc	4260	GCUGGGACAGUAUAUCCAGCCGA
AD-239317.1	3669	gsgsgacaGfuAfUfAfuccagccgauL96	3965	asUfscggCfuGfGfauauAfcUfgucccsasg	4261	CUGGGACAGUAUAUCCAGCCGAU
AD-239318.1	3670	gsgsacagUfaUfAfUfccagccgauaL96	3966	usAfsucgGfcUfGfgauaUfaCfugucccsca	4262	UGGGACAGUAUAUCCAGCCGAUC
AD-239321.1	3671	csasguauAfuCfCfAfgccgaucuuaL96	3967	usAfsagaUfcGfGfcuggAfuAfuacugsusc	4263	GACAGUAUAUCCAGCCGAUCUUC
AD-239332.1	3672	gscscgauCfuUfCfUfcagcaccaaaL96	3968	usUfsuggUfgCfUfgagaAfgAfucggcsusg	4264	CAGCCGAUCUUCUCAGCACCAAG
AD-239337.1	3673	uscsuucuCfaGfCfAfccaaggaugaL96	3969	usCfsaucCfuUfGfgugcUfgAfgaagasusc	4265	GAUCUUCUCAGCACCAAGGAUGA
AD-239348.1	3674	cscsaaggAfuGfAfAfgagauuaccaL96	3970	usGfsguaAfuCfUfcuucAfuCfcuuggsusg	4266	CACCAAGGAUGAAGAGAUUACCA
AD-239362.1	3675	asusuaccAfaGfAfCfauuugagguaL96	3971	usAfsccuCfaAfAfugucUfuGfguaauscsu	4267	AGAUUACCAAGACAUUUGAGGUC
AD-239366.1	3676	cscsaagaCfaUfUfUfgaggucaacaL96	3972	usGfsuugAfcCfUfcaaaUfgUfcuuggsusa	4268	UACCAAGACAUUUGAGGUCAACA
AD-239368.1	3677	asasgacaUfuUfGfAfggucaacauaL96	3973	usAfsuguUfgAfCfcucaAfaUfgucuusgsg	4269	CCAAGACAUUUGAGGUCAACAUC
AD-239372.1	3678	csasuuugAfgGfUfCfaacauccuaaL96	3974	usUfsaggAfuGfUfugacCfuCfaaaugsusc	4270	GACAUUUGAGGUCAACAUCCUAG
AD-239373.1	3679	asusuugaGfgUfCfAfacauccuagaL96	3975	usCfsuagGfaUfGfuugaCfcUfcaaausgsu	4271	ACAUUUGAGGUCAACAUCCUAGG
AD-239379.1	3680	gsgsucaaCfaUfCfCfuaggacauuuL96	3976	asAfsaugUfcCfUfaggaUfgUfugaccsusc	4272	GAGGUCAACAUCCUAGGACAUUU
AD-239380.1	3681	gsuscaacAfuCfCfUfaggacauuuuL96	3977	asAfsaauGfuCfCfuaggAfuGfuugacscsu	4273	AGGUCAACAUCCUAGGACAUUUU
AD-239387.1	3682	uscscuagGfaCfAfUfuuuuggaucaL96	3978	usGfsaucCfaAfAfaaugUfcCfuaggasusg	4274	CAUCCUAGGACAUUUUUGGAUCA
AD-239397.1	3683	ususuuugGfaUfCfAfcaaaagcacuL96	3979	asGfsugcUfuUfUfgugaUfcCfaaaaasusg	4275	CAUUUUUGGAUCACAAAAGCACU
AD-239411.1	3684	asasgcacUfuCfUfUfccaucgaugaL96	3980	usCfsaucGfaUfGfgaagAfaGfugcuususu	4276	AAAAGCACUUCUUCCAUCGAUGA
AD-239412.1	3685	asgscacuUfcUfUfCfcaucgaugauL96	3981	asUfscauCfgAfUfggaaGfaAfgugcususu	4277	AAAGCACUUCUUCCAUCGAUGAU
AD-239431.1	3686	asusggagAfgAfAfAfucauggccaaL96	3982	usUfsggcCfaUfGfauuuCfuCfuccauscsa	4278	UGAUGGAGAGAAAUCAUGGCCAC
AD-239433.1	3687	gsgsagagAfaAfUfCfauggccacauL96	3983	asUfsgugGfcCfAfugauUfuCfucuccsasu	4279	AUGGAGAGAAAUCAUGGCCACAU
AD-239436.1	3688	gsasgaaaUfcAfUfGfgccacaucguL96	3984	asCfsgauGfuGfGfccauGfaUfuucucsusc	4280	GAGAGAAAUCAUGGCCACAUCGU
AD-239437.1	3689	asgsaaauCfaUfGfGfccacaucguaL96	3985	usAfscgaUfgUfGfgccaUfgAfuuucuscsu	4281	AGAGAAAUCAUGGCCACAUCGUC
AD-239438.1	3690	gsasaaucAfuGfGfCfcacaucgucaL96	3986	usGfsacgAfuGfUfggccAfuGfauuucsusc	4282	GAGAAAUCAUGGCCACAUCGUCA
AD-239439.1	3691	asasaucaUfgGfCfCfacaucgucaaL96	3987	usUfsgacGfaUfGfuggcCfaUfgauuuscsu	4283	AGAAAUCAUGGCCACAUCGUCAC
AD-239450.1	3692	ascsaucgUfcAfCfAfguggcuucaaL96	3988	usUfsgaaGfcCfAfcuguGfaCfgaugusgsg	4284	CCACAUCGUCACAGUGGCUUCAG
AD-239451.1	3693	csasucguCfaCfAfGfuggcuucaguL96	3989	asCfsugaAfgCfCfacugUfgAfcgaugsusg	4285	CACAUCGUCACAGUGGCUUCAGU

AD-239452.1	3694	asuscgucAfcAfGfUfggcuucaguaL96	3990	usAfscugAfaGfCfcacuGfuGfacgausgsu	4286	ACAUCGUCACAGUGGCUUCAGUG
AD-239453.1	3695	uscsgucaCfaGfUfGfgcuucaguguL96	3991	asCfsacuGfaAfGfccacUfgUfgacgasusg	4287	CAUCGUCACAGUGGCUUCAGUGU
AD-239475.1	3696	csgsgccaCfgAfAfGfggauuccuuaL96	3992	usAfsaggAfaUfCfccuuCfgUfggccgscsa	4288	UGCGGCCACGAAGGGAUUCCUUA
AD-239476.1	3697	gsgsccacGfaAfGfGfgauuccuuaaL96	3993	usUfsaagGfaAfUfcccuUfcGfuggccsgsc	4289	GCGGCCACGAAGGGAUUCCUUAC
AD-239478.1	3698	cscsacgaAfgGfGfAfuuccuuaccuL96	3994	asGfsguaAfgGfAfauccCfuUfcguggscsc	4290	GGCCACGAAGGGAUUCCUUACCU
AD-239479.1	3699	csascgaaGfgGfAfUfuccuuaccuaL96	3995	usAfsgguAfaGfGfaaucCfcUfucgugsgsc	4291	GCCACGAAGGGAUUCCUUACCUC
AD-239480.1	3700	ascsgaagGfgAfUfUfccuuaccucaL96	3996	usGfsaggUfaAfGfgaauCfcCfuucgusgsg	4292	CCACGAAGGGAUUCCUUACCUCA
AD-239482.1	3701	gsasagggAfuUfCfCfuuaccucauaL96	3997	usAfsugaGfgUfAfaggaAfuCfccuucsgsu	4293	ACGAAGGGAUUCCUUACCUCAUC
AD-239483.1	3702	asasgggaUfuCfCfUfuaccucaucaL96	3998	usGfsaugAfgGfUfaaggAfaUfcccuuscsg	4294	CGAAGGGAUUCCUUACCUCAUCC
AD-239499.1	3703	csasucccAfuAfUfUfguuccagcaaL96	3999	usUfsgcuGfgAfAfcaauAfuGfggaugsasg	4295	CUCAUCCCAUAUUGUUCCAGCAA
AD-239510.1	3704	gsusuccaGfcAfAfAfuuugccgcuaL96	4000	usAfsgcgGfcAfAfauuuGfcUfggaacsasa	4296	UUGUUCCAGCAAAUUUGCCGCUG
AD-239520.1	3705	asusuugcCfgCfUfGfuuggcuuucaL96	4001	usGfsaaaGfcCfAfacagCfgGfcaaaususu	4297	AAAUUUGCCGCUGUUGGCUUUCA
AD-239521.1	3706	ususugccGfcUfGfUfuggcuuucaaL96	4002	usUfsgaaAfgCfCfaacaGfcGfgcaaasusu	4298	AAUUUGCCGCUGUUGGCUUUCAC
AD-239522.1	3707	ususgccgCfuGfUfUfggcuuucacaL96	4003	usGfsugaAfaGfCfcaacAfgCfggcaasasu	4299	AUUUGCCGCUGUUGGCUUUCACA
AD-239534.1	3708	gscsuuucAfcAfGfAfggucugacauL96	4004	asUfsgucAfgAfCfcucuGfuGfaaagcscsa	4300	UGGCUUUCACAGAGGUCUGACAU
AD-239539.1	3709	csascagaGfgUfCfUfgacaucagaaL96	4005	usUfscugAfuGfUfcagaCfcUfcugugsasa	4301	UUCACAGAGGUCUGACAUCAGAA
AD-239544.1	3710	asgsgucuGfaCfAfUfcagaacuucaL96	4006	usGfsaagUfuCfUfgaugUfcAfgaccuscsu	4302	AGAGGUCUGACAUCAGAACUUCA
AD-239566.1	3711	gscscuugGfgAfAfAfaacugguauaL96	4007	usAfsuacCfaGfUfuuuuCfcCfaaggcscsu	4303	AGGCCUUGGGAAAAACUGGUAUC
AD-239578.1	3712	ascsugguAfuCfAfAfaaccucauguL96	4008	asCfsaugAfgGfUfuuugAfuAfccagususu	4304	AAACUGGUAUCAAAACCUCAUGU
AD-239579.1	3713	csusgguaUfcAfAfAfaccucauguaL96	4009	usAfscauGfaGfGfuuuuGfaUfaccagsusu	4305	AACUGGUAUCAAAACCUCAUGUC
AD-239611.1	3714	ususugugAfaUfAfCfuggguucacaL96	4010	usGfsugaAfcCfCfaguaUfuCfacaaasasa	4306	UUUUUGUGAAUACUGGGUUCACC
AD-239612.1	3715	ususgugaAfuAfCfUfggguucaccaL96	4011	usGfsgugAfaCfCfcaguAfuUfcacaasasa	4307	UUUUGUGAAUACUGGGUUCACCA
AD-239613.1	3716	usgsugaaUfaCfUfGfgguucaccaaL96	4012	usUfsgguGfaAfCfccagUfaUfucacasasa	4308	UUUGUGAAUACUGGGUUCACCAA
AD-239617.1	3717	asasuacuGfgGfUfUfcaccaaaaauL96	4013	asUfsuuuUfgGfUfgaacCfcAfguauuscsa	4309	UGAAUACUGGGUUCACCAAAAAU
AD-239618.1	3718	asusacugGfgUfUfCfaccaaaaauaL96	4014	usAfsuuuUfuGfGfugaaCfcCfaguaususc	4310	GAAUACUGGGUUCACCAAAAAUC
AD-239637.1	3719	uscscaagCfaCfAfAfgauuauggcaL96	4015	usGfsccaUfaAfUfcuugUfgCfuuggasusu	4311	AAUCCAAGCACAAGAUUAUGGCC
AD-239641.1	3720	asgscacaAfgAfUfUfauggccuguaL96	4016	usAfscagGfcCfAfuaauCfuUfgugcususg	4312	CAAGCACAAGAUUAUGGCCUGUA
AD-239642.1	3721	gscsacaaGfaUfUfAfuggccuguauL96	4017	asUfsacaGfgCfCfauaaUfcUfugugcsusu	4313	AAGCACAAGAUUAUGGCCUGUAU
AD-239643.1	3722	csascaagAfuUfAfUfggccuguauuL96	4018	asAfsuacAfgGfCfcauaAfuCfuugugscsu	4314	AGCACAAGAUUAUGGCCUGUAUU
AD-239645.1	3723	csasagauUfaUfGfGfccuguauugaL96	4019	usCfsaauAfcAfGfgccaUfaAfucuugsusg	4315	CACAAGAUUAUGGCCUGUAUUGG
AD-239647.1	3724	asgsauuaUfgGfCfCfuguauuggaaL96	4020	usUfsccaAfuAfCfaggcCfaUfaaucususg	4316	CAAGAUUAUGGCCUGUAUUGGAG
AD-239649.1	3725	asusuaugGfcCfUfGfuauuggagaaL96	4021	usUfscucCfaAfUfacagGfcCfauaauscsu	4317	AGAUUAUGGCCUGUAUUGGAGAC
AD-239650.1	3726	ususauggCfcUfGfUfauuggagacaL96	4022	usGfsucuCfcAfAfuacaGfgCfcauaasusc	4318	GAUUAUGGCCUGUAUUGGAGACA
AD-239653.1	3727	usgsgccuGfuAfUfUfggagacagauL96	4023	asUfscugUfcUfCfcaauAfcAfggccasusa	4319	UAUGGCCUGUAUUGGAGACAGAU
AD-239654.1	3728	gsgsccugUfaUfUfGfgagacagauaL96	4024	usAfsucuGfuCfUfccaaUfaCfaggccsasu	4320	AUGGCCUGUAUUGGAGACAGAUG

AD-239662.1	3729	ususggagAfcAfGfAfugaagucguaL96	4025	usAfscgaCfuUfCfaucuGfuCfuccaasusa	4321	UAUUGGAGACAGAUGAAGUCGUA
AD-239668.1	3730	ascsagauGfaAfGfUfcguaagaaguL96	4026	asCfsuucUfuAfCfgacuUfcAfucuguscsu	4322	AGACAGAUGAAGUCGUAAGAAGU
AD-239669.1	3731	csasgaugAfaGfUfCfguaagaaguaL96	4027	usAfscuuCfuUfAfcgacUfuCfaucugsusc	4323	GACAGAUGAAGUCGUAAGAAGUC
AD-239670.1	3732	asgsaugaAfgUfCfGfuaagaagucuL96	4028	asGfsacuUfcUfUfacgaCfuUfcaucusgsu	4324	ACAGAUGAAGUCGUAAGAAGUCU
AD-239671.1	3733	gsasugaaGfuCfGfUfaagaagucuaL96	4029	usAfsgacUfuCfUfuacgAfcUfucaucsusg	4325	CAGAUGAAGUCGUAAGAAGUCUG
AD-239674.1	3734	gsasagucGfuAfAfGfaagucugauaL96	4030	usAfsucaGfaCfUfucuuAfcGfacuucsasu	4326	AUGAAGUCGUAAGAAGUCUGAUA
AD-239676.1	3735	asgsucguAfaGfAfAfgucugauagaL96	4031	usCfsuauCfaGfAfcuucUfuAfcgacususc	4327	GAAGUCGUAAGAAGUCUGAUAGA
AD-239681.1	3736	usasagaaGfuCfUfGfauagauggaaL96	4032	usUfsccaUfcUfAfucagAfcUfucuuascsg	4328	CGUAAGAAGUCUGAUAGAUGGAA
AD-239682.1	3737	asasgaagUfcUfGfAfuagauggaauL96	4033	asUfsuccAfuCfUfaucaGfaCfuucuusasc	4329	GUAAGAAGUCUGAUAGAUGGAAU
AD-239684.1	3738	gsasagucUfgAfUfAfgauggaauaaL96	4034	usUfsauuCfcAfUfcuauCfaGfacuucsusu	4330	AAGAAGUCUGAUAGAUGGAAUAC
AD-239685.1	3739	asasgucuGfaUfAfGfauggaauacuL96	4035	asGfsuauUfcCfAfucuaUfcAfgacuuscsu	4331	AGAAGUCUGAUAGAUGGAAUACU
AD-239697.1	3740	usgsgaauAfcUfUfAfccaauaagaaL96	4036	usUfscuuAfuUfGfguaaGfuAfuuccasusc	4332	GAUGGAAUACUUACCAAUAAGAA
AD-239713.1	3741	asasugauUfuUfUfGfuuccaucguaL96	4037	usAfscgaUfgGfAfacaaAfaAfucauususu	4333	AAAAUGAUUUUUGUUCCAUCGUA
AD-239714.1	3742	asusgauuUfuUfGfUfuccaucguauL96	4038	asUfsacgAfuGfGfaacaAfaAfaucaususu	4334	AAAUGAUUUUUGUUCCAUCGUAU
AD-239717.1	3743	asususuuGfuUfCfCfaucguauauaL96	4039	usAfsuauAfcGfAfuggaAfcAfaaaauscsa	4335	UGAUUUUUGUUCCAUCGUAUAUC
AD-239721.1	3744	ususguucCfaUfCfGfuauaucaauaL96	4040	usAfsuugAfuAfUfacgaUfgGfaacaasasa	4336	UUUUGUUCCAUCGUAUAUCAAUA
AD-239723.1	3745	gsusuccaUfcGfUfAfuaucaauauaL96	4041	usAfsuauUfgAfUfauacGfaUfggaacsasa	4337	UUGUUCCAUCGUAUAUCAAUAUC
AD-239724.1	3746	ususccauCfgUfAfUfaucaauaucuL96	4042	asGfsauaUfuGfAfuauaCfgAfuggaascsa	4338	UGUUCCAUCGUAUAUCAAUAUCU
AD-239725.1	3747	uscscaucGfuAfUfAfucaauaucuuL96	4043	asAfsgauAfuUfGfauauAfcGfauggasasc	4339	GUUCCAUCGUAUAUCAAUAUCUU
AD-239726.1	3748	cscsaucgUfaUfAfUfcaauaucuuuL96	4044	asAfsagaUfaUfUfgauaUfaCfgauggsasa	4340	UUCCAUCGUAUAUCAAUAUCUUU
AD-239755.1	3749	ascsagaaGfuUfUfCfuuccugaacaL96	4045	usGfsuucAfgGfAfagaaAfcUfucugusasg	4341	CUACAGAAGUUUCUUCCUGAACG
AD-239757.1	3750	asgsaaguUfuCfUfUfccugaacgcaL96	4046	usGfscguUfcAfGfgaagAfaAfcuucusgsu	4342	ACAGAAGUUUCUUCCUGAACGCG
AD-239759.1	3751	asasguuuCfuUfCfCfugaacgcgcaL96	4047	usGfscgcGfuUfCfaggaAfgAfaacuuscsu	4343	AGAAGUUUCUUCCUGAACGCGCC
AD-239761.1	3752	gsusuucuUfcCfUfGfaacgcgccuaL96	4048	usAfsggcGfcGfUfucagGfaAfgaaacsusu	4344	AAGUUUCUUCCUGAACGCGCCUC
AD-239764.1	3753	uscsuuccUfgAfAfCfgcgccucagaL96	4049	usCfsugaGfgCfGfcguuCfaGfgaagasasa	4345	UUUCUUCCUGAACGCGCCUCAGC
AD-239778.1	3754	cscsucagCfgAfUfUfuuaaaucguaL96	4050	usAfscgaUfuUfAfaaauCfgCfugaggscsg	4346	CGCCUCAGCGAUUUUAAAUCGUA
AD-239779.1	3755	csuscagcGfaUfUfUfuaaaucguauL96	4051	asUfsacgAfuUfUfaaaaUfcGfcugagsgsc	4347	GCCUCAGCGAUUUUAAAUCGUAU
AD-239780.1	3756	uscsagcgAfuUfUfUfaaaucguauaL96	4052	usAfsuacGfaUfUfuaaaAfuCfgcugasgsg	4348	CCUCAGCGAUUUUAAAUCGUAUG
AD-239781.1	3757	csasgcgaUfuUfUfAfaaucguaugaL96	4053	usCfsauaCfgAfUfuuaaAfaUfcgcugsasg	4349	CUCAGCGAUUUUAAAUCGUAUGC
AD-239782.1	3758	asgscgauUfuUfAfAfaucguaugcaL96	4054	usGfscauAfcGfAfuuuaAfaAfucgcusgsa	4350	UCAGCGAUUUUAAAUCGUAUGCA
AD-239783.1	3759	gscsgauuUfuAfAfAfucguaugcaaL96	4055	usUfsgcaUfaCfGfauuuAfaAfaucgcsusg	4351	CAGCGAUUUUAAAUCGUAUGCAG
AD-239784.1	3760	csgsauuuUfaAfAfUfcguaugcagaL96	4056	usCfsugcAfuAfCfgauuUfaAfaaucgscsu	4352	AGCGAUUUUAAAUCGUAUGCAGA
AD-239785.1	3761	gsasuuuuAfaAfUfCfguaugcagaaL96	4057	usUfscugCfaUfAfcgauUfuAfaaaucsgsc	4353	GCGAUUUUAAAUCGUAUGCAGAA
AD-239786.1	3762	asususuuaAfaUfCfGfuaugcagaauL96	4058	asUfsucuGfcAfUfacgaUfuUfaaaauscsg	4354	CGAUUUUAAAUCGUAUGCAGAAU
AD-239787.1	3763	ususuuaaAfuCfGfUfaugcagaauaL96	4059	usAfsuucUfgCfAfuacgAfuUfuaaaasusc	4355	GAUUUUAAAUCGUAUGCAGAAUA

AD-239791.1	3764	asasaucgUfaUfGfCfagaauauucaL96	4060	usGfsaauAfuUfCfugcaUfaCfgauuusasa	4356	UUAAAUCGUAUGCAGAAUAUUCA
AD-239793.1	3765	asuscguaUfgCfAfGfaauauucaauL96	4061	asUfsugaAfuAfUfucugCfaUfacgaususu	4357	AAAUCGUAUGCAGAAUAUUCAAU
AD-239806.1	3766	usasuucaAfuUfUfGfaagcaguggguL96	4062	asCfscacUfgCfUfucaaAfuUfgaauasusu	4358	AAUAUUCAAUUUGAAGCAGUGGU
AD-239839.1	3767	gsasauaaAfuAfAfGfcuccagccaaL96	4063	usUfsggcUfgGfAfgcuuAfuUfuauucsasu	4359	AUGAAUAAAUAAGCUCCAGCCAG
AD-239840.1	3768	asasuaaaUfaAfGfCfuccagccagaL96	4064	usCfsuggCfuGfGfagcuUfaUfuuauuscsa	4360	UGAAUAAAUAAGCUCCAGCCAGA
AD-239854.1	3769	asgsccagAfgAfUfGfuaugcaugauL96	4065	asUfscauGfcAfUfacauCfuCfuggcusgsg	4361	CCAGCCAGAGAUGUAUGCAUGAU
AD-239855.1	3770	gscscagaGfaUfGfUfaugcaugauaL96	4066	usAfsucaUfgCfAfuacaUfcUfcuggcsusg	4362	CAGCCAGAGAUGUAUGCAUGAUA
AD-239876.1	3771	asusaugaAfuAfGfUfuucgaaucaaL96	4067	usUfsgauUfcGfAfaacuAfuUfcauauscsa	4363	UGAUAUGAAUAGUUUCGAAUCAA
AD-239877.1	3772	usasugaaUfaGfUfUfucgaaucaauL96	4068	asUfsugaUfuCfGfaaacUfaUfucauasusc	4364	GAUAUGAAUAGUUUCGAAUCAAU
AD-239881.1	3773	asasuaguUfuCfGfAfaucaaugcuaL96	4069	usAfsgcaUfuGfAfuucgAfaAfcuauuscsa	4365	UGAAUAGUUUCGAAUCAAUGCUG
AD-239905.1	3774	ususcaguCfcUfGfAfuaauauuaaaL96	4070	usUfsuaaUfaUfUfaucaGfgAfcugaasasa	4366	UUUUCAGUCCUGAUAAUAUUAAA
AD-239914.1	3775	asasaaacAfuUfGfGfuuuggcacuaL96	4071	usAfsgugCfcAfAfaccaAfuGfuuuuusasa	4367	UUAAAAACAUUGGUUUGGCACUA
AD-239915.1	3776	asasaacaUfuGfGfUfuuggcacuaaL96	4072	usUfsaguGfcCfAfaaccAfaUfguuuususa	4368	UAAAAACAUUGGUUUGGCACUAG
AD-239941.1	3777	gsuscaaaCfgAfAfCfaagauuaauuL96	4073	asAfsuuaAfuCfUfuguuCfgUfuugacsusg	4369	CAGUCAAACGAACAAGAUUAAUU
AD-239944.1	3778	asasacgaAfcAfAfGfauuaauuacaL96	4074	usGfsuaaUfuAfAfucuuGfuUfcguuusgsa	4370	UCAAACGAACAAGAUUAAUUACC
AD-239945.1	3779	asascgaaCfaAfGfAfuuaauuaccuL96	4075	asGfsguaAfuUfAfaucuUfgUfucguususg	4371	CAAACGAACAAGAUUAAUUACCU
AD-239946.1	3780	ascsgaacAfaGfAfUfuaauuaccuaL96	4076	usAfsgguAfaUfUfaaucUfuGfuucgususu	4372	AAACGAACAAGAUUAAUUACCUG
AD-239947.1	3781	csgsaacaAfgAfUfUfaauuaccuguL96	4077	asCfsaggUfaAfUfuaauCfuUfguucgsusu	4373	AACGAACAAGAUUAAUUACCUGU
AD-239977.1	3782	uscsucaaGfaAfUfAfuuuacguaguL96	4078	asCfsuacGfuAfAfauauUfcUfugagasasa	4374	UUUCUCAAGAAUAUUUACGUAGU
AD-239979.1	3783	uscsaagaAfuAfUfUfuacguaguuuL96	4079	asAfsacuAfcGfUfaaauAfuUfcuugasgsa	4375	UCUCAAGAAUAUUUACGUAGUUU
AD-239980.1	3784	csasagaaUfaUfUfUfacguaguuuuL96	4080	asAfsaacUfaCfGfuaaaUfaUfucuugsasg	4376	CUCAAGAAUAUUUACGUAGUUUU
AD-239998.1	3785	ususucauAfgGfUfCfuguuuuuccuL96	4081	asGfsgaaAfaAfCfagacCfuAfugaaasasa	4377	UUUUUCAUAGGUCUGUUUUUCCU
AD-240019.1	3786	ususcaugCfcUfCfUfuaaaaacuuaL96	4082	usAfsaguUfuUfUfaagaGfgCfaugaasasg	4378	CUUUCAUGCCUCUUAAAAACUUC
AD-240031.1	3787	asasaaacUfuCfUfGfugcuuacauaL96	4083	usAfsuguAfaGfCfacagAfaGfuuuuusasa	4379	UUAAAAACUUCUGUGCUUACAUA
AD-240032.1	3788	asasaacuUfcUfGfUfgcuuacauaaL96	4084	usUfsaugUfaAfGfcacaGfaAfguuuususa	4380	UAAAAACUUCUGUGCUUACAUAA
AD-240033.1	3789	asasacuuCfuGfUfGfcuuacauaaaL96	4085	usUfsuauGfuAfAfgcacAfgAfaguuususu	4381	AAAAACUUCUGUGCUUACAUAAA
AD-240064.1	3790	ususuuucCfaUfUfUfaaagguggaaL96	4086	usUfsccaCfcUfUfuaaaUfgGfaaaaasusa	4382	UAUUUUUCCAUUUAAAGGUGGAC
AD-240090.1	3791	csusaccuCfcCfUfAfaaaguaaauaL96	4087	usAfsuuuAfcUfUfuuagGfgAfgguagscsu	4383	AGCUACCUCCCUAAAAGUAAAUA
AD-240091.1	3792	usasccucCfcUfAfAfaaguaaauaaL96	4088	usUfsauuUfaCfUfuuuaGfgGfagguasgsc	4384	GCUACCUCCCUAAAAGUAAAUAC
AD-240108.1	3793	usascaaaGfaGfAfAfcuuauuuacaL96	4089	usGfsuaaAfuAfAfguucUfcUfuuguasusu	4385	AAUACAAAGAGAACUUAUUUACA
AD-240117.1	3794	asascuuaUfuUfAfCfacagggaagaL96	4090	usCfsuucCfcUfGfuguaAfaUfaaguuscsu	4386	AGAACUUAUUUACACAGGGAAGG
AD-240124.1	3795	ususacacAfgGfGfAfagguuuaagaL96	4091	usCfsuuaAfaCfCfuuccCfuGfuguaasasu	4387	AUUUACACAGGGAAGGUUUAAGA
AD-240125.1	3796	usascacaGfgGfAfAfgguuuaagaaL96	4092	usUfscuuAfaAfCfcuucCfcUfguguasasa	4388	UUUACACAGGGAAGGUUUAAGAC
AD-240126.1	3797	ascsacagGfgAfAfGfguuuaagacuL96	4093	asGfsucuUfaAfAfccuuCfcCfugugusasa	4389	UUACACAGGGAAGGUUUAAGACU
AD-240135.1	3798	asgsguuuAfaGfAfCfuguucaaguaL96	4094	usAfscuuGfaAfCfagucUfuAfaaccususc	4390	GAAGGUUUAAGACUGUUCAAGUA

AD-240138.1	3799	ususuaagAfcUfGfUfucaaguagcaL96	4095	usGfscuaCfuUfGfaacaGfuCfuuaaascsc	4391	GGUUUAAGACUGUUCAAGUAGCA
AD-240140.1	3800	usasagacUfgUfUfCfaaguagcauuL96	4096	asAfsugcUfaCfUfugaaCfaGfucuuasasa	4392	UUUAAGACUGUUCAAGUAGCAUU
AD-240142.1	3801	asgsacugUfuCfAfAfguagcauucaL96	4097	usGfsaauGfcUfAfcuugAfaCfagucususa	4393	UAAGACUGUUCAAGUAGCAUUCC
AD-240145.1	3802	csusguucAfaGfUfAfgcauuccaauL96	4098	asUfsuggAfaUfGfcuacUfuGfaacagsusc	4394	GACUGUUCAAGUAGCAUUCCAAU
AD-240147.1	3803	gsusucaaGfuAfGfCfauuccaaucuL96	4099	asGfsauuGfgAfAfugcuAfcUfugaacsasg	4395	CUGUUCAAGUAGCAUUCCAAUCU
AD-240148.1	3804	ususcaagUfaGfCfAfuuccaaucuaL96	4100	usAfsgauUfgGfAfaugcUfaCfuugaascsa	4396	UGUUCAAGUAGCAUUCCAAUCUG
AD-240154.1	3805	usasgcauUfcCfAfAfucuguagccaL96	4101	usGfsgcuAfcAfGfauugGfaAfugcuascsu	4397	AGUAGCAUUCCAAUCUGUAGCCA
AD-240155.1	3806	asgscauuCfcAfAfUfcuguagccauL96	4102	asUfsggcUfaCfAfgauuGfgAfaugcusasc	4398	GUAGCAUUCCAAUCUGUAGCCAU
AD-240156.1	3807	gscsauucCfaAfUfCfuguagccauaL96	4103	usAfsuggCfuAfCfagauUfgGfaaugcsusa	4399	UAGCAUUCCAAUCUGUAGCCAUG
AD-240171.1	3808	gscscaugCfcAfCfAfgaauaucaaaL96	4104	usUfsugaUfaUfUfcuguGfgCfauggcsusa	4400	UAGCCAUGCCACAGAAUAUCAAC
AD-240172.1	3809	cscsaugcCfaCfAfGfaauaucaacaL96	4105	usGfsuugAfuAfUfucugUfgGfcauggscsu	4401	AGCCAUGCCACAGAAUAUCAACA
AD-240192.1	3810	asasgaacAfcAfGfAfaugagugcaaL96	4106	usUfsgcaCfuCfAfuucuGfuGfuucuusgsu	4402	ACAAGAACACAGAAUGAGUGCAC
AD-240227.1	3811	gsusuucaGfcAfGfGfcagcuuuauaL96	4107	usAfsuaaAfgCfUfgccuGfcUfgaaacsusu	4403	AAGUUUCAGCAGGCAGCUUUAUC
AD-240228.1	3812	ususucagCfaGfGfCfagcuuuaucuL96	4108	asGfsauaAfaGfCfugccUfgCfugaaascsu	4404	AGUUUCAGCAGGCAGCUUUAUCU
AD-240237.1	3813	gscsagcuUfuAfUfCfucaaccuggaL96	4109	usCfscagGfuUfGfagauAfaAfgcugcscsu	4405	AGGCAGCUUUAUCUCAACCUGGA
AD-240245.1	3814	asuscucaAfcCfUfGfgacauauuuuL96	4110	asAfsaauAfuGfUfccagGfuUfgagausasa	4406	UUAUCUCAACCUGGACAUAUUUU
AD-240276.1	3815	asusuugaAfaGfAfUfuucccuagcaL96	4111	usGfscuaGfgGfAfaaucUfuUfcaaausgsc	4407	GCAUUUGAAAGAUUUCCCUAGCC
AD-240278.1	3816	ususgaaaGfaUfUfUfcccuagccuaL96	4112	usAfsggcUfaGfGfgaaaUfcUfuucaasasu	4408	AUUUGAAAGAUUUCCCUAGCCUC
AD-240279.1	3817	usgsaaagAfuUfUfCfccuagccucuL96	4113	asGfsaggCfuAfGfggaaAfuCfuuucasasa	4409	UUUGAAAGAUUUCCCUAGCCUCU
AD-240280.1	3818	gsasaagaUfuUfCfCfcuagccucuuL96	4114	asAfsgagGfcUfAfgggaAfaUfcuuucsasa	4410	UUGAAAGAUUUCCCUAGCCUCUU
AD-240308.1	3819	csasuuagCfcCfAfAfaacggugcaaL96	4115	usUfsgcaCfcGfUfuuugGfgCfuaaugsasa	4411	UUCAUUAGCCCAAAACGGUGCAA
AD-240309.1	3820	asusuagcCfcAfAfAfacggugcaaaL96	4116	usUfsugcAfcCfGfuuuuGfgGfcuaausgsa	4412	UCAUUAGCCCAAAACGGUGCAAC
AD-240310.1	3821	ususagccCfaAfAfAfcggugcaacuL96	4117	asGfsuugCfaCfCfguuuUfgGfgcuaasusg	4413	CAUUAGCCCAAAACGGUGCAACU
AD-240311.1	3822	usasgcccAfaAfAfCfggugcaacuaL96	4118	usAfsguuGfcAfCfcguuUfuGfggcuasasu	4414	AUUAGCCCAAAACGGUGCAACUC
AD-240312.1	3823	asgscccaAfaAfCfGfgugcaacucuL96	4119	asGfsaguUfgCfAfccguUfuUfgggcusasa	4415	UUAGCCCAAAACGGUGCAACUCU
AD-240313.1	3824	gscsccaaAfaCfGfGfugcaacucuaL96	4120	usAfsgagUfuGfCfaccgUfuUfugggcsusa	4416	UAGCCCAAAACGGUGCAACUCUA
AD-240315.1	3825	cscsaaaaCfgGfUfGfcaacucuauuL96	4121	asAfsuagAfgUfUfgcacCfgUfuuuggsgsc	4417	GCCCAAAACGGUGCAACUCUAUU
AD-240317.1	3826	asasaacgGfuGfCfAfacucuauucuL96	4122	asGfsaauAfgAfGfuugcAfcCfguuuusgsg	4418	CCAAAACGGUGCAACUCUAUUCU
AD-240318.1	3827	asasacggUfgCfAfAfcucuauucuaL96	4123	usAfsgaaUfaGfAfguugCfaCfcguuususg	4419	CAAAACGGUGCAACUCUAUUCUG
AD-240319.1	3828	asascgguGfcAfAfCfucuauucugaL96	4124	usCfsagaAfuAfGfaguuGfcAfccguususu	4420	AAAACGGUGCAACUCUAUUCUGG
AD-240322.1	3829	gsgsugcaAfcUfCfUfauucuggacuL96	4125	asGfsuccAfgAfAfuagaGfuUfgcaccsgsu	4421	ACGGUGCAACUCUAUUCUGGACU
AD-240324.1	3830	usgscaacUfcUfAfUfucuggacuuuL96	4126	asAfsaguCfcAfGfaauaGfaGfuugcascsc	4422	GGUGCAACUCUAUUCUGGACUUU
AD-240326.1	3831	csasacucUfaUfUfCfuggacuuuauL96	4127	asUfsaaaGfuCfCfagaaUfaGfaguugscsa	4423	UGCAACUCUAUUCUGGACUUUAU
AD-240327.1	3832	asascucuAfuUfCfUfggacuuuauuL96	4128	asAfsuaaAfgUfCfcagaAfuAfgaguusgsc	4424	GCAACUCUAUUCUGGACUUUAUU
AD-240333.1	3833	asusucugGfaCfUfUfuauuacuugaL96	4129	usCfsaagUfaAfUfaaagUfcCfagaausasg	4425	CUAUUCUGGACUUUAUUACUUGA

AD-240364.1	3834	usgsuauaAfcUfCfUfgaaguccacaL96	4130	usGfsuggAfcUfUfcagaGfuUfauacasgsa	4426	UCUGUAUAACUCUGAAGUCCACC
AD-240365.1	3835	gsusauaaCfuCfUfGfaaguccaccaL96	4131	usGfsgugGfaCfUfucagAfgUfuauacsasg	4427	CUGUAUAACUCUGAAGUCCACCA
AD-240375.1	3836	gsasagucCfaCfCfAfaaaguggacaL96	4132	usGfsuccAfcUfUfuuggUfgGfacuucsasg	4428	CUGAAGUCCACCAAAAGUGGACC
AD-240378.1	3837	gsusccacCfaAfAfAfguggacccuaL96	4133	usAfsgggUfcCfAfcuuuUfgGfuggacsusu	4429	AAGUCCACCAAAAGUGGACCCUC
AD-240381.1	3838	csasccaaAfaGfUfGfgacccucuauL96	4134	asUfsagaGfgGfUfccacUfuUfuggugsgsa	4430	UCCACCAAAAGUGGACCCUCUAU
AD-240382.1	3839	ascscaaaAfgUfGfGfacccucuauaL96	4135	usAfsuagAfgGfGfuccaCfuUfuuggusgsg	4431	CCACCAAAAGUGGACCCUCUAUA
AD-240383.1	3840	cscsaaaaGfuGfGfAfcccucuauauL96	4136	asUfsauaGfaGfGfguccAfcUfuuuggsusg	4432	CACCAAAAGUGGACCCUCUAUAU
AD-240385.1	3841	asasaaguGfgAfCfCfcucuauauuuL96	4137	asAfsauaUfaGfAfggguCfcAfcuuuusgsg	4433	CCAAAAGUGGACCCUCUAUAUUU
AD-240386.1	3842	asasagugGfaCfCfCfucuauauuuaL96	4138	usAfsaauAfuAfGfagggUfcCfacuuususg	4434	CAAAAGUGGACCCUCUAUAUUUC
AD-240387.1	3843	asasguggAfcCfCfUfcuauauuucaL96	4139	usGfsaaaUfaUfAfgaggGfuCfcacuususu	4435	AAAAGUGGACCCUCUAUAUUUCC
AD-240419.1	3844	asusacauUfaUfGfAfaaggugaccaL96	4140	usGfsgucAfcCfUfuucaUfaAfuguauscsu	4436	AGAUACAUUAUGAAAGGUGACCG
AD-240420.1	3845	usascauuAfuGfAfAfaggugaccgaL96	4141	usCfsgguCfaCfCfuuucAfuAfauguasusc	4437	GAUACAUUAUGAAAGGUGACCGA
AD-240421.1	3846	ascsauuaUfgAfAfAfgggugaccgaaL96	4142	usUfscggUfcAfCfcuuuCfaUfaaugusasu	4438	AUACAUUAUGAAAGGUGACCGAC
AD-240422.1	3847	csasuuauGfaAfAfGfgugaccgacuL96	4143	asGfsucgGfuCfAfccuuUfcAfuaaugsusa	4439	UACAUUAUGAAAGGUGACCGACU
AD-240423.1	3848	asusuaugAfaAfGfGfugaccgacuaL96	4144	usAfsgucGfgUfCfaccuUfuCfauaausgsu	4440	ACAUUAUGAAAGGUGACCGACUC
AD-240431.1	3849	asgsgugaCfcGfAfCfucuauuuuaaL96	4145	usUfsaaaAfuAfGfagucGfgUfcaccususu	4441	AAAGGUGACCGACUCUAUUUUAA
AD-240446.1	3850	asuscucaGfaAfUfUfuuaaguucuaL96	4146	usAfsgaaCfuUfAfaaauUfcUfgagaususu	4442	AAAUCUCAGAAUUUUAAGUUCUA
AD-240474.1	3851	csusuucaUfaUfAfUfccuugguccaL96	4147	usGfsgacCfaAfGfgauaUfaUfgaaagscsa	4443	UGCUUUCAUAUAUCCUUGGUCCC
AD-240475.1	3852	ususucauAfuAfUfCfcuuggucccaL96	4148	usGfsggaCfcAfAfggauAfuAfugaaasgsc	4444	GCUUUCAUAUAUCCUUGGUCCCA
AD-240476.1	3853	ususcauaUfaUfCfCfuuggucccaaL96	4149	usUfsgggAfcCfAfaggaUfaUfaugaasasg	4445	CUUUCAUAUAUCCUUGGUCCCAG
AD-240490.1	3854	gsuscccaGfaGfAfUfguuuagacaaL96	4150	usUfsgucUfaAfAfcaucUfcUfgggacscsa	4446	UGGUCCCAGAGAUGUUUAGACAA
AD-240494.1	3855	csasgagaUfgUfUfUfagacaauuuuL96	4151	asAfsaauUfgUfCfuaaaCfaUfcucugsgsg	4447	CCCAGAGAUGUUUAGACAAUUUU
AD-240495.1	3856	asgsagauGfuUfUfAfgacaauuuuaL96	4152	usAfsaaaUfuGfUfcuaaAfcAfucucusgsg	4448	CCAGAGAUGUUUAGACAAUUUUA
AD-240501.1	3857	gsusuuagAfcAfAfUfuuuaggcucaL96	4153	usGfsagcCfuAfAfaauuGfuCfuaaacsasu	4449	AUGUUUAGACAAUUUUAGGCUCA
AD-240502.1	3858	ususuagaCfaAfUfUfuuaggcucaaL96	4154	usUfsgagCfcUfAfaaauUfgUfcuaaascsa	4450	UGUUUAGACAAUUUUAGGCUCAA
AD-240503.1	3859	ususagacAfaUfUfUfuaggcucaaaL96	4155	usUfsugaGfcCfUfaaaaUfuGfucuaasasc	4451	GUUUAGACAAUUUUAGGCUCAAA
AD-240504.1	3860	usasgacaAfuUfUfUfaggcucaaaaL96	4156	usUfsuugAfgCfCfuaaaAfuUfgucuasasa	4452	UUUAGACAAUUUUAGGCUCAAAA
AD-240505.1	3861	asgsacaaUfuUfUfAfggcucaaaaaL96	4157	usUfsuuuGfaGfCfcuaaAfaUfugucusasa	4453	UUAGACAAUUUUAGGCUCAAAAA
AD-240507.1	3862	ascsaauuUfuAfGfGfcucaaaaauuL96	4158	asAfsuuuUfuGfAfgccuAfaAfauuguscsu	4454	AGACAAUUUUAGGCUCAAAAAUU
AD-240512.1	3863	ususuaggCfuCfAfAfaaauuaaagaL96	4159	usCfsuuuAfaUfUfuuugAfgCfcuaaasasu	4455	AUUUUAGGCUCAAAAAUUAAAGC
AD-240513.1	3864	ususaggcUfcAfAfAfaauuaaagcuL96	4160	asGfscuuUfaAfUfuuuuGfaGfccuaasasa	4456	UUUUAGGCUCAAAAAUUAAAGCU
AD-240514.1	3865	usasggcuCfaAfAfAfauuaaagcuaL96	4161	usAfsgcuUfuAfAfuuuuUfgAfgccuasasa	4457	UUUAGGCUCAAAAAUUAAAGCUA
AD-240538.1	3866	csasggaaAfaGfGfAfacuguacugaL96	4162	usCfsaguAfcAfGfuuccUfuUfuccugsusg	4458	CACAGGAAAAGGAACUGUACUGG
AD-240540.1	3867	gsgsaaaaGfgAfAfCfuguacuggcuL96	4163	asGfsccaGfuAfCfaguuCfcUfuuuccsusg	4459	CAGGAAAAGGAACUGUACUGGCU
AD-240542.1	3868	asasaaggAfaCfUfGfuacuggcuauL96	4164	asUfsagcCfaGfUfacagUfuCfcuuuuscsc	4460	GGAAAAGGAACUGUACUGGCUAU

AD-240545.1	3869	asgsgaacUfgUfAfCfuggcuauuaaL96	4165	usUfsaauAfgCfCfaguaCfaGfuuccususu	4461	AAAGGAACUGUACUGGCUAUUAC
AD-240546.1	3870	gsgsaacuGfuAfCfUfggcuauuacaL96	4166	usGfsuaaUfaGfCfcaguAfcAfguuccsusu	4462	AAGGAACUGUACUGGCUAUUACA
AD-240779.1	3871	usasauccGfaCfUfCfccacuacauaL96	4167	usAfsuguAfgUfGfggagUfcGfgauuasusu	4463	AAUAAUCCGACUCCCACUACAUC
AD-240782.1	3872	uscscgacUfcCfCfAfcuacaucaaaL96	4168	usUfsugaUfgUfAfguggGfaGfucggasusu	4464	AAUCCGACUCCCACUACAUCAAG
AD-240787.1	3873	csuscccaCfuAfCfAfucaagacuaaL96	4169	usUfsaguCfuUfGfauguAfgUfgggagsusc	4465	GACUCCCACUACAUCAAGACUAA
AD-240788.1	3874	uscsccacUfaCfAfUfcaagacuaauL96	4170	asUfsuagUfcUfUfgaugUfaGfugggasgsu	4466	ACUCCCACUACAUCAAGACUAAU
AD-240789.1	3875	cscscacuAfcAfUfCfaagacuaauaL96	4171	usAfsuuaGfuCfUfugauGfuAfgugggsasg	4467	CUCCCACUACAUCAAGACUAAUC
AD-240790.1	3876	cscsacuaCfaUfCfAfagacuaaucuL96	4172	asGfsauuAfgUfCfuugaUfgUfaguggsgsa	4468	UCCCACUACAUCAAGACUAAUCU
AD-240792.1	3877	ascsuacaUfcAfAfGfacuaaucuuaL96	4173	usAfsagaUfuAfGfucuuGfaUfguagusgsg	4469	CCACUACAUCAAGACUAAUCUUG
AD-240793.1	3878	csusacauCfaAfGfAfcuaaucuuguL96	4174	asCfsaagAfuUfAfgucuUfgAfuguagsusg	4470	CACUACAUCAAGACUAAUCUUGU
AD-240794.1	3879	usascaucAfaGfAfCfuaaucuuguuL96	4175	asAfscaaGfaUfUfagucUfuGfauguasgsu	4471	ACUACAUCAAGACUAAUCUUGUU
AD-240795.1	3880	ascsaucaAfgAfCfUfaaucuuguuuL96	4176	asAfsacaAfgAfUfuaguCfuUfgaugusasg	4472	CUACAUCAAGACUAAUCUUGUUU
AD-240826.1	3881	gsusauuaUfaGfAfAfugcuuuugcaL96	4177	usGfscaaAfaGfCfauucUfaUfaauacsasu	4473	AUGUAUUAUAGAAUGCUUUUGCA
AD-240830.1	3882	usasuagaAfuGfCfUfuuugcauggaL96	4178	usCfscauGfcAfAfaagcAfuUfcuauasasu	4474	AUUAUAGAAUGCUUUUGCAUGGA
AD-240833.1	3883	asgsaaugCfuUfUfUfgcauggacuaL96	4179	usAfsgucCfaUfGfcaaaAfgCfauucusasu	4475	AUAGAAUGCUUUUGCAUGGACUA
AD-240834.1	3884	gsasaugcUfuUfUfGfcauggacuauL96	4180	asUfsaguCfcAfUfgcaaAfaGfcauucsusa	4476	UAGAAUGCUUUUGCAUGGACUAU
AD-240837.1	3885	usgscuuuUfgCfAfUfggacuauccuL96	4181	asGfsgauAfgUfCfcaugCfaAfaagcasusu	4477	AAUGCUUUUGCAUGGACUAUCCU
AD-240839.1	3886	csusuuugCfaUfGfGfacuauccucuL96	4182	asGfsaggAfuAfGfuccaUfgCfaaaagscsa	4478	UGCUUUUGCAUGGACUAUCCUCU
AD-240843.1	3887	usgscaugGfaCfUfAfuccucuuguuL96	4183	asAfscaaGfaGfGfauagUfcCfaugcasasa	4479	UUUGCAUGGACUAUCCUCUUGUU
AD-240844.1	3888	gscsauggAfcUfAfUfccucuuguuuL96	4184	asAfsacaAfgAfGfgauaGfuCfcaugcsasa	4480	UUGCAUGGACUAUCCUCUUGUUU
AD-240871.1	3889	asasauaaCfcUfCfUfuguaguuauaL96	4185	usAfsuaaCfuAfCfaagaGfgUfuauuususu	4481	AAAAAUAACCUCUUGUAGUUAUA
AD-240875.1	3890	asasccucUfuGfUfAfguuauaaaauL96	4186	asUfsuuuAfuAfAfcuacAfaGfagguusasu	4482	AUAACCUCUUGUAGUUAUAAAAU

Table 4. HSD17B13 *in vitro* 50nM screen in Cos-7 (Dual-Luciferase psiCHECK2 vector)

Duplex Name	% of Human Message Remaining 50nM	STDEV 50nM
AD-238911.1	56.0	9.0
AD-238912.1	103.7	14.5
AD-238913.1	51.6	9.4
AD-238929.1	51.8	10.1
AD-238930.1	63.6	6.7
AD-238932.1	53.7	10.3
AD-238960.1	35.1	3.6
AD-238979.1	25.6	4.7
AD-238991.1	31.8	2.0
AD-239009.1	81.1	15.9
AD-239015.1	94.7	11.3
AD-239016.1	63.8	4.5
AD-239017.1	45.4	9.9
AD-239018.1	68.7	10.7
AD-239019.1	36.9	7.4
AD-239020.1	52.7	5.1
AD-239031.1	19.4	2.5
AD-239062.1	33.5	6.4
AD-239066.1	45.5	3.8
AD-239103.1	12.8	1.3
AD-239110.1	14.0	2.1
AD-239118.1	57.0	8.6
AD-239119.1	38.6	1.6
AD-239131.1	65.9	9.1
AD-239132.1	39.4	13.4
AD-239133.1	31.7	3.2
AD-239146.1	13.5	1.6
AD-239155.1	27.5	1.9
AD-239156.1	81.1	12.5
AD-239177.1	27.7	5.2
AD-239178.1	60.6	7.0
AD-239179.1	42.9	8.4
AD-239180.1	83.8	16.0
AD-239181.1	43.2	8.0
AD-239182.1	34.0	5.5
AD-239183.1	24.3	3.1
AD-239185.1	82.9	12.6
AD-239186.1	89.0	9.8
AD-239187.1	85.1	18.1
AD-239188.1	64.5	3.0
AD-239189.1	70.7	8.9
AD-239190.1	91.9	7.9

AD-239191.1	58.9	10.3
AD-239192.1	60.7	17.3
AD-239193.1	61.9	8.1
AD-239194.1	74.4	6.2
AD-239196.1	94.7	17.1
AD-239198.1	100.9	22.5
AD-239199.1	47.3	12.8
AD-239203.1	40.4	2.3
AD-239214.1	33.3	6.2
AD-239215.1	38.9	8.4
AD-239239.1	53.4	7.2
AD-239240.1	27.8	1.8
AD-239241.1	51.4	11.1
AD-239242.1	17.8	2.1
AD-239243.1	54.1	12.2
AD-239245.1	51.6	9.6
AD-239246.1	21.8	4.1
AD-239247.1	30.9	5.0
AD-239250.1	54.2	8.4
AD-239251.1	15.9	6.0
AD-239253.1	22.4	5.0
AD-239254.1	47.2	15.2
AD-239255.1	49.1	5.7
AD-239290.1	31.4	8.3
AD-239291.1	27.9	8.6
AD-239292.1	30.2	4.2
AD-239293.1	51.8	16.1
AD-239304.1	61.4	11.8
AD-239312.1	99.1	12.9
AD-239313.1	95.8	5.0
AD-239314.1	84.2	4.7
AD-239316.1	52.2	2.2
AD-239317.1	27.7	4.6
AD-239318.1	33.6	8.4
AD-239321.1	37.5	3.1
AD-239332.1	28.5	5.9
AD-239337.1	52.0	17.0
AD-239348.1	26.0	4.3
AD-239362.1	49.7	7.9
AD-239366.1	68.4	10.0
AD-239368.1	26.9	3.5
AD-239372.1	48.0	6.3
AD-239373.1	50.8	12.0
AD-239379.1	21.5	6.9
AD-239380.1	18.1	3.2
AD-239387.1	16.6	1.6
AD-239397.1	15.3	2.3
AD-239411.1	46.6	12.2

AD-239412.1	76.0	19.4
AD-239431.1	60.2	8.3
AD-239433.1	58.5	11.7
AD-239436.1	77.6	5.7
AD-239437.1	46.9	6.2
AD-239438.1	89.3	27.8
AD-239439.1	61.7	13.6
AD-239450.1	67.4	4.5
AD-239451.1	38.9	7.3
AD-239452.1	84.0	17.0
AD-239453.1	69.1	4.1
AD-239475.1	77.3	13.1
AD-239476.1	67.4	15.1
AD-239478.1	79.3	6.2
AD-239479.1	58.0	4.6
AD-239480.1	26.6	2.8
AD-239482.1	24.3	5.8
AD-239483.1	39.7	8.7
AD-239499.1	53.4	11.4
AD-239510.1	64.1	7.5
AD-239520.1	21.1	3.2
AD-239521.1	26.4	7.7
AD-239522.1	34.2	4.4
AD-239534.1	64.5	14.1
AD-239539.1	68.8	10.5
AD-239544.1	48.5	10.2
AD-239566.1	43.3	5.3
AD-239578.1	19.3	1.8
AD-239579.1	67.0	7.5
AD-239611.1	43.1	10.0
AD-239612.1	54.7	2.8
AD-239613.1	69.7	12.4
AD-239617.1	108.1	8.3
AD-239618.1	32.5	8.9
AD-239637.1	29.8	7.2
AD-239641.1	52.6	8.7
AD-239642.1	11.4	2.0
AD-239643.1	17.2	5.2
AD-239645.1	30.5	8.5
AD-239647.1	33.6	4.5
AD-239649.1	38.4	2.2
AD-239650.1	79.5	16.5
AD-239653.1	42.8	7.3
AD-239654.1	74.4	7.0
AD-239662.1	26.8	7.9
AD-239668.1	27.3	3.8
AD-239669.1	27.7	6.0
AD-239670.1	23.1	3.0

AD-239671.1	21.1	7.9
AD-239674.1	16.4	4.9
AD-239676.1	31.3	6.6
AD-239681.1	19.4	5.5
AD-239682.1	39.9	2.9
AD-239684.1	56.3	9.9
AD-239685.1	29.4	6.0
AD-239697.1	26.9	2.2
AD-239713.1	28.4	4.6
AD-239714.1	10.4	1.1
AD-239717.1	18.3	1.5
AD-239721.1	14.4	3.7
AD-239723.1	54.7	4.1
AD-239724.1	18.5	4.7
AD-239725.1	27.2	7.2
AD-239726.1	29.8	4.7
AD-239755.1	14.3	11.2
AD-239757.1	36.0	4.1
AD-239759.1	23.8	5.5
AD-239761.1	73.7	8.8
AD-239764.1	91.7	7.8
AD-239778.1	25.3	8.7
AD-239779.1	20.0	4.1
AD-239780.1	28.9	7.3
AD-239781.1	14.1	3.5
AD-239782.1	22.3	3.8
AD-239783.1	10.1	1.7
AD-239784.1	16.6	5.5
AD-239785.1	15.0	3.4
AD-239786.1	11.9	0.8
AD-239787.1	8.6	2.1
AD-239791.1	15.8	2.3
AD-239793.1	9.9	0.5
AD-239806.1	33.1	11.4
AD-239839.1	40.2	8.9
AD-239840.1	47.9	5.6
AD-239854.1	27.8	9.0
AD-239855.1	16.6	1.4
AD-239876.1	25.6	10.2
AD-239877.1	8.9	0.9
AD-239881.1	11.1	2.7
AD-239905.1	18.2	1.8
AD-239914.1	28.2	4.6
AD-239915.1	37.4	8.6
AD-239941.1	18.0	6.7
AD-239944.1	35.4	5.9
AD-239945.1	18.5	2.6
AD-239946.1	19.5	6.6

AD-239947.1	17.5	4.3
AD-239977.1	13.7	2.7
AD-239979.1	12.5	3.8
AD-239980.1	12.9	2.6
AD-239998.1	32.1	2.1
AD-240019.1	25.1	3.2
AD-240031.1	12.4	2.4
AD-240032.1	30.6	3.2
AD-240033.1	30.8	1.5
AD-240064.1	19.6	4.1
AD-240090.1	96.3	8.5
AD-240091.1	53.6	4.7
AD-240108.1	29.4	1.9
AD-240117.1	85.3	10.6
AD-240124.1	78.2	7.7
AD-240125.1	82.3	17.8
AD-240126.1	56.2	2.0
AD-240135.1	33.4	13.3
AD-240138.1	35.3	4.7
AD-240140.1	12.7	3.5
AD-240142.1	15.9	3.9
AD-240145.1	15.1	1.1
AD-240147.1	24.6	3.7
AD-240148.1	18.9	4.5
AD-240154.1	62.0	4.5
AD-240155.1	24.9	5.6
AD-240156.1	22.8	5.7
AD-240171.1	28.6	5.1
AD-240172.1	36.6	5.3
AD-240192.1	32.6	3.8
AD-240227.1	54.8	10.6
AD-240228.1	51.8	10.9
AD-240237.1	44.2	10.9
AD-240245.1	85.3	14.5
AD-240276.1	27.6	5.2
AD-240278.1	16.7	2.8
AD-240279.1	16.6	7.6
AD-240280.1	13.2	3.3
AD-240308.1	40.6	5.6
AD-240309.1	59.7	8.3
AD-240310.1	43.0	15.0
AD-240311.1	85.9	12.1
AD-240312.1	58.6	8.7
AD-240313.1	32.1	2.0
AD-240315.1	36.0	6.5
AD-240317.1	28.0	1.8
AD-240318.1	18.9	2.2
AD-240319.1	49.2	4.4

AD-240322.1	47.2	7.2
AD-240324.1	31.4	1.6
AD-240326.1	21.3	3.6
AD-240327.1	24.9	5.4
AD-240333.1	12.0	2.4
AD-240364.1	57.4	7.4
AD-240365.1	92.1	2.3
AD-240375.1	97.7	21.7
AD-240378.1	41.5	5.6
AD-240381.1	22.4	7.1
AD-240382.1	22.5	5.9
AD-240383.1	27.0	3.2
AD-240385.1	23.2	4.1
AD-240386.1	29.9	3.4
AD-240387.1	45.7	5.2
AD-240419.1	76.4	17.2
AD-240420.1	50.1	8.4
AD-240421.1	40.9	6.3
AD-240422.1	44.9	11.0
AD-240423.1	30.4	6.5
AD-240431.1	28.7	3.5
AD-240446.1	13.9	1.7
AD-240474.1	41.8	5.0
AD-240475.1	70.9	15.3
AD-240476.1	15.7	3.4
AD-240490.1	27.9	6.3
AD-240494.1	13.8	4.5
AD-240495.1	19.6	0.9
AD-240501.1	47.6	5.9
AD-240502.1	18.7	3.8
AD-240503.1	19.6	7.0
AD-240504.1	17.2	2.6
AD-240505.1	18.3	3.4
AD-240507.1	23.8	3.3
AD-240512.1	24.6	2.4
AD-240513.1	70.6	9.0
AD-240514.1	22.4	3.1
AD-240538.1	40.7	4.2
AD-240540.1	46.7	8.3
AD-240542.1	21.1	4.0
AD-240545.1	26.7	4.4
AD-240546.1	35.2	3.1
AD-240779.1	31.2	4.4
AD-240782.1	27.9	2.8
AD-240787.1	27.4	4.6
AD-240788.1	16.9	3.9
AD-240789.1	32.5	2.9
AD-240790.1	18.9	5.1

AD-240792.1	28.4	9.9
AD-240793.1	22.4	1.9
AD-240794.1	13.9	1.1
AD-240795.1	25.9	5.2
AD-240826.1	15.2	1.9
AD-240830.1	32.1	7.2
AD-240833.1	25.1	5.0
AD-240834.1	15.3	3.1
AD-240837.1	29.2	5.8
AD-240839.1	14.3	2.6
AD-240843.1	8.4	1.7
AD-240844.1	33.8	8.1
AD-240871.1	18.9	3.2
AD-240875.1	18.0	1.6

Table 5. HSD17B13 *in vitro* 50nM screen in Primary Human Hepatocytes

Duplex Name	% of Human Message Remaining 50nM	STDEV 50nM
AD-238911.1	116.8	40.6
AD-238912.1	83.9	15.4
AD-238913.1	96.3	14.1
AD-238929.1	82.9	14.7
AD-238930.1	86.4	6.6
AD-238932.1	72.4	23.3
AD-238960.1	64.8	28.2
AD-238979.1	48.1	25.1
AD-238991.1	31.3	7.3
AD-239009.1	34.1	9.3
AD-239015.1	90.4	15.8
AD-239016.1	51.7	13.0
AD-239017.1	31.8	10.1
AD-239018.1	75.5	16.0
AD-239019.1	56.0	22.6
AD-239020.1	59.9	19.3
AD-239031.1	46.6	17.3
AD-239062.1	61.9	21.9
AD-239066.1	61.1	17.3
AD-239103.1	41.0	21.7
AD-239110.1	31.8	7.7
AD-239118.1	48.3	3.7
AD-239119.1	56.2	12.7
AD-239131.1	75.2	18.1
AD-239132.1	90.1	34.9
AD-239133.1	52.0	10.7

AD-239146.1	72.1	35.4
AD-239155.1	39.1	9.8
AD-239156.1	79.3	24.4
AD-239177.1	55.1	15.6
AD-239178.1	72.0	21.4
AD-239179.1	57.8	10.5
AD-239180.1	36.3	8.4
AD-239181.1	60.6	19.7
AD-239182.1	42.4	6.4
AD-239183.1	29.3	13.1
AD-239185.1	68.4	21.1
AD-239186.1	87.7	23.4
AD-239187.1	83.2	14.4
AD-239188.1	54.2	13.2
AD-239189.1	74.5	31.3
AD-239190.1	57.4	3.5
AD-239191.1	49.8	21.9
AD-239192.1	33.9	13.5
AD-239193.1	96.3	36.6
AD-239194.1	63.1	18.3
AD-239196.1	43.5	11.6
AD-239198.1	93.8	8.0
AD-239199.1	44.2	21.5
AD-239203.1	68.2	19.0
AD-239214.1	40.3	8.3
AD-239215.1	71.6	25.3
AD-239239.1	53.9	32.4
AD-239240.1	23.8	6.5
AD-239241.1	56.2	10.0
AD-239242.1	46.0	15.0
AD-239243.1	97.6	73.4
AD-239245.1	84.7	9.2
AD-239246.1	37.6	11.2
AD-239247.1	36.5	15.9
AD-239250.1	34.1	6.8
AD-239251.1	19.3	3.7
AD-239253.1	26.3	6.9
AD-239254.1	52.5	13.7
AD-239255.1	52.8	18.1
AD-239290.1	46.3	30.0
AD-239291.1	53.1	25.1
AD-239292.1	49.8	18.6
AD-239293.1	49.5	15.6
AD-239304.1	32.9	10.3
AD-239312.1	83.1	13.5
AD-239313.1	57.4	16.5
AD-239314.1	85.7	13.7
AD-239316.1	50.9	32.4

AD-239317.1	28.0	3.5
AD-239318.1	64.4	26.9
AD-239321.1	34.8	6.9
AD-239332.1	42.0	13.9
AD-239337.1	29.1	11.0
AD-239348.1	22.5	10.5
AD-239362.1	67.8	29.4
AD-239366.1	67.1	26.2
AD-239368.1	41.2	17.8
AD-239372.1	46.4	6.0
AD-239373.1	27.8	4.1
AD-239379.1	19.4	5.7
AD-239380.1	26.5	9.0
AD-239387.1	30.5	14.6
AD-239397.1	18.9	5.4
AD-239411.1	41.8	17.0
AD-239412.1	79.2	22.8
AD-239431.1	39.5	15.3
AD-239433.1	36.9	12.1
AD-239436.1	101.1	17.3
AD-239437.1	37.6	20.8
AD-239438.1	54.0	9.7
AD-239439.1	31.8	6.5
AD-239450.1	67.0	22.6
AD-239451.1	42.4	15.3
AD-239452.1	57.4	3.0
AD-239453.1	45.9	5.9
AD-239475.1	27.2	5.0
AD-239476.1	41.4	16.7
AD-239478.1	38.7	5.7
AD-239479.1	44.0	19.6
AD-239480.1	49.2	10.7
AD-239482.1	31.6	9.4
AD-239483.1	37.5	8.3
AD-239499.1	56.0	12.2
AD-239510.1	51.1	20.1
AD-239520.1	26.5	15.5
AD-239521.1	33.4	19.0
AD-239522.1	36.2	18.2
AD-239534.1	30.7	17.4
AD-239539.1	76.9	31.7
AD-239544.1	21.3	10.9
AD-239566.1	39.1	8.1
AD-239578.1	19.9	12.4
AD-239579.1	24.7	6.7
AD-239611.1	38.8	34.7
AD-239612.1	60.9	15.4
AD-239613.1	76.4	15.6

AD-239617.1	186.1	52.1
AD-239618.1	32.0	5.2
AD-239637.1	22.8	2.8
AD-239641.1	35.9	14.0
AD-239642.1	31.5	28.5
AD-239643.1	12.0	1.7
AD-239645.1	29.6	11.6
AD-239647.1	24.9	7.3
AD-239649.1	35.0	4.2
AD-239650.1	51.2	3.7
AD-239653.1	48.8	26.5
AD-239654.1	105.2	35.2
AD-239662.1	27.5	12.0
AD-239668.1	31.5	9.1
AD-239669.1	42.4	24.3
AD-239670.1	53.3	17.1
AD-239671.1	26.2	11.1
AD-239674.1	17.3	9.5
AD-239676.1	42.1	13.1
AD-239681.1	24.9	11.4
AD-239682.1	12.7	4.5
AD-239684.1	15.2	1.4
AD-239685.1	24.9	6.1
AD-239697.1	15.1	6.2
AD-239713.1	24.6	7.4
AD-239714.1	23.6	18.1
AD-239717.1	36.6	33.7
AD-239721.1	7.3	3.4
AD-239723.1	47.2	12.1
AD-239724.1	29.1	7.8
AD-239725.1	17.7	15.4
AD-239726.1	45.9	13.2
AD-239755.1	19.0	4.6
AD-239757.1	28.6	3.2
AD-239759.1	10.7	3.3
AD-239761.1	60.2	11.2
AD-239764.1	56.4	15.6
AD-239778.1	45.9	32.9
AD-239779.1	18.2	12.0
AD-239780.1	34.5	22.1
AD-239781.1	30.1	16.8
AD-239782.1	37.3	12.4
AD-239783.1	13.0	6.8
AD-239784.1	43.1	14.0
AD-239785.1	9.9	8.9
AD-239786.1	16.9	10.0
AD-239787.1	15.9	9.3
AD-239791.1	11.7	5.4

AD-239793.1	11.1	3.2
AD-239806.1	29.4	13.5
AD-239839.1	60.6	13.8
AD-239840.1	36.7	23.2
AD-239854.1	39.0	20.3
AD-239855.1	31.6	5.2
AD-239876.1	34.6	10.8
AD-239877.1	35.8	21.8
AD-239881.1	47.0	11.9
AD-239905.1	36.6	8.2
AD-239914.1	30.4	13.9
AD-239915.1	51.3	25.7
AD-239941.1	111.8	60.8
AD-239944.1	63.6	23.9
AD-239945.1	58.6	23.0
AD-239946.1	65.3	28.6
AD-239947.1	77.7	16.6
AD-239977.1	54.5	16.5
AD-239979.1	61.4	14.4
AD-239980.1	87.8	41.2
AD-239998.1	54.8	14.7
AD-240019.1	76.7	23.6
AD-240031.1	63.1	18.5
AD-240032.1	51.6	13.5
AD-240033.1	69.7	41.4
AD-240064.1	81.0	32.4
AD-240090.1	145.8	80.6
AD-240091.1	75.2	17.1
AD-240108.1	62.2	18.9
AD-240117.1	54.4	2.3
AD-240124.1	63.3	25.7
AD-240125.1	68.6	18.1
AD-240126.1	77.4	10.9
AD-240135.1	64.9	33.1
AD-240138.1	59.3	17.7
AD-240140.1	65.2	21.2
AD-240142.1	42.9	6.6
AD-240145.1	58.2	10.2
AD-240147.1	56.7	14.3
AD-240148.1	35.0	12.2
AD-240154.1	39.2	19.5
AD-240155.1	57.2	22.1
AD-240156.1	71.9	28.3
AD-240171.1	66.4	22.8
AD-240172.1	50.4	12.9
AD-240192.1	43.5	3.8
AD-240227.1	62.1	19.7
AD-240228.1	50.6	12.7

AD-240237.1	67.2	9.5
AD-240245.1	99.3	21.4
AD-240276.1	49.9	16.6
AD-240278.1	31.8	6.1
AD-240279.1	46.2	2.4
AD-240280.1	68.4	16.4
AD-240308.1	72.7	15.4
AD-240309.1	85.8	2.0
AD-240310.1	58.9	16.1
AD-240311.1	74.2	21.0
AD-240312.1	83.3	7.3
AD-240313.1	70.4	15.1
AD-240315.1	66.1	7.6
AD-240317.1	52.0	11.1
AD-240318.1	65.1	24.1
AD-240319.1	38.8	7.7
AD-240322.1	69.9	10.1
AD-240324.1	79.6	37.5
AD-240326.1	29.8	3.0
AD-240327.1	62.6	11.3
AD-240333.1	60.3	31.5
AD-240364.1	81.0	16.8
AD-240365.1	104.1	31.5
AD-240375.1	111.2	18.0
AD-240378.1	85.1	33.8
AD-240381.1	87.8	18.3
AD-240382.1	51.9	9.5
AD-240383.1	45.6	13.2
AD-240385.1	53.5	6.6
AD-240386.1	63.3	6.8
AD-240387.1	75.8	26.0
AD-240419.1	81.2	11.1
AD-240420.1	69.3	32.6
AD-240421.1	93.8	17.0
AD-240422.1	75.6	38.5
AD-240423.1	75.7	14.1
AD-240431.1	53.2	2.4
AD-240446.1	93.2	30.6
AD-240474.1	74.7	22.8
AD-240475.1	74.4	29.5
AD-240476.1	37.2	2.4
AD-240490.1	82.0	34.8
AD-240494.1	62.3	14.1
AD-240495.1	102.5	39.4
AD-240501.1	33.9	4.9
AD-240502.1	40.6	5.7
AD-240503.1	63.4	31.4
AD-240504.1	55.0	7.7

AD-240505.1	73.0	22.1
AD-240507.1	68.3	23.1
AD-240512.1	55.0	19.6
AD-240513.1	54.9	14.8
AD-240514.1	33.8	16.7
AD-240538.1	51.3	13.3
AD-240540.1	72.1	11.2
AD-240542.1	60.0	9.0
AD-240545.1	45.9	23.8
AD-240546.1	46.2	18.4
AD-240779.1	64.8	22.4
AD-240782.1	77.7	20.3
AD-240787.1	59.6	16.9
AD-240788.1	54.2	12.0
AD-240789.1	58.9	24.6
AD-240790.1	54.0	14.7
AD-240792.1	67.2	9.2
AD-240793.1	54.9	14.6
AD-240794.1	69.3	18.8
AD-240795.1	34.5	7.2
AD-240826.1	56.5	16.8
AD-240830.1	63.7	14.4
AD-240833.1	84.9	28.4
AD-240834.1	50.2	15.1
AD-240837.1	46.3	16.3
AD-240839.1	54.9	18.4
AD-240843.1	46.4	13.9
AD-240844.1	38.2	10.3
AD-240871.1	92.8	35.8
AD-240875.1	72.0	13.2

Table 6. HSD17B13 *in vitro* 50nM screen in Primary Cynomolgus Hepatocytes

Duplex Name	%of Cyno Message Remaining 50nM	STDEV 50nM
AD-238911.1	81.2	8.9
AD-238912.1	87.5	6.8
AD-238913.1	62.3	4.1
AD-238929.1	67.1	22.3
AD-238930.1	42.1	4.0
AD-238932.1	54.8	12.2
AD-238960.1	24.6	5.2
AD-238979.1	11.1	7.5
AD-238991.1	30.8	6.2
AD-239009.1	11.4	1.1
AD-239015.1	21.2	3.0

AD-239016.1	7.2	1.4
AD-239017.1	8.9	1.8
AD-239018.1	39.2	4.6
AD-239019.1	22.0	5.5
AD-239020.1	8.8	2.8
AD-239031.1	19.5	7.5
AD-239062.1	20.6	5.6
AD-239066.1	75.5	16.3
AD-239103.1	88.4	33.4
AD-239110.1	11.2	3.0
AD-239118.1	23.1	6.3
AD-239119.1	23.4	4.2
AD-239131.1	98.9	9.0
AD-239132.1	86.0	18.5
AD-239133.1	24.3	8.7
AD-239146.1	11.4	2.8
AD-239155.1	39.4	21.3
AD-239156.1	52.8	11.0
AD-239177.1	23.1	6.7
AD-239178.1	46.3	4.6
AD-239179.1	40.3	8.7
AD-239180.1	21.8	6.2
AD-239181.1	45.5	5.9
AD-239182.1	17.7	3.8
AD-239183.1	10.6	1.5
AD-239185.1	55.9	7.2
AD-239186.1	77.7	13.0
AD-239187.1	61.1	6.8
AD-239188.1	41.0	1.5
AD-239189.1	11.6	2.1
AD-239190.1	48.8	7.9
AD-239191.1	9.0	4.1
AD-239192.1	35.0	12.1
AD-239193.1	68.1	4.9
AD-239194.1	26.7	1.7
AD-239196.1	56.6	10.2
AD-239198.1	80.5	11.0
AD-239199.1	32.8	4.6
AD-239203.1	36.9	6.3
AD-239214.1	15.3	2.7
AD-239215.1	28.9	6.5
AD-239239.1	17.0	2.8
AD-239240.1	15.6	4.4
AD-239241.1	16.8	9.9
AD-239242.1	16.5	5.9
AD-239243.1	13.3	4.2
AD-239245.1	13.7	2.9
AD-239246.1	12.9	8.2

AD-239247.1	18.0	6.5
AD-239250.1	49.8	6.5
AD-239251.1	6.8	0.5
AD-239253.1	11.5	3.8
AD-239254.1	47.4	4.6
AD-239255.1	16.4	7.2
AD-239290.1	75.5	25.9
AD-239291.1	92.3	27.1
AD-239292.1	9.8	2.7
AD-239293.1	46.8	6.3
AD-239304.1	30.7	8.9
AD-239312.1	15.0	3.2
AD-239313.1	8.7	2.4
AD-239314.1	100.1	18.8
AD-239316.1	40.0	9.5
AD-239317.1	12.3	2.0
AD-239318.1	9.3	1.8
AD-239321.1	9.2	2.4
AD-239332.1	48.0	12.4
AD-239337.1	15.4	7.5
AD-239348.1	21.1	6.0
AD-239362.1	75.3	6.7
AD-239366.1	30.7	11.1
AD-239368.1	24.6	6.2
AD-239372.1	45.5	2.7
AD-239373.1	33.3	7.5
AD-239379.1	8.1	2.6
AD-239380.1	7.2	1.1
AD-239387.1	36.2	5.3
AD-239397.1	12.3	3.4
AD-239411.1	31.6	10.7
AD-239412.1	59.5	7.0
AD-239431.1	13.2	7.9
AD-239433.1	33.0	10.1
AD-239436.1	71.5	14.7
AD-239437.1	10.4	2.6
AD-239438.1	12.3	2.7
AD-239439.1	79.2	11.8
AD-239450.1	61.3	2.2
AD-239451.1	29.7	8.7
AD-239452.1	78.7	17.3
AD-239453.1	38.5	10.6
AD-239475.1	11.4	2.2
AD-239476.1	39.5	6.9
AD-239478.1	59.3	9.4
AD-239479.1	14.7	3.6
AD-239480.1	31.6	6.6
AD-239482.1	13.7	3.3

AD-239483.1	14.1	3.8
AD-239499.1	111.5	13.7
AD-239510.1	16.0	4.0
AD-239520.1	11.3	5.2
AD-239521.1	19.8	3.7
AD-239522.1	12.5	3.8
AD-239534.1	31.1	8.4
AD-239539.1	9.3	3.5
AD-239544.1	24.0	3.2
AD-239566.1	11.9	7.0
AD-239578.1	25.7	5.5
AD-239579.1	28.1	5.9
AD-239611.1	37.4	7.8
AD-239612.1	36.2	8.4
AD-239613.1	13.5	3.3
AD-239617.1	46.2	9.3
AD-239618.1	15.9	1.2
AD-239637.1	33.6	13.4
AD-239641.1	42.3	7.4
AD-239642.1	34.4	5.7
AD-239643.1	9.7	2.0
AD-239645.1	16.1	3.4
AD-239647.1	19.0	4.0
AD-239649.1	70.4	6.0
AD-239650.1	65.8	12.5
AD-239653.1	16.4	3.6
AD-239654.1	18.3	6.5
AD-239662.1	8.4	4.1
AD-239668.1	13.2	4.2
AD-239669.1	53.6	14.0
AD-239670.1	14.4	3.6
AD-239671.1	12.1	2.9
AD-239674.1	14.8	4.0
AD-239676.1	20.9	4.8
AD-239681.1	9.4	0.6
AD-239682.1	8.9	1.3
AD-239684.1	12.0	2.9
AD-239685.1	10.8	3.7
AD-239697.1	11.8	3.3
AD-239713.1	11.4	1.8
AD-239714.1	7.8	2.8
AD-239717.1	10.4	1.5
AD-239721.1	27.2	6.4
AD-239723.1	81.2	14.9
AD-239724.1	11.0	3.7
AD-239725.1	24.1	3.0
AD-239726.1	27.3	7.7
AD-239755.1	7.8	3.3

AD-239757.1	30.3	3.4
AD-239759.1	6.7	1.7
AD-239761.1	49.7	11.8
AD-239764.1	53.5	11.4
AD-239778.1	26.8	7.8
AD-239779.1	63.3	20.5
AD-239780.1	85.5	17.8
AD-239781.1	26.4	6.0
AD-239782.1	22.6	6.7
AD-239783.1	9.7	1.9
AD-239784.1	20.2	3.8
AD-239785.1	23.6	6.7
AD-239786.1	38.3	6.1
AD-239787.1	27.6	2.5
AD-239791.1	17.8	2.1
AD-239793.1	6.8	1.2
AD-239806.1	27.8	2.9
AD-239839.1	11.9	5.6
AD-239840.1	10.3	1.8
AD-239854.1	58.6	8.9
AD-239855.1	23.3	9.3
AD-239876.1	42.8	20.3
AD-239877.1	30.6	10.4
AD-239881.1	53.4	5.5
AD-239905.1	50.1	17.6
AD-239914.1	37.3	5.2
AD-239915.1	34.8	5.7
AD-239941.1	66.8	14.1
AD-239944.1	117.7	12.5
AD-239945.1	23.2	2.7
AD-239946.1	14.0	5.9
AD-239947.1	25.8	1.6
AD-239977.1	27.3	4.4
AD-239979.1	25.5	4.8
AD-239980.1	35.5	6.4
AD-239998.1	32.7	4.0
AD-240019.1	17.9	2.6
AD-240031.1	15.3	1.9
AD-240032.1	23.4	2.4
AD-240033.1	22.2	3.7
AD-240064.1	47.1	5.2
AD-240090.1	25.7	5.9
AD-240091.1	31.4	8.2
AD-240108.1	118.3	27.0
AD-240117.1	56.6	5.6
AD-240124.1	43.5	8.1
AD-240125.1	54.0	6.8
AD-240126.1	30.7	7.0

AD-240135.1	14.7	0.8
AD-240138.1	36.6	13.8
AD-240140.1	33.6	10.9
AD-240142.1	19.4	4.7
AD-240145.1	27.6	9.1
AD-240147.1	18.1	3.4
AD-240148.1	9.0	1.7
AD-240154.1	23.0	1.0
AD-240155.1	18.2	1.7
AD-240156.1	15.1	2.2
AD-240171.1	29.9	6.9
AD-240172.1	31.9	8.0
AD-240192.1	39.7	5.7
AD-240227.1	71.4	15.6
AD-240228.1	35.8	22.3
AD-240237.1	43.3	17.3
AD-240245.1	41.5	5.1
AD-240276.1	20.6	4.4
AD-240278.1	11.6	1.8
AD-240279.1	20.1	0.5
AD-240280.1	51.0	9.5
AD-240308.1	80.5	19.3
AD-240309.1	63.5	10.3
AD-240310.1	45.2	10.3
AD-240311.1	42.6	14.8
AD-240312.1	22.3	1.3
AD-240313.1	21.6	4.5
AD-240315.1	26.4	8.2
AD-240317.1	17.8	3.6
AD-240318.1	20.5	2.5
AD-240319.1	23.5	6.5
AD-240322.1	37.5	2.7
AD-240324.1	37.1	13.9
AD-240326.1	11.2	3.4
AD-240327.1	28.7	4.0
AD-240333.1	32.0	5.8
AD-240364.1	34.1	13.5
AD-240365.1	58.8	18.7
AD-240375.1	86.7	17.8
AD-240378.1	49.8	14.8
AD-240381.1	56.0	12.0
AD-240382.1	35.7	7.9
AD-240383.1	27.5	5.5
AD-240385.1	15.8	2.0
AD-240386.1	18.7	2.0
AD-240387.1	33.3	13.0
AD-240419.1	32.8	4.2
AD-240420.1	31.5	4.5

AD-240421.1	21.5	4.7
AD-240422.1	19.9	4.6
AD-240423.1	13.1	2.3
AD-240431.1	16.1	3.3
AD-240446.1	16.6	3.5
AD-240474.1	28.7	10.8
AD-240475.1	32.7	11.9
AD-240476.1	11.0	1.8
AD-240490.1	38.5	5.6
AD-240494.1	37.3	14.0
AD-240495.1	17.4	4.6
AD-240501.1	29.5	6.7
AD-240502.1	16.3	1.2
AD-240503.1	12.4	2.5
AD-240504.1	15.6	4.4
AD-240505.1	44.8	15.3
AD-240507.1	47.0	12.7
AD-240512.1	31.9	3.9
AD-240513.1	44.2	3.8
AD-240514.1	13.0	2.4
AD-240538.1	35.5	6.4
AD-240540.1	40.0	12.4
AD-240542.1	65.6	15.4
AD-240545.1	18.7	2.3
AD-240546.1	32.4	5.0
AD-240779.1	33.8	8.0
AD-240782.1	33.6	7.3
AD-240787.1	35.4	3.4
AD-240788.1	12.5	1.3
AD-240789.1	42.6	8.0
AD-240790.1	21.9	2.1
AD-240792.1	22.0	2.8
AD-240793.1	22.7	3.7
AD-240794.1	37.5	9.5
AD-240795.1	18.9	1.9
AD-240826.1	38.9	6.9
AD-240830.1	32.9	2.4
AD-240833.1	41.6	9.4
AD-240834.1	17.2	3.6
AD-240837.1	42.1	7.9
AD-240839.1	18.4	3.7
AD-240843.1	17.1	5.9
AD-240844.1	19.8	3.8
AD-240871.1	16.2	2.1
AD-240875.1	48.1	27.7

Example 2. iRNA Design, Synthesis, and Selection

This Example describes methods for the design, synthesis, and selection of additional HSD17B13 iRNA agents.

Bioinformatics

A set of siRNAs targeting the human hydroxysteroid 17-beta dehydrogenase 13 gene (HSD17B13; human NCBI refseqID NM_178135.4; NCBI GeneID: 345275) as well the toxicology-species HSD17B13 ortholog from cynomolgus monkey: XM_005555367.2 was designed using custom R and Python scripts. All the siRNA designs have a perfect match to the human HSD17B13 transcript and a subset either perfect or near-perfect matches to the cynomolgus monkey ortholog. The human NM_178135 REFSEQ mRNA, version 4, has a length of 2397 bases. The rationale and method for the set of siRNA designs is as follows: the predicted efficacy for every potential 23mer siRNA from position 10 through the end was determined with a random forest model derived from the direct measure of mRNA knockdown from several thousand distinct siRNA designs targeting a diverse set of vertebrate genes. For each strand of the siRNA, a custom Python script was used in a brute force search to measure the number and positions of mismatches between the siRNA and all potential alignments in the human transcriptome. Extra weight was given to mismatches in the seed region, defined here as positions 2-9 of the antisense oligonucleotide, as well the cleavage site of the siRNA, defined here as positions 10-11 of the antisense oligonucleotide. The relative weight of the mismatches was 2.8, 1.2, 1 for seed mismatches, cleavage site, and other positions up through antisense position 19. Mismatches in the first position were ignored. A specificity score was calculated for each strand by summing the value of each weighted mismatch. Preference was given to siRNAs whose antisense score in human and cynomolgus monkey was >= 2 and predicted efficacy was >= 50% knockdown.

In vitro Cos-7 (Dual-Luciferase psiCHECK2 Human HSD17B13 vector) and Primary Cynomolgus Hepatocytes screening

Dual-Glo® Luciferase assay

Cos-7 cells (ATCC, Manassas, VA) were grown to near confluence at 37°C in an atmosphere of 5% CO_2 in DMEM (ATCC) supplemented with 10% FBS, before being released from the plate by trypsinization. Multi-dose experiments were performed at 10nM and 0.1nM. siRNA and psiCHECK2-HSD17B13 (NM_178135 cloned into XhoI-NotI sites) plasmid transfection was carried out by adding 5µl of siRNA duplexes and 5µl (5ng) of psiCHECK2-HSD17B13 plasmid per well along with 4.9µl of Opti-MEM plus 0.1µl 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 35µl of fresh complete media. The transfected cells were incubated at 37°C in an atmosphere of 5% CO_2.

Forty-eight hours after the siRNAs and psiCHECK2-HSD17B13 plasmid were transfected; Firefly (transfection control) and Renilla (fused to HSD17B13 target sequence) luciferase were measured. First, media was removed from cells. Then Firefly luciferase activity was measured by adding 20µl of Dual-Glo® Luciferase Reagent equal to the culture medium volume to each well and mixing. 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. 20µl of room temperature Dual-Glo® Stop & Glo® Reagent was added 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 quenched the firefly luciferase signal and sustained luminescence for the Renilla luciferase reaction. siRNA activity was determined by normalizing the Renilla (HSD17B13) 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 at n=2 or greater.

Cell culture and transfections

Primary Cynomolgus Hepatocytes (Bioreclamation/IVT) were transfected by adding 4.9µl of Opti-MEM plus 0.1µl of RNAiMAX per well (Invitrogen, Carlsbad CA. cat # 13778-150) to 5µl of siRNA duplexes per well, with 4 replicates of each SiRNA duplex, into a 384-well plate, and incubating the plate at room temperature for 15 minutes. 40µl of InVitroGRO CP plating media (Bioreclamation/IVT) containing ~5 $x10^3$ cells were then added to the siRNA mixture. Cells were incubated for 48 hours prior to RNA purification. Multi-dose experiments were performed at 10nM and 0.1nM.

Total RNA isolation using DYNABEADS mRNA Isolation Kit

RNA was isolated using an automated protocol on a BioTek-EL406 platform using DYNABEADs (Invitrogen, cat#61012). Briefly, 70µl of Lysis/Binding Buffer and 10µl of lysis buffer containing 3µl of magnetic beads were added to the plate with cells. Plates were incubated on an electromagnetic shaker for 10 minutes at room temperature and then magnetic beads were captured and the supernatant was removed. Bead-bound RNA was then washed 2 times with 150µl Wash Buffer A and once with Wash Buffer B. Beads were then washed with 150µl Elution Buffer, re-captured and supernatant removed.

cDNA synthesis using ABI High capacity cDNA reverse transcription kit (Applied Biosystems, Foster City, CA, Cat #4368813)

10µl of a master mix containing 1µl 10X Buffer, 0.4µl 25X dNTPs, 1µl 10x Random primers, 0.5µl Reverse Transcriptase, 0.5µl RNase inhibitor and 6.6µl of H_2O per reaction was added to RNA

isolated above. Plates were sealed, mixed, and incubated on an electromagnetic shaker for 10 minutes at room temperature, followed by 2h at 37°C.

Real time PCR

2µl of cDNA were added to a master mix containing 0.5µl of Cyno GAPDH TaqMan Probe (forward primer: 5'-GCATCCTGGGCTACACTGA-3' (SEQ ID NO: 4483), reverse primer: 5'-TGGGTGTCGCTGTTGAAGTC-3' (SEQ ID NO: 4484), probe: 5'HEX-CCAGGTGGTCTCCTCC-3'BHQ-1 (SEQ ID NO: 4485)), and 0.5µl HSD17B13 cynomolgus probe (Mf02888851_m1) and 5µl Lightcycler 480 probe master mix (Roche Cat # 04887301001) per well in a 384-well plate (Roche cat # 04887301001). Real time PCR was done in a LightCycler480 Real Time PCR system (Roche). Each duplex was tested at least two times and data were normalized to cells transfected with a non-targeting control siRNA. To calculate relative fold change, real time data were analyzed using the ΔΔCt method and normalized to assays performed with cells transfected with a non-targeting control siRNA.

Results

Table 7 provides HSD17B13 ELF7 GNA7 modified sequences. Table 8 provides HSD17B13 ELF7 GNA7 unmodified sequences. Results from the HSD17B13 ELF7 GNA7 modified sequences *in vitro* 10nM screen in Cos-7 and primary cynomolgus hepatocytes are summarized in Table 9.

Similarly, Table 10 provides HSD17B13 NonF DNA modified sequences. Table 11 provides HSD17B13 NonF DNA unmodified sequences. Shown in Table 12 are results from the HSD17B13 NonF DNA modified sequences *in vitro* 10nM screen in Cos-7 and primary cynomolgus hepatocytes. "NonF" indicates that these RNAi agents lack fluoro modifications.

Table 7. HSD17B13 ELF7 GNA7 Modified Sequence*

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-286958.1	asgsuaccUfcCfUfCfccuaggacuaL96	2981	usAfsgucc(Tgn)agggagGfaGfguacusgsu	302	ACAGUACCUCCUCCCUAGGACUA	602
AD-287001.1	uscscuucUfgCfUfUfcugaucaccaL96	2982	usGfsguga(Tgn)cagaagCfaGfaaggasusu	303	AAUCCUUCUGCUUCUGAUCACCA	603
AD-287012.1	csasucauCfuAfCfUfccuacuuggaL96	2983	usCfscaag(Tgn)aggaguAfgAfugaugsgsu	304	ACCAUCAUCUACUCCUACUUGGA	604
AD-287014.1	uscsuacuCfcUfAfCfuuggagucguL96	2984	asCfsgacu(Cgn)caaguaGfgAfguagasusg	305	CAUCUACUCCUACUUGGAGUCGU	605
AD-287015.1	csusacucCfuAfCfUfuggagucguuL96	2985	asAfscgac(Tgn)ccaaguAfgGfaguagsasu	306	AUCUACUCCUACUUGGAGUCGUU	606
AD-287017.1	gsusaccuCfcUfCfCfcuaggacuauL96	2986	asUfsaguc(Cgn)uagggaGfgAfgguacsusg	307	CAGUACCUCCUCCCUAGGACUAC	607
AD-287026.1	ascsacaaGfgAfCfUfgaaccagaauL96	2987	asUfsucug(Ggn)uucaguCfcUfugugusasg	308	CUACACAAGGACUGAACCAGAAG	608
AD-287059.1	ascscaucAfuCfUfAfcuccuacuuuL96	2988	asAfsagua(Ggn)gaguagAfuGfauggusgsa	309	UCACCAUCAUCUACUCCUACUUG	609
AD-287060.1	cscsaucaUfcUfAfCfuccuacuuguL96	2989	asCfsaagu(Agn)ggaguaGfaUfgauggsusg	310	CACCAUCAUCUACUCCUACUUGG	610
AD-287061.1	asuscaucUfaCfUfCfcuacuuggauL96	2990	asUfsccaa(Ggn)uaggagUfaGfaugausgsg	311	CCAUCAUCUACUCCUACUUGGAG	611
AD-287062.1	csasucuaCfuCfCfUfacuuggaguuL96	2991	asAfscucc(Agn)aguaggAfgUfagaugsasu	312	AUCAUCUACUCCUACUUGGAGUC	612
AD-287064.1	usascuccUfaCfUfUfggagucguuuL96	2992	asAfsacga(Cgn)uccaagUfaGfgaguasgsa	313	UCUACUCCUACUUGGAGUCGUUG	613
AD-287065.1	ascsuccuAfcUfUfGfgagucguuguL96	2993	asCfsaacg(Agn)cuccaaGfuAfggagusasg	314	CUACUCCUACUUGGAGUCGUUGG	614
AD-287066.1	csusccuaCfuUfGfGfagucguugguL96	2994	asCfscaac(Ggn)acuccaAfgUfaggagsusa	315	UACUCCUACUUGGAGUCGUUGGU	615
AD-287126.1	uscscuacUfuGfGfAfgucguugguuL96	2995	asAfsccaa(Cgn)gacuccAfaGfuaggasgsu	316	ACUCCUACUUGGAGUCGUUGGUG	616
AD-287200.1	asascugcAfgCfUfGfagugccgaaaL96	2996	usUfsucgg(Cgn)acucagCfuGfcaguususc	317	GAAACUGCAGCUGAGUGCCGAAA	617
AD-287201.1	ascsugcaGfcUfGfAfgugccgaaaaL96	2997	usUfsuucg(Ggn)cacucaGfcUfgcagususu	318	AAACUGCAGCUGAGUGCCGAAAA	618
AD-287202.1	usgscagcUfgAfGfUfgccgaaaacuL96	2998	asGfsuuuu(Cgn)ggcacuCfaGfcugcasgsu	319	ACUGCAGCUGAGUGCCGAAAACU	619
AD-287203.1	gscsagcuGfaGfUfGfccgaaaacuaL96	2999	usAfsguuu(Tgn)cggcacUfcAfgcugcsasg	320	CUGCAGCUGAGUGCCGAAAACUA	620
AD-287205.1	asgsugccGfaAfAfAfcuaggcgucaL96	3000	usGfsacgc(Cgn)uaguuuUfcGfgcacuscsa	321	UGAGUGCCGAAAACUAGGCGUCA	621
AD-287206.1	usgsccgaAfaAfCfUfaggcgucacuL96	3001	asGfsugac(Ggn)ccuaguUfuUfcggcascsu	322	AGUGCCGAAAACUAGGCGUCACU	622
AD-287227.1	csusguggGfaUfAfUfuaauaagcguL96	3002	asCfsgcuu(Agn)uuaauaUfcCfcacagsasa	323	UUCUGUGGGAUAUUAAUAAGCGC	623
AD-287246.1	csusgcagCfuGfAfGfugccgaaaauL96	24	asUfsuuuc(Ggn)gcacucAfgCfugcagsusu	324	AACUGCAGCUGAGUGCCGAAAAC	624
AD-287247.1	csasgcugAfgUfGfCfcgaaaacuauL96	25	asUfsaguu(Tgn)ucggcaCfuCfagcugscsa	325	UGCAGCUGAGUGCCGAAAACUAG	625
AD-287248.1	asgscugaGfuGfCfCfgaaaacuaguL96	26	asCfsuagu(Tgn)uucggcAfcUfcagcusgsc	326	GCAGCUGAGUGCCGAAAACUAGG	626
AD-287249.1	gscsugagUfgCfCfGfaaaacuagguL96	27	asCfscuag(Tgn)uuucggCfaCfucagcsusg	327	CAGCUGAGUGCCGAAAACUAGGC	627
AD-287250.1	csusgaguGfcCfGfAfaaacuaggcuL96	28	asGfsccua(Ggn)uuuucgGfcAfcucagscsu	328	AGCUGAGUGCCGAAAACUAGGCG	628
AD-287251.1	gsasgugcCfgAfAfAfacuaggcguuL96	29	asAfscgcc(Tgn)aguuuuCfgGfcacucsasg	329	CUGAGUGCCGAAAACUAGGCGUC	629
AD-287252.1	gsusgccgAfaAfAfCfuaggcgucauL96	30	asUfsgacg(Cgn)cuaguuUfuCfggcacsusc	330	GAGUGCCGAAAACUAGGCGUCAC	630
AD-287253.1	gscscgaaAfaCfUfAfggcgucacuuL96	31	asAfsguga(Cgn)gccuagUfuUfucggcsasc	331	GUGCCGAAAACUAGGCGUCACUG	631
AD-287254.1	cscsgaaaAfcUfAfGfgcgucacuguL96	32	asCfsagug(Agn)cgccuaGfuUfuucggscsa	332	UGCCGAAAACUAGGCGUCACUGC	632
AD-287258.1	ascsuaggCfgUfCfAfcugcgcauguL96	33	asCfsaugc(Ggn)cagugaCfgCfcuagususu	333	AAACUAGGCGUCACUGCGCAUGC	633

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-287287.1	gsasucuaUfcGfCfUfcucuaaaucaL96	34	usGfsauuu(Agn)gagagcGfaUfagaucsusc	334	GAGAUCUAUCGCUCUCUAAAUCA	634
AD-287288.1	csusaucgCfuCfUfCfuaaaucagguL96	35	asCfscuga(Tgn)uuagagAfgCfgauagsasu	335	AUCUAUCGCUCUCUAAAUCAGGU	635
AD-287289.1	asuscgcuCfuCfUfAfaaucaggugaL96	36	usCfsaccu(Ggn)auuuagAfgAfgcgausasg	336	CUAUCGCUCUCUAAAUCAGGUGA	636
AD-287290.1	uscsgcucUfcUfAfAfaucaggugaaL96	37	usUfscacc(Tgn)gauuuaGfaGfagcgasusa	337	UAUCGCUCUCUAAAUCAGGUGAA	637
AD-287293.1	uscsucuaAfaUfCfAfggugaagaaaL96	38	usUfsucuu(Cgn)accugaUfuUfagagasgsc	338	GCUCUCUAAAUCAGGUGAAGAAA	638
AD-287316.1	gsusggugAfaUfAfAfugcugggacaL96	39	usGfsuccc(Agn)gcauuaUfuCfaccacsgsa	339	UCGUGGUGAAUAAUGCUGGGACA	639
AD-287320.1	gsasauaaUfgCfUfGfggacaguauaL96	40	usAfsuacu(Ggn)ucccagCfaUfuauucsasc	340	GUGAAUAAUGCUGGGACAGUAUA	640
AD-287321.1	asasuaauGfcUfGfGfgacaguauauL96	41	asUfsauac(Tgn)gucccaGfcAfuuauuscsa	341	UGAAUAAUGCUGGGACAGUAUAU	641
AD-287324.1	gsgsgacaGfuAfUfAfuccagccgauL96	42	asUfscggc(Tgn)ggauauAfcUfgucccsasg	342	CUGGGACAGUAUAUCCAGCCGAU	642
AD-287325.1	gsascaguAfuAfUfCfcagccgaucuL96	43	asGfsaucg(Ggn)cuggauAfuAfcugucscsc	343	GGGACAGUAUAUCCAGCCGAUCU	643
AD-287326.1	ascsaguaUfaUfCfCfagccgaucuuL96	44	asAfsgauc(Ggn)gcuggaUfaUfacugucsc	344	GGACAGUAUAUCCAGCCGAUCUU	644
AD-287327.1	asgsuauaUfcCfAfGfccgaucuucuL96	45	asGfsaaga(Tgn)cggcugGfaUfauacusgsu	345	ACAGUAUAUCCAGCCGAUCUUCU	645
AD-287344.1	asuscuauCfgCfUfCfucuaaaucauL96	46	asUfsgauu(Tgn)agagagCfgAfuagauscsu	346	AGAUCUAUCGCUCUCUAAAUCAG	646
AD-287346.1	usasucgcUfcUfCfUfaaaucagguuL96	47	asAfsccug(Agn)uuuagaGfaGfcgauasgsa	347	UCUAUCGCUCUCUAAAUCAGGUG	647
AD-287347.1	csgscucuCfuAfAfAfucaggugaauL96	48	asUfsucac(Cgn)ugauuuAfgAfgagcgsasu	348	AUCGCUCUCUAAAUCAGGUGAAG	648
AD-287366.1	csgsugguGfaAfUfAfaugcugggauL96	49	asUfsccca(Ggn)cauuauUfcAfccacgsasu	349	AUCGUGGUGAAUAAUGCUGGGAC	649
AD-287367.1	usgsgugaAfuAfAfUfgcugggacauL96	50	asUfsgucc(Cgn)agcauuAfuUfcaccascsg	350	CGUGGUGAAUAAUGCUGGGACAG	650
AD-287370.1	asusgcugGfgAfCfAfguauauccauL96	51	asUfsggau(Agn)uacuguCfcCfagcaususa	351	UAAUGCUGGGACAGUAUAUCCAG	651
AD-287371.1	usgscuggGfaCfAfGfuauauccaguL96	52	asCfsugga(Tgn)auacugUfcCfcagcasusu	352	AAUGCUGGGACAGUAUAUCCAGC	652
AD-287372.1	gscsugggAfcAfGfUfauauccagcuL96	53	asGfscugg(Agn)uauacuGfuCfccagcsasu	353	AUGCUGGGACAGUAUAUCCAGCC	653
AD-287373.1	csusgggaCfaGfUfAfuauccagccuL96	54	asGfsgcug(Ggn)auauacUfgUfcccagscsa	354	UGCUGGGACAGUAUAUCCAGCCG	654
AD-287374.1	gsgsacagUfaUfAfUfccagccgauuL96	55	asAfsucgg(Cgn)uggauaUfaCfuguccscsa	355	UGGGACAGUAUAUCCAGCCGAUC	655
AD-287375.1	csasguauAfuCfCfAfgccgaucuuuL96	56	asAfsagau(Cgn)ggcuggAfuAfuacugsusc	356	GACAGUAUAUCCAGCCGAUCUUC	656
AD-287391.1	cscsaaggAfuGfAfAfgagauuaccaL96	57	usGfsguaa(Tgn)cucuucAfuCfcuuggsusg	357	CACCAAGGAUGAAGAGAUUACCA	657
AD-287392.1	csasaggaUfgAfAfGfagauuaccaaL96	58	usUfsggua(Agn)ucucuuCfaUfccuugsgsu	358	ACCAAGGAUGAAGAGAUUACCAA	658
AD-287406.1	ususugagGfuCfAfAfcauccuaggaL96	59	usCfscuag(Ggn)auguugAfcCfucaaasusg	359	CAUUUGAGGUCAACAUCCUAGGA	659
AD-287407.1	usgsagguCfaAfCfAfuccuaggacaL96	60	usGfsuccu(Agn)ggauguUfgAfccucasasa	360	UUUGAGGUCAACAUCCUAGGACA	660
AD-287408.1	gsasggucAfaCfAfUfccuaggacauL96	61	asUfsgucc(Tgn)aggaugUfuGfaccucsasa	361	UUGAGGUCAACAUCCUAGGACAU	661
AD-287410.1	gsgsucaaCfaUfCfCfuaggacauuuL96	62	asAfsaugu(Cgn)cuaggaUfgUfugaccsusc	362	GAGGUCAACAUCCUAGGACAUUU	662
AD-287411.1	gsuscaacAfuCfCfUfaggacauuuuL96	63	asAfsaaug(Tgn)ccuaggAfuGfuugacscsu	363	AGGUCAACAUCCUAGGACAUUUU	663
AD-287413.1	ascsauccUfaGfGfAfcauuuuuggaL96	64	usCfscaaa(Agn)auguccUfaGfgaugususg	364	CAACAUCCUAGGACAUUUUUGGA	664
AD-287414.1	csasuccuAfgGfAfCfauuuuuggauL96	65	asUfsccaa(Agn)aaugucCfuAfggaugsusu	365	AACAUCCUAGGACAUUUUUGGAU	665
AD-287415.1	uscscuagGfaCfAfUfuuuuggaucaL96	66	usGfsaucc(Agn)aaaaugUfcCfuaggasusg	366	CAUCCUAGGACAUUUUUGGAUCA	666

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-287418.1	asgsgacaUfuUfUfUfggaucacaaaL96	67	usUfsugug(Agn)uccaaaAfaUfguccusasg	367	CUAGGACAUUUUUGGAUCACAAA	667
AD-287419.1	gsgsacauUfuUfUfGfgaucacaaaaL96	68	usUfsuugu(Ggn)auccaaAfaAfuguccsusa	368	UAGGACAUUUUUGGAUCACAAAA	668
AD-287421.1	ususuuugGfaUfCfAfcaaaagcacuL96	69	asGfsugcu(Tgn)uugugaUfcCfaaaaasusg	369	CAUUUUUGGAUCACAAAAGCACU	669
AD-287424.1	usgsgaucAfcAfAfAfagcacuucuuL96	70	asAfsgaag(Tgn)gcuuuuGfuGfauccasasa	370	UUUGGAUCACAAAAGCACUUCUU	670
AD-287427.1	csasaaagCfaCfUfUfcuuccaucgaL96	71	usCfsgaug(Ggn)aagaagUfgCfuuuugsusg	371	CACAAAAGCACUUCUUCCAUCGA	671
AD-287428.1	asasaagcAfcUfUfCfuuccaucgauL96	72	asUfscgau(Ggn)gaagaaGfuGfcuuuusgsu	372	ACAAAAGCACUUCUUCCAUCGAU	672
AD-287429.1	asasgcacUfuCfUfUfccaucgaugaL96	73	usCfsaucg(Agn)uggaagAfaGfugcuususu	373	AAAAGCACUUCUUCCAUCGAUGA	673
AD-287430.1	asgscacuUfcUfUfCfcaucgaugauL96	74	asUfscauc(Ggn)auggaaGfaAfgugcususu	374	AAAGCACUUCUUCCAUCGAUGAU	674
AD-287441.1	gsgsagagAfaAfUfCfauggccacauL96	75	asUfsgugg(Cgn)caugauUfuCfucuccsasu	375	AUGGAGAGAAAUCAUGGCCACAU	675
AD-287453.1	ascscaagGfaUfGfAfagagauuacuL96	76	asGfsuaau(Cgn)ucuucaUfcCfuuggusgsc	376	GCACCAAGGAUGAAGAGAUUACC	676
AD-287462.1	asgsacauUfuGfAfGfgucaacaucuL96	77	asGfsaugu(Tgn)gaccucAfaAfugucususg	377	CAAGACAUUUGAGGUCAACAUCC	677
AD-287463.1	csasuuugAfgGfUfCfaacauccuauL96	78	asUfsagga(Tgn)guugacCfuCfaaaugsusc	378	GACAUUUGAGGUCAACAUCCUAG	678
AD-287464.1	asususugaGfgUfCfAfacauccuaguL96	79	asCfsuagg(Agn)uguugaCfcUfcaaausgsu	379	ACAUUUGAGGUCAACAUCCUAGG	679
AD-287465.1	ususgaggUfcAfAfCfauccuaggauL96	80	asUfsccua(Ggn)gauguuGfaCfcucaasasu	380	AUUUGAGGUCAACAUCCUAGGAC	680
AD-287466.1	csasacauCfcUfAfGfgacauuuuugL96	81	csAfsaaaa(Tgn)guccuaGfgAfuguugsasc	381	GUCAACAUCCUAGGACAUUUUUG	681
AD-287467.1	asascaucCfuAfGfGfacauuuuuguL96	82	asCfsaaaa(Agn)uguccuAfgGfauguusgsa	382	UCAACAUCCUAGGACAUUUUUGG	682
AD-287468.1	asusccuaGfgAfCfAfuuuuuggauuL96	83	asAfsucca(Agn)aaauguCfcUfaggausgsu	383	ACAUCCUAGGACAUUUUUGGAUC	683
AD-287469.1	cscsuaggAfcAfUfUfuuuggaucauL96	84	asUfsgauc(Cgn)aaaaauGfuCfcuaggsasu	384	AUCCUAGGACAUUUUUGGAUCAC	684
AD-287470.1	gsascauuUfuUfGfGfaucacaaaauL96	85	asUfsuuug(Tgn)gauccaAfaAfaugucscsu	385	AGGACAUUUUUGGAUCACAAAAG	685
AD-287474.1	gsgsaucaCfaAfAfAfgcacuucuuuL96	86	asAfsagaa(Ggn)ugcuuuUfgUfgauccsasa	386	UUGGAUCACAAAAGCACUUCUUC	686
AD-287476.1	csascaaaAfgCfAfCfuucuuccauuL96	87	asAfsugga(Agn)gaagugCfuUfuugugsasu	387	AUCACAAAAGCACUUCUUCCAUC	687
AD-287477.1	ascsaaaaGfcAfCfUfucuuccaucuL96	88	asGfsaugg(Agn)agaaguGfcUfuuugusgsa	388	UCACAAAAGCACUUCUUCCAUCG	688
AD-287478.1	asasagcaCfuUfCfUfuccaucgauuL96	89	asAfsucga(Tgn)ggaagaAfgUfgcuuususg	389	CAAAAGCACUUCUUCCAUCGAUG	689
AD-287479.1	gscsacuuCfuUfCfCfcaucgaugauuL96	90	asAfsucau(Cgn)gauggaAfgAfagugcsusu	390	AAGCACUUCUUCCAUCGAUGAUG	690
AD-287491.1	asgsaaauCfaUfGfGfccacaucguuL96	91	asAfscgau(Ggn)uggccaUfgAfuuucuscsu	391	AGAGAAAUCAUGGCCACAUCGUC	691
AD-287492.1	asasaucaUfgGfCfCfacaucgucauL96	92	asUfsgacg(Agn)uguggcCfaUfgauuuscsu	392	AGAAAUCAUGGCCACAUCGUCAC	692
AD-287517.1	ususccuuAfcCfUfCfaucccauauuL96	93	asAfsuaug(Ggn)gaugagGfuAfaggaasusc	393	GAUUCCUUACCUCAUCCCAUAUU	693
AD-287520.1	ascscucaUfcCfCfAfuauuguuccaL96	94	usGfsgaac(Agn)auauggGfaUfgaggusasa	394	UUACCUCAUCCCAUAUUGUUCCA	694
AD-287521.1	uscsauccCfaUfAfUfuguuccagcaL96	95	usGfscugg(Agn)acaauaUfgGfgaugasgsg	395	CCUCAUCCCAUAUUGUUCCAGCA	695
AD-287522.1	csasucccAfuAfUfUfguuccagcaaL96	96	usUfsgcug(Ggn)aacaauAfuGfggaugsasg	396	CUCAUCCCAUAUUGUUCCAGCAA	696
AD-287524.1	uscsccauAfuUfGfUfuccagcaaauL96	97	asUfsuugc(Tgn)ggaacaAfuAfugggasusg	397	CAUCCCAUAUUGUUCCAGCAAAU	697
AD-287525.1	cscscauaUfuGfUfUfccagcaaauuL96	98	asAfsuuug(Cgn)uggaacAfaUfaugggsasu	398	AUCCCAUAUUGUUCCAGCAAAUU	698
AD-287537.1	usgsuuggCfuUfUfCfacagaggucuL96	99	asGfsaccu(Cgn)ugugaaAfgCfcaacasgsc	399	GCUGUUGGCUUUCACAGAGGUCU	699

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-287539.1	gsgscuuuCfaCfAfGfaggucugacaL96	100	usGfsucag(Agn)ccucugUfgAfaagccsasa	400	UUGGCUUUCACAGAGGUCUGACA	700
AD-287540.1	gscsuuucAfcAfGfAfggucugacauL96	101	asUfsguca(Ggn)accucuGfuGfaaagcscsa	401	UGGCUUUCACAGAGGUCUGACAU	701
AD-287543.1	csascagaGfgUfCfUfgacaucagaaL96	102	usUfscuga(Tgn)gucagaCfcUfcugugsasa	402	UUCACAGAGGUCUGACAUCAGAA	702
AD-287546.1	asgsgucuGfaCfAfUfcagaacuucaL96	103	usGfsaagu(Tgn)cugaugUfcAfgaccuscsu	403	AGAGGUCUGACAUCAGAACUUCA	703
AD-287568.1	uscscuuaCfcUfCfAfucccauauuuL96	104	asAfsauau(Ggn)ggaugaGfgUfaaggasasu	404	AUUCCUUACCUCAUCCCAUAUUG	704
AD-287591.1	ususcacaGfaGfGfUfcugacaucauL96	105	asUfsgaug(Tgn)cagaccUfcUfgugaasasg	405	CUUUCACAGAGGUCUGACAUCAG	705
AD-287610.1	ususgggaAfaAfAfCfugguaucaaaL96	106	usUfsugau(Agn)ccaguuUfuUfcccaasgsg	406	CCUUGGGAAAAACUGGUAUCAAA	706
AD-287615.1	ascsugguAfuCfAfAfaaccucauguL96	107	asCfsauga(Ggn)guuuugAfuAfccagususu	407	AAACUGGUAUCAAAACCUCAUGU	707
AD-287616.1	usgsguauCfaAfAfAfccucaugucuL96	108	asGfsacau(Ggn)agguuuUfgAfuaccasgsu	408	ACUGGUAUCAAAACCUCAUGUCU	708
AD-287627.1	csuscugcCfcAfGfUfuuuugugaauL96	109	asUfsucac(Agn)aaaacuGfgGfcagagsasc	409	GUCUCUGCCCAGUUUUUGUGAAU	709
AD-287632.1	ususuuugUfgAfAfUfacuggguucaL96	110	usGfsaacc(Cgn)aguauuCfaCfaaaaascsu	410	AGUUUUUGUGAAUACUGGGUUCA	710
AD-287633.1	ususgugaAfuAfCfUfggguucaccaL96	111	usGfsguga(Agn)cccaguAfuUfcacaasasa	411	UUUUGUGAAUACUGGGUUCACCA	711
AD-287634.1	usgsugaaUfaCfUfGfgguucaccaaL96	112	usUfsggug(Agn)acccagUfaUfucacasasa	412	UUUGUGAAUACUGGGUUCACCAA	712
AD-287636.1	usgsaauaCfuGfGfGfuucaccaaaaL96	113	usUfsuugg(Tgn)gaacccAfgUfauucascsa	413	UGUGAAUACUGGGUUCACCAAAA	713
AD-287637.1	gsasauacUfgGfGfUfucaccaaaaaL96	114	usUfsuuug(Ggn)ugaaccCfaGfuauucsasc	414	GUGAAUACUGGGUUCACCAAAAA	714
AD-287638.1	asasuacuGfgGfUfUfcaccaaaaauL96	115	asUfsuuuu(Ggn)gugaacCfcAfguauuscsa	415	UGAAUACUGGGUUCACCAAAAAU	715
AD-287647.1	asasaaauCfcAfAfGfcacaagauuaL96	116	usAfsaucu(Tgn)gugcuuGfgAfuuuuusgsg	416	CCAAAAAUCCAAGCACAAGAUUA	716
AD-287648.1	asasaaucCfaAfGfCfacaagauuauL96	117	asUfsaauc(Tgn)ugugcuUfgGfauuuususg	417	CAAAAAUCCAAGCACAAGAUUAU	717
AD-287651.1	asgscacaAfgAfUfUfauggccuguaL96	118	usAfscagg(Cgn)cauaauCfuUfgugcususg	418	CAAGCACAAGAUUAUGGCCUGUA	718
AD-287652.1	gscsacaaGfaUfUfAfuggccuguauL96	119	asUfsacag(Ggn)ccauaaUfcUfugugcsusu	419	AAGCACAAGAUUAUGGCCUGUAU	719
AD-287653.1	csascaagAfuUfAfUfggccuguauuL96	120	asAfsuaca(Ggn)gccauaAfuCfuugugcscsu	420	AGCACAAGAUUAUGGCCUGUAUU	720
AD-287654.1	asasgauuAfuGfGfCfcuguauuggaL96	121	usCfscaau(Agn)caggccAfuAfaucuusgsu	421	ACAAGAUUAUGGCCUGUAUUGGA	721
AD-287655.1	gsasuuauGfgCfCfUfguauuggagaL96	122	usCfsucca(Agn)uacaggCfcAfuaaucsusu	422	AAGAUUAUGGCCUGUAUUGGAGA	722
AD-287656.1	ususauggCfcUfGfUfauuggagacaL96	123	usGfsucuc(Cgn)aauacaGfgCfcauaasusc	423	GAUUAUGGCCUGUAUUGGAGACA	723
AD-287658.1	usgsgccuGfuAfUfUfggagacagauL96	124	asUfscugu(Cgn)uccaauAfcAfggccasusa	424	UAUGGCCUGUAUUGGAGACAGAU	724
AD-287659.1	gscscuguAfuUfGfGfagacagaugaL96	125	usCfsaucu(Ggn)ucuccaAfuAfcaggcscsa	425	UGGCCUGUAUUGGAGACAGAUGA	725
AD-287679.1	csusgguaUfcAfAfAfaccucauguuL96	126	asAfscaug(Agn)gguuuuGfaUfaccagsusu	426	AACUGGUAUCAAAACCUCAUGUC	726
AD-287680.1	gsgsuaucAfaAfAfCfcucaugucuuL96	127	asAfsgaca(Tgn)gagguuUfuGfauaccsasg	427	CUGGUAUCAAAACCUCAUGUCUC	727
AD-287683.1	uscsaaaaCfcUfCfAfugucucugcuL96	128	asGfscaga(Ggn)acaugaGfgUfuuugasusa	428	UAUCAAAACCUCAUGUCUCUGCC	728
AD-287690.1	cscscaguUfuUfUfGfugaauacuguL96	129	asCfsagua(Tgn)ucacaaAfaAfcugggscsa	429	UGCCCAGUUUUUGUGAAUACUGG	729
AD-287693.1	ususuuguGfaAfUfAfcuggguucauL96	130	asUfsgaac(Cgn)caguauUfcAfcaaaasasc	430	GUUUUUGUGAAUACUGGGUUCAC	730
AD-287694.1	ususugugAfaUfAfCfuggguucacuL96	131	asGfsugaa(Cgn)ccaguaUfuCfacaaasasa	431	UUUUUGUGAAUACUGGGUUCACC	731
AD-287695.1	asusacugGfgUfUfCfaccaaaaauuL96	132	asAfsuuuu(Tgn)ggugaaCfcCfaguaususc	432	GAAUACUGGGUUCACCAAAAAUC	732

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-287696.1	usascuggGfuUfCfAfccaaaaaucuL96	133	asGfsauuu(Tgn)uggugaAfcCfcaguasusu	433	AAUACUGGGUUCACCAAAAAUCC	733
AD-287700.1	csasccaaAfaAfUfCfcaagcacaauL96	134	asUfsugug(Cgn)uuggauUfuUfuggugsasa	434	UUCACCAAAAAUCCAAGCACAAG	734
AD-287701.1	asasauccAfaGfCfAfcaagauuauuL96	135	asAfsuaau(Cgn)uugugcUfuGfgauuususu	435	AAAAAUCCAAGCACAAGAUUAUG	735
AD-287702.1	asasuccaAfgCfAfCfaagauuauguL96	136	asCfsauaa(Tgn)cuugugCfuUfggauususu	436	AAAAUCCAAGCACAAGAUUAUGG	736
AD-287703.1	asusccaaGfcAfCfAfagauuaugguL96	137	asCfscaua(Agn)ucuuguGfcUfuggaususu	437	AAAUCCAAGCACAAGAUUAUGGC	737
AD-287704.1	uscscaagCfaCfAfAfgauuauggcuL96	138	asGfsccau(Agn)aucuugUfgCfuuggasusu	438	AAUCCAAGCACAAGAUUAUGGCC	738
AD-287706.1	ascsaagaUfuAfUfGfgccuguauuuL96	139	asAfsauac(Agn)ggccauAfaUfcuugusgsc	439	GCACAAGAUUAUGGCCUGUAUUG	739
AD-287707.1	csasagauUfaUfGfGfccuguauuguL96	140	asCfsaaua(Cgn)aggccaUfaAfucuugsusg	440	CACAAGAUUAUGGCCUGUAUUGG	740
AD-287709.1	asusuaugGfcCfUfGfuauuggagauL96	141	asUfscucc(Agn)auacagGfcCfauaauscsu	441	AGAUUAUGGCCUGUAUUGGAGAC	741
AD-287711.1	gsgsccugUfaUfUfGfgagacagauuL96	142	asAfsucug(Tgn)cuccaaUfaCfaggccsasu	442	AUGGCCUGUAUUGGAGACAGAUG	742
AD-287724.1	gsusaagaAfgUfCfUfgauagauggaL96	143	usCfscauc(Tgn)aucagaCfuUfcuuacsgsa	443	UCGUAAGAAGUCUGAUAGAUGGA	743
AD-287725.1	usasagaaGfuCfUfGfauagauggaaL96	144	usUfsccau(Cgn)uaucagAfcUfucuuascsg	444	CGUAAGAAGUCUGAUAGAUGGAA	744
AD-287726.1	asasgaagUfcUfGfAfuagauggaauL96	145	asUfsucca(Tgn)cuaucaGfaCfuucuusasc	445	GUAAGAAGUCUGAUAGAUGGAAU	745
AD-287727.1	asgsaaguCfuGfAfUfagauggaauaL96	146	usAfsuucc(Agn)ucuaucAfgAfcuucususa	446	UAAGAAGUCUGAUAGAUGGAAUA	746
AD-287728.1	asasgucuGfaUfAfGfauggaauacuL96	147	asGfsuauu(Cgn)caucuaUfcAfgacuuscsu	447	AGAAGUCUGAUAGAUGGAAUACU	747
AD-287735.1	asgsauggAfaUfAfCfuuaccaauaaL96	148	usUfsauug(Ggn)uaaguaUfuCfcaucusasu	448	AUAGAUGGAAUACUUACCAAUAA	748
AD-287736.1	asusggaaUfaCfUfUfaccaauaagaL96	149	usCfsuuau(Tgn)gguaagUfaUfuccauscsu	449	AGAUGGAAUACUUACCAAUAAGA	749
AD-287737.1	usgsgaauAfcUfUfAfccaauaagaaL96	150	usUfscuua(Tgn)ugguaaGfuAfuuccasusc	450	GAUGGAAUACUUACCAAUAAGAA	750
AD-287738.1	gsgsaauaCfuUfAfCfcaauaagaaaL96	151	usUfsucuu(Agn)uugguaAfgUfauuccsasu	451	AUGGAAUACUUACCAAUAAGAAA	751
AD-287739.1	gsasauacUfuAfCfCfaauaagaaaaL96	152	usUfsuucu(Tgn)auugguAfaGfuauucscsa	452	UGGAAUACUUACCAAUAAGAAAA	752
AD-287740.1	asasuacuUfaCfCfAfauaagaaaauL96	153	asUfsuuuc(Tgn)uauuggUfaAfguauuscsc	453	GGAAUACUUACCAAUAAGAAAAU	753
AD-287778.1	ususucuuCfcUfGfAfacgcgccucaL96	154	usGfsaggc(Ggn)cguucaGfgAfagaaascsu	454	AGUUUCUUCCUGAACGCGCCUCA	754
AD-287793.1	gsasuuuuAfaAfUfCfguaugcagaaL96	155	usUfscugc(Agn)uacgauUfuAfaaaucsgsc	455	GCGAUUUUAAAUCGUAUGCAGAA	755
AD-287795.1	ususuuaaAfuCfGfUfaugcagaauaL96	156	usAfsuucu(Ggn)cauacgAfuUfuaaaasusc	456	GAUUUUAAAUCGUAUGCAGAAUA	756
AD-287798.1	asasaucgUfaUfGfCfagaauauucaL96	157	usGfsaaua(Tgn)ucugcaUfaCfgauuusasa	457	UUAAAUCGUAUGCAGAAUAUUCA	757
AD-287800.1	asuscguaUfgCfAfGfaauauucaauL96	158	asUfsugaa(Tgn)auucugCfaUfacgaususu	458	AAAUCGUAUGCAGAAUAUUCAAU	758
AD-287801.1	uscsguauGfcAfGfAfauauucaauuL96	159	asAfsuuga(Agn)uauucuGfcAfuacgasusu	459	AAUCGUAUGCAGAAUAUUCAAUU	759
AD-287802.1	csgsuaugCfaGfAfAfuauucaauuuL96	160	asAfsauug(Agn)auauucUfgCfauacgsasu	460	AUCGUAUGCAGAAUAUUCAAUUU	760
AD-287804.1	asusgcagAfaUfAfUfucaauuugaaL96	161	usUfscaaa(Tgn)ugaauaUfuCfugcausasc	461	GUAUGCAGAAUAUUCAAUUUGAA	761
AD-287810.1	gsasagucUfgAfUfAfgauggaauauL96	162	asUfsauuc(Cgn)aucuauCfaGfacuucsusu	462	AAGAAGUCUGAUAGAUGGAAUAC	762
AD-287811.1	uscsugauAfgAfUfGfgaauacuuauL96	163	asUfsaagu(Agn)uuccauCfuAfucagascsu	463	AGUCUGAUAGAUGGAAUACUUAC	763
AD-287813.1	gsasuggaAfuAfCfUfuaccaauaauL96	164	asUfsuauu(Ggn)guaaguAfuUfccaucsusa	464	UAGAUGGAAUACUUACCAAUAAG	764
AD-287837.1	ascsagaaGfuUfUfCfuuccugaacuL96	165	asGfsuuca(Ggn)gaagaaAfcUfucugusasg	465	CUACAGAAGUUUCUUCCUGAACG	765

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-287839.1	asgsaaguUfuCfUfUfccugaacgcuL96	166	asGfscguu(Cgn)aggaagAfaAfcuucusgsu	466	ACAGAAGUUUCUUCCUGAACGCG	766
AD-287841.1	asasguuuCfuUfCfCfugaacgcgcuL96	167	asGfscgcg(Tgn)ucaggaAfgAfaacuuscsu	467	AGAAGUUUCUUCCUGAACGCGCC	767
AD-287842.1	gsusuucuUfcCfUfGfaacgcgccuuL96	168	asAfsggcg(Cgn)guucagGfaAfgaaacsusu	468	AAGUUUCUUCCUGAACGCGCCUC	768
AD-287844.1	uscsuuccUfgAfAfCfgcgccucaguL96	169	asCfsugag(Ggn)cgcguuCfaGfgaagasasa	469	UUUCUUCCUGAACGCGCCUCAGC	769
AD-287854.1	gscsagaaUfaUfUfCfaauuugaaguL96	170	asCfsuuca(Agn)auugaaUfaUfucugcsasu	470	AUGCAGAAUAUUCAAUUUGAAGC	770
AD-287856.1	asasuauuCfaAfUfUfugaagcaguuL96	171	asAfscugc(Tgn)ucaaauUfgAfauauuscsu	471	AGAAUAUUCAAUUUGAAGCAGUG	771
AD-287857.1	usasuucaAfuUfUfGfaagcagugguL96	172	asCfscacu(Ggn)cuucaaAfuUfgaauasusu	472	AAUAUUCAAUUUGAAGCAGUGGU	772
AD-287893.1	gsasuguaUfgCfAfUfgauaaugauaL96	173	usAfsucau(Tgn)aucaugCfaUfacaucsusc	473	GAGAUGUAUGCAUGAUAAUGAUA	773
AD-287917.1	csasaugcUfgCfAfAfagcuuuauuuL96	174	asAfsauaa(Agn)gcuuugCfaGfcauugsasu	474	AUCAAUGCUGCAAAGCUUUAUUU	774
AD-287924.1	asasagcuUfuAfUfUfucacauuuuuL96	175	asAfsaaau(Ggn)ugaaauAfaAfgcuuusgsc	475	GCAAAGCUUUAUUUCACAUUUUU	775
AD-287934.1	asasuuugAfaGfCfAfgugguuggcuL96	176	asGfsccaa(Cgn)cacugcUfuCfaaauusgsa	476	UCAAUUUGAAGCAGUGGUUGGCC	776
AD-287969.1	asasugcuGfcAfAfAfgcuuuauuucL96	177	gsAfsaaua(Agn)agcuuuGfcAfgcauusgsa	477	UCAAUGCUGCAAAGCUUUAUUUC	777
AD-287970.1	usgscugcAfaAfGfCfuuuauuucauL96	178	asUfsgaaa(Tgn)aaagcuUfuGfcagcasusu	478	AAUGCUGCAAAGCUUUAUUUCAC	778
AD-287982.1	asasaaacAfuUfGfGfuuuggcacuaL96	179	usAfsgugc(Cgn)aaaccaAfuGfuuuuusasa	479	UUAAAAACAUUGGUUUGGCACUA	779
AD-288005.1	asgsauuaAfuUfAfCfcugucuuccuL96	180	asGfsgaag(Agn)cagguaAfuUfaaucususg	480	CAAGAUUAAUUACCUGUCUUCCU	780
AD-288006.1	asusuaauUfaCfCfUfgucuuccuguL96	181	asCfsagga(Agn)gacaggUfaAfuuaauscsu	481	AGAUUAAUUACCUGUCUUCCUGU	781
AD-288008.1	usasauuaCfcUfGfUfcuuccuguuuL96	182	asAfsacag(Ggn)aagacaGfgUfaauuasasu	482	AUUAAUUACCUGUCUUCCUGUUU	782
AD-288010.1	usasccugUfcUfUfCfcuguuucucaL96	183	usGfsagaa(Agn)caggaaGfaCfagguasasu	483	AUUACCUGUCUUCCUGUUUCUCA	783
AD-288011.1	ascscuguCfuUfCfCfuguuucucaaL96	184	usUfsgaga(Agn)acaggaAfgAfcaggusasa	484	UUACCUGUCUUCCUGUUUCUCAA	784
AD-288015.1	uscsuuccUfgUfUfUfcucaagaauaL96	185	usAfsuucu(Tgn)gagaaaCfaGfgaagascsa	485	UGUCUUCCUGUUUCUCAAGAAUA	785
AD-288046.1	ususuuccUfuUfCfAfugccucuuaaL96	186	usUfsaaga(Ggn)gcaugaAfaGfgaaaasasc	486	GUUUUUCCUUUCAUGCCUCUUAA	786
AD-288049.1	uscscuuuCfaUfGfCfcucuuaaaaaL96	187	usUfsuuua(Agn)gaggcaUfgAfaaggasasa	487	UUUCCUUUCAUGCCUCUUAAAAA	787
AD-288050.1	csusuucaUfgCfCfUfcuuaaaaacuL96	188	asGfsuuuu(Tgn)aagaggCfaUfgaaagsgsa	488	UCCUUUCAUGCCUCUUAAAAACU	788
AD-288076.1	asasaacaUfuGfGfUfuuggcacuauL96	189	asUfsagug(Cgn)caaaccAfaUfguuuususa	489	UAAAAACAUUGGUUUGGCACUAG	789
AD-288092.1	gsasuuaaUfuAfCfCfugucuuccuuL96	190	asAfsggaa(Ggn)acagguAfaUfuaaucsusu	490	AAGAUUAAUUACCUGUCUUCCUG	790
AD-288094.1	ususaccuGfuCfUfUfccuguuucuuL96	191	asAfsgaaa(Cgn)aggaagAfcAfgguaasusu	491	AAUUACCUGUCUUCCUGUUUCUC	791
AD-288095.1	cscsugucUfuCfCfUfguuucucaauL96	192	asUfsugag(Agn)aacaggAfaGfacaggsusa	492	UACCUGUCUUCCUGUUUCUCAAG	792
AD-288108.1	gsgsucugUfuUfUfUfccuuucauguL96	193	asCfsauga(Agn)aggaaaAfaCfagaccsusa	493	UAGGUCUGUUUUUCCUUUCAUGC	793
AD-288109.1	gsuscuguUfuUfUfCfcuuucaugcuL96	194	asGfscaug(Agn)aaggaaAfaAfcagacscsu	494	AGGUCUGUUUUUCCUUUCAUGCC	794
AD-288173.1	ususauuuAfcAfCfAfgggaagguuuL96	195	asAfsaccu(Tgn)cccuguGfuAfaauaasgsu	495	ACUUAUUUACACAGGGAAGGUUU	795
AD-288174.1	usasuuuaCfaCfAfGfggaagguuuaL96	196	usAfsaacc(Tgn)ucccugUfgUfaaauasasg	496	CUUAUUUACACAGGGAAGGUUUA	796
AD-288176.1	ususacacAfgGfGfAfagguuuaagaL96	197	usCfsuuaa(Agn)ccuuccCfuGfuguaasasu	497	AUUUACACAGGGAAGGUUUAAGA	797
AD-288177.1	ascsacagGfgAfAfGfguuuaagacuL96	198	asGfsucuu(Agn)aaccuuCfcCfugugusasa	498	UUACACAGGGAAGGUUUAAGACU	798

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-288180.1	gsgsgaagGfuUfUfAfagacuguucaL96	199	usGfsaaca(Ggn)ucuuaaAfcCfuucccsusg	499	CAGGGAAGGUUUAAGACUGUUCA	799
AD-288181.1	gsgsaaggUfuUfAfAfgacuguucaaL96	200	usUfsgaac(Agn)gucuuaAfaCfcuuccscsu	500	AGGGAAGGUUUAAGACUGUUCAA	800
AD-288183.1	asgsguuuAfaGfAfCfuguucaaguaL96	201	usAfscuug(Agn)acagucUfuAfaaccususc	501	GAAGGUUUAAGACUGUUCAAGUA	801
AD-288184.1	ususuaagAfcUfGfUfucaaguagcaL96	202	usGfscuac(Tgn)ugaacaGfuCfuuaaascsc	502	GGUUUAAGACUGUUCAAGUAGCA	802
AD-288186.1	usasagacUfgUfUfCfaaguagcauuL96	203	asAfsugcu(Agn)cuugaaCfaGfucuuasasa	503	UUUAAGACUGUUCAAGUAGCAUU	803
AD-288187.1	gsascuguUfcAfAfGfuagcauuccaL96	204	usGfsgaau(Ggn)cuacuuGfaAfcagucsusu	504	AAGACUGUUCAAGUAGCAUUCCA	804
AD-288188.1	ascsuguuCfaAfGfUfagcauuccaaL96	205	usUfsggaa(Tgn)gcuacuUfgAfacaguscsu	505	AGACUGUUCAAGUAGCAUUCCAA	805
AD-288189.1	csusguucAfaGfUfAfgcauuccaauL96	206	asUfsugga(Agn)ugcuacUfuGfaacagsusc	506	GACUGUUCAAGUAGCAUUCCAAU	806
AD-288190.1	gsusucaaGfuAfGfCfauuccaaucuL96	207	asGfsauug(Ggn)aaugcuAfcUfugaacsasg	507	CUGUUCAAGUAGCAUUCCAAUCU	807
AD-288192.1	csasaguaGfcAfUfUfccaaucuguaL96	208	usAfscaga(Tgn)uggaauGfcUfacuugsasa	508	UUCAAGUAGCAUUCCAAUCUGUA	808
AD-288193.1	usasgcauUfcCfAfAfucuguagccaL96	209	usGfsgcua(Cgn)agauugGfaAfugcuascsu	509	AGUAGCAUUCCAAUCUGUAGCCA	809
AD-288194.1	asgscauuCfcAfAfUfcuguagccauL96	210	asUfsggcu(Agn)cagauuGfgAfaugcusasc	510	GUAGCAUUCCAAUCUGUAGCCAU	810
AD-288227.1	asascuuaUfuUfAfCfacagggaaguL96	211	asCfsuucc(Cgn)uguguaAfaUfaaguuscsu	511	AGAACUUAUUUACACAGGGAAGG	811
AD-288229.1	usascacaGfgGfAfAfgguuuaagauL96	212	asUfscuua(Agn)accuucCfcUfguguasasa	512	UUUACACAGGGAAGGUUUAAGAC	812
AD-288230.1	csascaggGfaAfGfGfuuuaagacuuL96	213	asAfsgucu(Tgn)aaaccuUfcCfcugugsusa	513	UACACAGGGAAGGUUUAAGACUG	813
AD-288231.1	asgsggaaGfgUfUfUfaagacuguuuL96	214	asAfsacag(Tgn)cuuaaaCfcUfucccusgsu	514	ACAGGGAAGGUUUAAGACUGUUC	814
AD-288232.1	gsasagguUfuAfAfGfacuguucaauL96	215	asUfsugaa(Cgn)agucuuAfaAfccuucscsc	515	GGGAAGGUUUAAGACUGUUCAAG	815
AD-288233.1	gsgsuuuaAfgAfCfUfguucaaguauL96	216	asUfsacuu(Ggn)aacaguCfuUfaaaccsusu	516	AAGGUUUAAGACUGUUCAAGUAG	816
AD-288235.1	asasgacuGfuUfCfAfaguagcauuuL96	217	asAfsaugc(Tgn)acuugaAfcAfgucuusasa	517	UUAAGACUGUUCAAGUAGCAUUC	817
AD-288236.1	asgsacugUfuCfAfAfguagcauucuL96	218	asGfsaaug(Cgn)uacuugAfaCfagucususa	518	UAAGACUGUUCAAGUAGCAUUCC	818
AD-288237.1	usgsuucaAfgUfAfGfcauuccaauuL96	219	asAfsuugg(Agn)augcuaCfuUfgaacasgsu	519	ACUGUUCAAGUAGCAUUCCAAUC	819
AD-288238.1	ususcaagUfaGfCfAfuuccaaucuuL96	220	asAfsgauu(Ggn)gaaugcUfaCfuugaascsa	520	UGUUCAAGUAGCAUUCCAAUCUG	820
AD-288290.1	gscsagcuUfuAfUfCfucaaccuggaL96	221	usCfscagg(Tgn)ugagauAfaAfgcugcscsu	521	AGGCAGCUUUAUCUCAACCUGGA	821
AD-288316.1	asgscauuUfgAfAfAfgauuucccuaL96	222	usAfsggga(Agn)aucuuuCfaAfaugcusgsa	522	UCAGCAUUUGAAAGAUUUCCCUA	822
AD-288318.1	usgsaaagAfuUfUfCfccuagccucuL96	223	asGfsaggc(Tgn)agggaaAfuCfuuucasasa	523	UUUGAAAGAUUUCCCUAGCCUCU	823
AD-288319.1	gsasaagaUfuUfCfCfcuagccucuuL96	224	asAfsgagg(Cgn)uagggaAfaUfcuuucsasa	524	UUGAAAGAUUUCCCUAGCCUCUU	824
AD-288324.1	ususcccuAfgCfCfUfcuuccuuuuuL96	225	asAfsaaag(Ggn)aagaggCfuAfgggaasasu	525	AUUUCCCUAGCCUCUUCCUUUUU	825
AD-288337.1	asasgaacAfcAfGfAfaugagugcauL96	226	asUfsgcac(Tgn)cauucuGfuGfuucuusgsu	526	ACAAGAACACAGAAUGAGUGCAC	826
AD-288338.1	gsasacacAfgAfAfUfgagugcacauL96	227	asUfsgugc(Agn)cucauuCfuGfuguucsusu	527	AAGAACACAGAAUGAGUGCACAG	827
AD-288339.1	asascacaGfaAfUfGfagugcacaguL96	228	asCfsugug(Cgn)acucauUfcUfguguuscsu	528	AGAACACAGAAUGAGUGCACAGC	828
AD-288340.1	csasgaauGfaGfUfGfcacagcuaauL96	229	asUfsuagc(Tgn)gugcacUfcAfuucugsusg	529	CACAGAAUGAGUGCACAGCUAAG	829
AD-288341.1	gsasaugaGfuGfCfAfcagcuaagauL96	230	asUfscuua(Ggn)cugugcAfcUfcauucsusg	530	CAGAAUGAGUGCACAGCUAAGAG	830
AD-288366.1	ususcagcAfuUfUfGfaaagauuucuL96	231	asGfsaaau(Cgn)uuucaaAfuGfcugaasusc	531	GAUUCAGCAUUUGAAAGAUUUCC	831

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-288369.1	csasuuugAfaAfGfAfuuucccuaguL96	232	asCfsuagg(Ggn)aaaucuUfuCfaaaugscsu	532	AGCAUUUGAAAGAUUUCCCUAGC	832
AD-288370.1	asususugaAfaGfAfUfuucccuagcuL96	233	asGfscuag(Ggn)gaaaucUfuUfcaaausgsc	533	GCAUUUGAAAGAUUUCCCUAGCC	833
AD-288391.1	asasaacgGfuGfCfAfacucuauucuL96	234	asGfsaaua(Ggn)aguugcAfcCfguuuusgsg	534	CCAAAACGGUGCAACUCUAUUCU	834
AD-288393.1	gsgsugcaAfcUfCfUfauucuggacuL96	235	asGfsucca(Ggn)aauagaGfuUfgcaccsgsu	535	ACGGUGCAACUCUAUUCUGGACU	835
AD-288394.1	gsusgcaaCfuCfUfAfuucuggacuuL96	236	asAfsgucc(Agn)gaauagAfgUfugcacscsg	536	CGGUGCAACUCUAUUCUGGACUU	836
AD-288395.1	usgscaacUfcUfAfUfucuggacuuuL96	237	asAfsaguc(Cgn)agaauaGfaGfuugcascsc	537	GGUGCAACUCUAUUCUGGACUUU	837
AD-288396.1	gscsaacuCfuAfUfUfcuggacuuuaL96	238	usAfsaagu(Cgn)cagaauAfgAfguugcsasc	538	GUGCAACUCUAUUCUGGACUUUA	838
AD-288397.1	csasacucUfaUfUfCfuggacuuuauL96	239	asUfsaaag(Tgn)ccagaaUfaGfaguugscsa	539	UGCAACUCUAUUCUGGACUUUAU	839
AD-288398.1	asascucuAfuUfCfUfggacuuuauuL96	240	asAfsuaaa(Ggn)uccagaAfuAfgaguusgsc	540	GCAACUCUAUUCUGGACUUUAUU	840
AD-288402.1	asususcugGfaCfUfUfuauuacuugaL96	241	usCfsaagu(Agn)auaaagUfcCfagaausasg	541	CUAUUCUGGACUUUAUUACUUGA	841
AD-288427.1	asgsuccaCfcAfAfAfaguggacccuL96	242	asGfsgguc(Cgn)acuuuuGfgUfggacususc	542	GAAGUCCACCAAAAGUGGACCCU	842
AD-288430.1	csascaaAfaGfUfGfgacccucuauL96	243	asUfsagag(Ggn)guccacUfuUfuggugsgsa	543	UCCACCAAAAGUGGACCCUCUAU	843
AD-288431.1	ascscaaaAfgUfGfGfacccucuauaL96	244	usAfsuaga(Ggn)gguccaCfuUfuuggusgsg	544	CCACCAAAAGUGGACCCUCUAUA	844
AD-288432.1	cscsaaaaGfuGfGfAfcccucuauauL96	245	asUfsauag(Agn)ggguccAfcUfuuuggsusg	545	CACCAAAAGUGGACCCUCUAUAU	845
AD-288433.1	csasaaagUfgGfAfCfccucuauauuL96	246	asAfsuaua(Ggn)agggucCfaCfuuuugsgsu	546	ACCAAAAGUGGACCCUCUAUAUU	846
AD-288434.1	asasaaguGfgAfCfCfcucuauauuuL96	247	asAfsauau(Agn)gaggguCfcAfcuuuusgsg	547	CCAAAAGUGGACCCUCUAUAUUU	847
AD-288466.1	asasacggUfgCfAfAfcucuauucuuL96	248	asAfsgaau(Agn)gaguugCfaCfcguuususg	548	CAAAACGGUGCAACUCUAUUCUG	848
AD-288467.1	asascgguGfcAfAfCfucuauucuguL96	249	asCfsagaa(Tgn)agaguuGfcAfccguususu	549	AAAACGGUGCAACUCUAUUCUGG	849
AD-288470.1	usasuucuGfgAfCfUfuuauuacuuuL96	250	asAfsagua(Agn)uaaaguCfcAfgaauasgsa	550	UCUAUUCUGGACUUUAUUACUUG	850
AD-288491.1	asasagugGfaCfCfCfucuauauuucL96	251	gsAfsaaua(Tgn)agagggUfcCfacuuususg	551	CAAAAGUGGACCCUCUAUAUUUC	851
AD-288492.1	asasguggAfcCfCfUfcuauauuucuL96	252	asGfsaaau(Agn)uagaggGfuCfcacuususu	552	AAAAGUGGACCCUCUAUAUUUCC	852
AD-288561.1	asusguuuAfgAfCfAfauuuuaggcuL96	253	asGfsccua(Agn)aauuguCfuAfaacauscsu	553	AGAUGUUUAGACAAUUUUAGGCU	853
AD-288562.1	gsusuuagAfcAfAfUfuuuaggcucaL96	254	usGfsagcc(Tgn)aaaauuGfuCfuaaacsasu	554	AUGUUUAGACAAUUUUAGGCUCA	854
AD-288563.1	ususuagaCfaAfUfUfuuaggcucaaL96	255	usUfsgagc(Cgn)uaaaauUfgUfcuaaascsa	555	UGUUUAGACAAUUUUAGGCUCAA	855
AD-288564.1	ususagacAfaUfUfUfuaggcucaaaL96	256	usUfsugag(Cgn)cuaaaaUfuGfucuaasasc	556	GUUUAGACAAUUUUAGGCUCAAA	856
AD-288565.1	usasgacaAfuUfUfUfaggcucaaaaL96	257	usUfsuuga(Ggn)ccuaaaAfuUfgucuasasa	557	UUUAGACAAUUUUAGGCUCAAAA	857
AD-288566.1	asgsacaaUfuUfUfAfggcucaaaaaL96	258	usUfsuuug(Agn)gccuaaAfaUfugucusasa	558	UUAGACAAUUUUAGGCUCAAAAA	858
AD-288567.1	gsascaauUfuUfAfGfgcucaaaaauL96	259	asUfsuuuu(Ggn)agccuaAfaAfuugucsusa	559	UAGACAAUUUUAGGCUCAAAAAU	859
AD-288572.1	ususaggcUfcAfAfAfaauuaaagcuL96	260	asGfscuuu(Agn)auuuuuGfaGfccuaasasa	560	UUUUAGGCUCAAAAAUUAAAGCU	860
AD-288573.1	usasggcuCfaAfAfAfauuaaagcuaL96	261	usAfsgcuu(Tgn)aauuuuUfgAfgccuasasa	561	UUUAGGCUCAAAAAUUAAAGCUA	861
AD-288574.1	asgsgcucAfaAfAfAfuuaaagcuaaL96	262	usUfsagcu(Tgn)uaauuuUfuGfagccusasa	562	UUAGGCUCAAAAAUUAAAGCUAA	862
AD-288575.1	gscsucaaAfaAfUfUfaaagcuaacaL96	263	usGfsuuag(Cgn)uuuaauUfuUfugagcscsu	563	AGGCUCAAAAAUUAAAGCUAACA	863
AD-288576.1	uscsaaaaAfuUfAfAfagcuaacacaL96	264	usGfsuguu(Agn)gcuuuaAfuUfuuugasgsc	564	GCUCAAAAAUUAAAGCUAACACA	864

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-288613.1	ususcauaUfaUfCfCfuuggucccauL96	265	asUfsggga(Cgn)caaggaUfaUfaugaasasg	565	CUUUCAUAUAUCCUUGGUCCCAG	865
AD-288620.1	gsasuguuUfaGfAfCfaauuuuagguL96	266	asCfscuaa(Agn)auugucUfaAfacaucsusc	566	GAGAUGUUUAGACAAUUUUAGGC	866
AD-288624.1	gsgscucaAfaAfAfUfuaaagcuaauL96	267	asUfsuagc(Tgn)uuaaauUfuUfgagccsusa	567	UAGGCUCAAAAAUUAAAGCUAAC	867
AD-288625.1	csuscaaaAfaUfUfAfaagcuaacauL96	268	asUfsguua(Ggn)cuuuaaUfuUfuugagscsc	568	GGCUCAAAAAUUAAAGCUAACAC	868
AD-288626.1	csasaaaaUfuAfAfAfgcuaacacauL96	269	asUfsgugu(Tgn)agcuuuAfaUfuuuugsasg	569	CUCAAAAAUUAAAGCUAACACAG	869
AD-288628.1	asasauuaAfaGfCfUfaacacaggaaL96	270	usUfsccug(Tgn)guuagcUfuUfaauuususu	570	AAAAAUUAAAGCUAACACAGGAA	870
AD-288634.1	usasacacAfgGfAfAfaaggaacuguL96	271	asCfsaguu(Cgn)cuuuucCfuGfuguuasgsc	571	GCUAACACAGGAAAAGGAACUGU	871
AD-288637.1	gsgsaaaaGfgAfAfCfuguacuggcuL96	272	asGfsccag(Tgn)acaguuCfcUfuuuccsusg	572	CAGGAAAAGGAACUGUACUGGCU	872
AD-288639.1	asasaaggAfaCfUfGfuacuggcuauL96	273	asUfsagcc(Agn)guacagUfuCfcuuuuscsc	573	GGAAAAGGAACUGUACUGGCUAU	873
AD-288642.1	gsgsaacuGfuAfCfUfggcuauuacaL96	274	usGfsuaau(Agn)gccaguAfcAfguuccsusu	574	AAGGAACUGUACUGGCUAUUACA	874
AD-288696.1	csasggaaAfaGfGfAfacuguacuguL96	275	asCfsagua(Cgn)aguuccUfuUfuccugsusg	575	CACAGGAAAAGGAACUGUACUGG	875
AD-288698.1	asgsgaacUfgUfAfCfuggcuauuauL96	276	asUfsaaua(Ggn)ccaguaCfaGfuuccususu	576	AAAGGAACUGUACUGGCUAUUAC	876
AD-288912.1	csuscccaCfuAfCfAfucaagacuaaL96	277	usUfsaguc(Tgn)ugauguAfgUfgggagsusc	577	GACUCCCACUACAUCAAGACUAA	877
AD-288913.1	uscsccacUfaCfAfUfcaagacuaauL96	278	asUfsuagu(Cgn)uugaugUfaGfugggasgsu	578	ACUCCCACUACAUCAAGACUAAU	878
AD-288914.1	cscsacuaCfaUfCfAfagacuaaucuL96	279	asGfsauua(Ggn)ucuugaUfgUfaguggsgsa	579	UCCCACUACAUCAAGACUAAUCU	879
AD-288915.1	csascuacAfuCfAfAfgacuaaucuuL96	280	asAfsgauu(Agn)gucuugAfuGfuagugsgsg	580	CCCACUACAUCAAGACUAAUCUU	880
AD-288916.1	csusacauCfaAfGfAfcuaaucuuguL96	281	asCfsaaga(Tgn)uagucuUfgAfuguagsusg	581	CACUACAUCAAGACUAAUCUUGU	881
AD-288917.1	usascaucAfaGfAfCfuaaucuuguuL96	282	asAfscaag(Agn)uuagucUfuGfauguasgsu	582	ACUACAUCAAGACUAAUCUUGUU	882
AD-288918.1	ascsaucaAfgAfCfUfaaucuuguuuL96	283	asAfsacaa(Ggn)auuaguCfuUfgaugusasg	583	CUACAUCAAGACUAAUCUUGUUU	883
AD-288933.1	gsusguuuUfuCfAfCfauguauuauaL96	284	usAfsuaau(Agn)caugugAfaAfaacacsasc	584	GUGUGUUUUUCACAUGUAUUAUA	884
AD-288937.1	uscsacauGfuAfUfUfauagaaugcuL96	285	asGfscauu(Cgn)uauaauAfcAfugugasasa	585	UUUCACAUGUAUUAUAGAAUGCU	885
AD-288938.1	csascaugUfaUfUfAfuagaaugcuuL96	286	asAfsgcau(Tgn)cuauaaUfaCfaugugsasa	586	UUCACAUGUAUUAUAGAAUGCUU	886
AD-288941.1	gsusauuaUfaGfAfAfugcuuuugcaL96	287	usGfscaaa(Agn)gcauucUfaUfaauacsasu	587	AUGUAUUAUAGAAUGCUUUUGCA	887
AD-288943.1	usasuagaAfuGfCfUfuuugcauggaL96	288	usCfscaug(Cgn)aaaagcAfuUfcuauasasu	588	AUUAUAGAAUGCUUUUGCAUGGA	888
AD-288945.1	asgsaaugCfuUfUfUfgcauggacuaL96	289	usAfsgucc(Agn)ugcaaaAfgCfauucusasu	589	AUAGAAUGCUUUUGCAUGGACUA	889
AD-288946.1	gsasaugcUfuUfUfGfcauggacuauL96	290	asUfsaguc(Cgn)augcaaAfaGfcauucsusa	590	UAGAAUGCUUUUGCAUGGACUAU	890
AD-288947.1	usgscuuuUfgCfAfUfggacuauccuL96	291	asGfsgaua(Ggn)uccaugCfaAfaagcasusu	591	AAUGCUUUUGCAUGGACUAUCCU	891
AD-288948.1	csusuuugCfaUfGfGfacuauccucuL96	292	asGfsagga(Tgn)aguccaUfgCfaaaagscsa	592	UGCUUUUGCAUGGACUAUCCUCU	892
AD-288950.1	ususgcauGfgAfCfUfauccucuuguL96	293	asCfsaaga(Ggn)gauaguCfcAfugcaasasa	593	UUUUGCAUGGACUAUCCUCUUGU	893
AD-288951.1	usgscaugGfaCfUfAfuccucuuguuL96	294	asAfscaag(Agn)ggauagUfcCfaugcasasa	594	UUUGCAUGGACUAUCCUCUUGUU	894
AD-288952.1	gscsauggAfcUfAfUfccucuuguuuL96	295	asAfsacaa(Ggn)aggauaGfuCfcaugcsasa	595	UUGCAUGGACUAUCCUCUUGUUU	895
AD-288956.1	gsgsacuaUfcCfUfCfuuguuuuuauL96	296	asUfsaaaa(Agn)caagagGfaUfaguccsasu	596	AUGGACUAUCCUCUUGUUUUUAU	896
AD-288957.1	gsascuauCfcUfCfUfuguuuuuauuL96	297	asAfsuaaa(Agn)acaagaGfgAfuagucscsa	597	UGGACUAUCCUCUUGUUUUUAUU	897

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA target sequence 5' to 3'	SEQ ID NO:
AD-288959.1	csusauccUfcUfUfGfuuuuuauuaaL96	298	usUfsaaua(Agn)aaacaaGfaGfgauagsusc	598	GACUAUCCUCUUGUUUUUAUUAA	898
AD-288981.1	cscscacuAfcAfUfCfaagacuaauuL96	299	asAfsuuag(Tgn)cuugauGfuAfgugggsasg	599	CUCCCACUACAUCAAGACUAAUC	899
AD-288982.1	ascsuacaUfcAfAfGfacuaaucuuuL96	300	asAfsagau(Tgn)agucuuGfaUfguagusgsg	600	CCACUACAUCAAGACUAAUCUUG	900
AD-288996.1	asusgcuuUfuGfCfAfuggacuaucuL96	301	asGfsauag(Tgn)ccaugcAfaAfagcaususc	601	GAAUGCUUUUGCAUGGACUAUCC	901

* Target: HSD17B13

Table 8. HSD17B13 ELF7 GNA7 Unmodified Sequence*

Duplex Name	Sense sequence 5' to 3'	SEQ ID NO:	Position in NM_178135.4	Antisense sequence 5' to 3'	SEQ ID NO:	Position in NM_178135.4
AD-286958.1	AGUACCUCCUCCCUAGGACUA	902	5-25	UAGUCCTAGGGAGGAGGUACUGU	1202	3-25
AD-287001.1	UCCUUCUGCUUCUGAUCACCA	903	85-105	UGGUGATCAGAAGCAGAAGGAUU	1203	83-105
AD-287012.1	CAUCAUCUACUCCUACUUGGA	904	104-124	UCCAAGTAGGAGUAGAUGAUGGU	1204	102-124
AD-287015.1	CUACUCCUACUUGGAGUCGUU	906	110-130	AACGACTCCAAGUAGGAGUAGAU	1206	108-130
AD-287017.1	GUACCUCCUCCCUAGGACUAU	907	6-26	AUAGUCCUAGGGAGGAGGUACUG	1207	4-26
AD-287026.1	ACACAAGGACUGAACCAGAAU	908	25-45	AUUCUGGUUCAGUCCUUGUGUAG	1208	23-45
AD-287059.1	ACCAUCAUCUACUCCUACUUU	909	102-122	AAAGUAGGAGUAGAUGAUGGUGA	1209	100-122
AD-287060.1	CCAUCAUCUACUCCUACUUGU	910	103-123	ACAAGUAGGAGUAGAUGAUGGUG	1210	101-123
AD-287061.1	AUCAUCUACUCCUACUUGGAU	911	105-125	AUCCAAGUAGGAGUAGAUGAUGG	1211	103-125
AD-287062.1	CAUCUACUCCUACUUGGAGUU	912	107-127	AACUCCAAGUAGGAGUAGAUGAU	1212	105-127
AD-287064.1	UACUCCUACUUGGAGUCGUUU	913	111-131	AAACGACUCCAAGUAGGAGUAGA	1213	109-131
AD-287065.1	ACUCCUACUUGGAGUCGUUGU	914	112-132	ACAACGACUCCAAGUAGGAGUAG	1214	110-132
AD-287126.1	UCCUACUUGGAGUCGUUGGUU	916	114-134	AACCAACGACUCCAAGUAGGAGU	1216	112-134
AD-287203.1	GCAGCUGAGUGCCGAAAACUA	920	294-314	UAGUUUTCGGCACUCAGCUGCAG	1220	292-314
AD-287227.1	CUGUGGGAUAUUAAUAAGCGU	923	258-278	ACGCUUAUUAAUAUCCCACAGAA	1223	256-278
AD-287246.1	CUGCAGCUGAGUGCCGAAAAU	924	292-312	AUUUUCGGCACUCAGCUGCAGUU	1224	290-312
AD-287247.1	CAGCUGAGUGCCGAAAACUAU	925	295-315	AUAGUUTUCGGCACUCAGCUGCA	1225	293-315
AD-287248.1	AGCUGAGUGCCGAAAACUAGU	926	296-316	ACUAGUTUUCGGCACUCAGCUGC	1226	294-316
AD-287249.1	GCUGAGUGCCGAAAACUAGGU	927	297-317	ACCUAGTUUUCGGCACUCAGCUG	1227	295-317
AD-287250.1	CUGAGUGCCGAAAACUAGGCU	928	298-318	AGCCUAGUUUUCGGCACUCAGCU	1228	296-318
AD-287251.1	GAGUGCCGAAAACUAGGCGUU	929	300-320	AACGCCTAGUUUUCGGCACUCAG	1229	298-320
AD-287252.1	GUGCCGAAAACUAGGCGUCAU	930	302-322	AUGACGCCUAGUUUUCGGCACUC	1230	300-322
AD-287253.1	GCCGAAAACUAGGCGUCACUU	931	304-324	AAGUGACGCCUAGUUUUCGGCAC	1231	302-324
AD-287254.1	CCGAAAACUAGGCGUCACUGU	932	305-325	ACAGUGACGCCUAGUUUUCGGCA	1232	303-325
AD-287258.1	ACUAGGCGUCACUGCGCAUGU	933	311-331	ACAUGCGCAGUGACGCCUAGUUU	1233	309-331
AD-287288.1	CUAUCGCUCUCUAAAUCAGGU	935	365-385	ACCUGATUUAGAGAGCGAUAGAU	1235	363-385
AD-287290.1	UCGCUCUCUAAAUCAGGUGAA	937	368-388	UUCACCTGAUUUAGAGAGCGAUA	1237	366-388
AD-287293.1	UCUCUAAAUCAGGUGAAGAAA	938	372-392	UUUCUUCACCUGAUUUAGAGAGC	1238	370-392
AD-287316.1	GUGGUGAAUAAUGCUGGGACA	939	414-434	UGUCCCAGCAUUAUUCACCACGA	1239	412-434
AD-287320.1	GAAUAAUGCUGGGACAGUAUA	940	419-439	UAUACUGUCCCAGCAUUAUUCAC	1240	417-439
AD-287321.1	AAUAAUGCUGGGACAGUAUAU	941	420-440	AUAUACTGUCCCAGCAUUAUUCA	1241	418-440

Duplex Name	Sense sequence 5' to 3'	SEQ ID NO:	Position in NM_178135.4	Antisense sequence 5' to 3'	SEQ ID NO:	Position in NM_178135.4
AD-287324.1	GGGACAGUAUAUCCAGCCGAU	942	429-449	AUCGGCTGGAUAUACUGUCCCAG	1242	427-449
AD-287325.1	GACAGUAUAUCCAGCCGAUCU	943	431-451	AGAUCGGCUGGAUAUACUGUCCC	1243	429-451
AD-287326.1	ACAGUAUAUCCAGCCGAUCUU	944	432-452	AAGAUCGGCUGGAUAUACUGUCC	1244	430-452
AD-287327.1	AGUAUAUCCAGCCGAUCUUCU	945	434-454	AGAAGATCGGCUGGAUAUACUGU	1245	432-454
AD-287344.1	AUCUAUCGCUCUCUAAAUCAU	946	363-383	AUGAUUTAGAGAGCGAUAGAUCU	1246	361-383
AD-287346.1	UAUCGCUCUCUAAAUCAGGUU	947	366-386	AACCUGAUUUAGAGAGCGAUAGA	1247	364-386
AD-287347.1	CGCUCUCUAAAUCAGGUGAAU	948	369-389	AUUCACCUGAUUUAGAGAGCGAU	1248	367-389
AD-287366.1	CGUGGUGAAUAAUGCUGGGAU	949	413-433	AUCCCAGCAUUAUUCACCACGAU	1249	411-433
AD-287367.1	UGGUGAAUAAUGCUGGGACAU	950	415-435	AUGUCCCAGCAUUAUUCACCACG	1250	413-435
AD-287370.1	AUGCUGGGACAGUAUAUCCAU	951	424-444	AUGGAUAUACUGUCCCAGCAUUA	1251	422-444
AD-287371.1	UGCUGGGACAGUAUAUCCAGU	952	425-445	ACUGGATAUACUGUCCCAGCAUU	1252	423-445
AD-287372.1	GCUGGGACAGUAUAUCCAGCU	953	426-446	AGCUGGAUAUACUGUCCCAGCAU	1253	424-446
AD-287373.1	CUGGGACAGUAUAUCCAGCCU	954	427-447	AGGCUGGAUAUACUGUCCCAGCA	1254	425-447
AD-287374.1	GGACAGUAUAUCCAGCCGAUU	955	430-450	AAUCGGCUGGAUAUACUGUCCCA	1255	428-450
AD-287375.1	CAGUAUAUCCAGCCGAUCUUU	956	433-453	AAAGAUCGGCUGGAUAUACUGUC	1256	431-453
AD-287391.1	CCAAGGAUGAAGAGAUUACCA	957	460-480	UGGUAATCUCUUCAUCCUUGGUG	1257	458-480
AD-287406.1	UUUGAGGUCAACAUCCUAGGA	959	486-506	UCCUAGGAUGUUGACCUCAAAUG	1259	484-506
AD-287407.1	UGAGGUCAACAUCCUAGGACA	960	488-508	UGUCCUAGGAUGUUGACCUCAAA	1260	486-508
AD-287408.1	GAGGUCAACAUCCUAGGACAU	961	489-509	AUGUCCTAGGAUGUUGACCUCAA	1261	487-509
AD-287411.1	GUCAACAUCCUAGGACAUUUU	963	492-512	AAAAUGTCCUAGGAUGUUGACCU	1263	490-512
AD-287413.1	ACAUCCUAGGACAUUUUUGGA	964	496-516	UCCAAAAAUGUCCUAGGAUGUUG	1264	494-516
AD-287414.1	CAUCCUAGGACAUUUUUGGAU	965	497-517	AUCCAAAAAUGUCCUAGGAUGUU	1265	495-517
AD-287418.1	AGGACAUUUUUGGAUCACAAA	967	503-523	UUUGUGAUCCAAAAAUGUCCUAG	1267	501-523
AD-287419.1	GGACAUUUUUGGAUCACAAAA	968	504-524	UUUUGUGAUCCAAAAAUGUCCUA	1268	502-524
AD-287421.1	UUUUUGGAUCACAAAAGCACU	969	509-529	AGUGCUTUUGUGAUCCAAAAAUG	1269	507-529
AD-287424.1	UGGAUCACAAAAGCACUUCUU	970	513-533	AAGAAGTGCUUUUGUGAUCCAAA	1270	511-533
AD-287427.1	CAAAAGCACUUCUUCCAUCGA	971	520-540	UCGAUGGAAGAAGUGCUUUUGUG	1271	518-540
AD-287428.1	AAAAGCACUUCUUCCAUCGAU	972	521-541	AUCGAUGGAAGAAGUGCUUUUGU	1272	519-541
AD-287453.1	ACCAAGGAUGAAGAGAUUACU	976	459-479	AGUAAUCUCUUCAUCCUUGGUGC	1276	457-479
AD-287462.1	AGACAUUUGAGGUCAACAUCU	977	481-501	AGAUGUTGACCUCAAAUGUCUUG	1277	479-501
AD-287463.1	CAUUUGAGGUCAACAUCCUAU	978	484-504	AUAGGATGUUGACCUCAAAUGUC	1278	482-504
AD-287464.1	AUUUGAGGUCAACAUCCUAGU	979	485-505	ACUAGGAUGUUGACCUCAAAUGU	1279	483-505
AD-287465.1	UUGAGGUCAACAUCCUAGGAU	980	487-507	AUCCUAGGAUGUUGACCUCAAAU	1280	485-507

Duplex Name	Sense sequence 5' to 3'	SEQ ID NO:	Position in NM_178135.4	Antisense sequence 5' to 3'	SEQ ID NO:	Position in NM_178135.4
AD-287466.1	CAACAUCCUAGGACAUUUUUG	981	494-514	CAAAAATGUCCUAGGAUGUUGAC	1281	492-514
AD-287467.1	AACAUCCUAGGACAUUUUUGU	982	495-515	ACAAAAAUGUCCUAGGAUGUUGA	1282	493-515
AD-287468.1	AUCCUAGGACAUUUUUGGAUU	983	498-518	AAUCCAAAAAUGUCCUAGGAUGU	1283	496-518
AD-287469.1	CCUAGGACAUUUUUGGAUCAU	984	500-520	AUGAUCCAAAAAUGUCCUAGGAU	1284	498-520
AD-287470.1	GACAUUUUUGGAUCACAAAAU	985	505-525	AUUUUGTGAUCCAAAAAUGUCCU	1285	503-525
AD-287474.1	GGAUCACAAAAGCACUUCUUU	986	514-534	AAAGAAGUGCUUUUGUGAUCCAA	1286	512-534
AD-287476.1	CACAAAAGCACUUCUUCCAUU	987	518-538	AAUGGAAGAAGUGCUUUUGUGAU	1287	516-538
AD-287477.1	ACAAAAGCACUUCUUCCAUCU	988	519-539	AGAUGGAAGAAGUGCUUUUGUGA	1288	517-539
AD-287478.1	AAAGCACUUCUUCCAUCGAUU	989	522-542	AAUCGATGGAAGAAGUGCUUUUG	1289	520-542
AD-287479.1	GCACUUCUUCCAUCGAUGAUU	990	525-545	AAUCAUCGAUGGAAGAAGUGCUU	1290	523-545
AD-287491.1	AGAAAUCAUGGCCACAUCGUU	991	549-569	AACGAUGUGGCCAUGAUUUCUCU	1291	547-569
AD-287492.1	AAAUCAUGGCCACAUCGUCAU	992	551-571	AUGACGAUGUGGCCAUGAUUUCU	1292	549-571
AD-287517.1	UUCCUUACCUCAUCCCAUAUU	993	601-621	AAUAUGGGAUGAGGUAAGGAAUC	1293	599-621
AD-287520.1	ACCUCAUCCCAUAUUGUUCCA	994	607-627	UGGAACAAUAUGGGAUGAGGUAA	1294	605-627
AD-287521.1	UCAUCCCAUAUUGUUCCAGCA	995	610-630	UGCUGGAACAAUAUGGGAUGAGG	1295	608-630
AD-287524.1	UCCCAUAUUGUUCCAGCAAAU	997	613-633	AUUUGCTGGAACAAUAUGGGAUG	1297	611-633
AD-287525.1	CCCAUAUUGUUCCAGCAAAUU	998	614-634	AAUUUGCUGGAACAAUAUGGGAU	1298	612-634
AD-287537.1	UGUUGGCUUUCACAGAGGUCU	999	641-661	AGACCUCUGUGAAAGCCAACAGC	1299	639-661
AD-287539.1	GGCUUUCACAGAGGUCUGACA	1000	645-665	UGUCAGACCUCUGUGAAAGCCAA	1300	643-665
AD-287543.1	CACAGAGGUCUGACAUCAGAA	1002	651-671	UUCUGATGUCAGACCUCUGUGAA	1302	649-671
AD-287546.1	AGGUCUGACAUCAGAACUUCA	1003	656-676	UGAAGUTCUGAUGUCAGACCUCU	1303	654-676
AD-287568.1	UCCUUACCUCAUCCCAUAUUU	1004	602-622	AAAUAUGGGAUGAGGUAAGGAAU	1304	600-622
AD-287591.1	UUCACAGAGGUCUGACAUCAU	1005	649-669	AUGAUGTCAGACCUCUGUGAAAG	1305	647-669
AD-287610.1	UUGGGAAAAACUGGUAUCAAA	1006	681-701	UUUGAUACCAGUUUUUCCCAAGG	1306	679-701
AD-287616.1	UGGUAUCAAAACCUCAUGUCU	1008	692-712	AGACAUGAGGUUUUGAUACCAGU	1308	690-712
AD-287627.1	CUCUGCCCAGUUUUUGUGAAU	1009	711-731	AUUCACAAAAACUGGGCAGAGAC	1309	709-731
AD-287632.1	UUUUUGUGAAUACUGGGUUCA	1010	721-741	UGAACCCAGUAUUCACAAAAACU	1310	719-741
AD-287636.1	UGAAUACUGGGUUCACCAAAA	1013	727-747	UUUUGGTGAACCCAGUAUUCACA	1313	725-747
AD-287637.1	GAAUACUGGGUUCACCAAAAA	1014	728-748	UUUUUGGUGAACCCAGUAUUCAC	1314	726-748
AD-287647.1	AAAAAUCCAAGCACAAGAUUA	1016	744-764	UAAUCUTGUGCUUGGAUUUUUGG	1316	742-764
AD-287648.1	AAAAUCCAAGCACAAGAUUAU	1017	745-765	AUAAUCTUGUGCUUGGAUUUUUG	1317	743-765
AD-287654.1	AAGAUUAUGGCCUGUAUUGGA	1021	758-778	UCCAAUACAGGCCAUAAUCUUGU	1321	756-778
AD-287655.1	GAUUAUGGCCUGUAUUGGAGA	1022	760-780	UCUCCAAUACAGGCCAUAAUCUU	1322	758-780

Duplex Name	Sense sequence 5' to 3'	SEQ ID NO:	Position in NM_178135.4	Antisense sequence 5' to 3'	SEQ ID NO:	Position in NM_178135.4
AD-287659.1	GCCUGUAUUGGAGACAGAUGA	1025	767-787	UCAUCUGUCUCCAAUACAGGCCA	1325	765-787
AD-287679.1	CUGGUAUCAAAACCUCAUGUU	1026	691-711	AACAUGAGGUUUUGAUACCAGUU	1326	689-711
AD-287680.1	GGUAUCAAAACCUCAUGUCUU	1027	693-713	AAGACATGAGGUUUUGAUACCAG	1327	691-713
AD-287683.1	UCAAAACCUCAUGUCUCUGCU	1028	697-717	AGCAGAGACAUGAGGUUUUGAUA	1328	695-717
AD-287690.1	CCCAGUUUUUGUGAAUACUGU	1029	716-736	ACAGUATUCACAAAAACUGGGCA	1329	714-736
AD-287693.1	UUUUGUGAAUACUGGGUUCAU	1030	722-742	AUGAACCCAGUAUUCACAAAAAC	1330	720-742
AD-287694.1	UUUGUGAAUACUGGGUUCACU	1031	723-743	AGUGAACCCAGUAUUCACAAAAA	1331	721-743
AD-287695.1	AUACUGGGUUCACCAAAAAUU	1032	730-750	AAUUUUTGGUGAACCCAGUAUUC	1332	728-750
AD-287696.1	UACUGGGUUCACCAAAAAUCU	1033	731-751	AGAUUUTUGGUGAACCCAGUAUU	1333	729-751
AD-287700.1	CACCAAAAAUCCAAGCACAAU	1034	740-760	AUUGUGCUUGGAUUUUUGGUGAA	1334	738-760
AD-287701.1	AAAUCCAAGCACAAGAUUAUU	1035	746-766	AAUAAUCUUGUGCUUGGAUUUUU	1335	744-766
AD-287702.1	AAUCCAAGCACAAGAUUAUGU	1036	747-767	ACAUAATCUUGUGCUUGGAUUUU	1336	745-767
AD-287703.1	AUCCAAGCACAAGAUUAUGGU	1037	748-768	ACCAUAAUCUUGUGCUUGGAUUU	1337	746-768
AD-287704.1	UCCAAGCACAAGAUUAUGGCU	1038	749-769	AGCCAUAAUCUUGUGCUUGGAUU	1338	747-769
AD-287706.1	ACAAGAUUAUGGCCUGUAUUU	1039	756-776	AAAUACAGGCCAUAAUCUUGUGC	1339	754-776
AD-287707.1	CAAGAUUAUGGCCUGUAUUGU	1040	757-777	ACAAUACAGGCCAUAAUCUUGUG	1340	755-777
AD-287709.1	AUUAUGGCCUGUAUUGGAGAU	1041	761-781	AUCUCCAAUACAGGCCAUAAUCU	1341	759-781
AD-287711.1	GGCCUGUAUUGGAGACAGAUU	1042	766-786	AAUCUGTCUCCAAUACAGGCCAU	1342	764-786
AD-287724.1	GUAAGAAGUCUGAUAGAUGGA	1043	792-812	UCCAUCTAUCAGACUUCUUACGA	1343	790-812
AD-287726.1	AAGAAGUCUGAUAGAUGGAAU	1045	794-814	AUUCCATCUAUCAGACUUCUUAC	1345	792-814
AD-287727.1	AGAAGUCUGAUAGAUGGAAUA	1046	795-815	UAUUCCAUCUAUCAGACUUCUUA	1346	793-815
AD-287735.1	AGAUGGAAUACUUACCAAUAA	1048	806-826	UUAUUGGUAAGUAUUCCAUCUAU	1348	804-826
AD-287736.1	AUGGAAUACUUACCAAUAAGA	1049	808-828	UCUUAUTGGUAAGUAUUCCAUCU	1349	806-828
AD-287737.1	UGGAAUACUUACCAAUAAGAA	1050	809-829	UUCUUATUGGUAAGUAUUCCAUC	1350	807-829
AD-287738.1	GGAAUACUUACCAAUAAGAAA	1051	810-830	UUUCUUAUUGGUAAGUAUUCCAU	1351	808-830
AD-287739.1	GAAUACUUACCAAUAAGAAAA	1052	811-831	UUUUCUTAUUGGUAAGUAUUCCA	1352	809-831
AD-287740.1	AAUACUUACCAAUAAGAAAAU	1053	812-832	AUUUUCTUAUUGGUAAGUAUUCC	1353	810-832
AD-287778.1	UUUCUUCCUGAACGCGCCUCA	1054	879-899	UGAGGCGCGUUCAGGAAGAAACU	1354	877-899
AD-287798.1	AAAUCGUAUGCAGAAUAUUCA	1057	908-928	UGAAUATUCUGCAUACGAUUUAA	1357	906-928
AD-287800.1	AUCGUAUGCAGAAUAUUCAAU	1058	910-930	AUUGAATAUUCUGCAUACGAUUU	1358	908-930
AD-287801.1	UCGUAUGCAGAAUAUUCAAUU	1059	911-931	AAUUGAAUAUUCUGCAUACGAUU	1359	909-931
AD-287802.1	CGUAUGCAGAAUAUUCAAUUU	1060	912-932	AAAUUGAAUAUUCUGCAUACGAU	1360	910-932
AD-287804.1	AUGCAGAAUAUUCAAUUUGAA	1061	915-935	UUCAAATUGAAUAUUCUGCAUAC	1361	913-935

Duplex Name	Sense sequence 5' to 3'	SEQ ID NO:	Position in NM_178135.4	Antisense sequence 5' to 3'	SEQ ID NO:	Position in NM_178135.4
AD-287810.1	GAAGUCUGAUAGAUGGAAUAU	1062	796-816	AUAUUCCAUCUAUCAGACUUCUU	1362	794-816
AD-287811.1	UCUGAUAGAUGGAAUACUUAU	1063	800-820	AUAAGUAUUCCAUCUAUCAGACU	1363	798-820
AD-287813.1	GAUGGAAUACUUACCAAUAAU	1064	807-827	AUUAUUGGUAAGUAUUCCAUCUA	1364	805-827
AD-287837.1	ACAGAAGUUUCUUCCUGAACU	1065	872-892	AGUUCAGGAAGAAACUUCUGUAG	1365	870-892
AD-287839.1	AGAAGUUUCUUCCUGAACGCU	1066	874-894	AGCGUUCAGGAAGAAACUUCUGU	1366	872-894
AD-287841.1	AAGUUUCUUCCUGAACGCGCU	1067	876-896	AGCGCGTUCAGGAAGAAACUUCU	1367	874-896
AD-287842.1	GUUUCUUCCUGAACGCGCCUU	1068	878-898	AAGGCGCGUUCAGGAAGAAACUU	1368	876-898
AD-287844.1	UCUUCCUGAACGCGCCUCAGU	1069	881-901	ACUGAGGCGCGUUCAGGAAGAAA	1369	879-901
AD-287854.1	GCAGAAUAUUCAAUUUGAAGU	1070	917-937	ACUUCAAAUUGAAUAUUCUGCAU	1370	915-937
AD-287856.1	AAUAUUCAAUUUGAAGCAGUU	1071	921-941	AACUGCTUCAAAUUGAAUAUUCU	1371	919-941
AD-287893.1	GAUGUAUGCAUGAUAAUGAUA	1073	989-1009	UAUCAUTAUCAUGCAUACAUCUC	1373	987-1009
AD-287917.1	CAAUGCUGCAAAGCUUUAUUU	1074	1025-1045	AAAUAAAGCUUUGCAGCAUUGAU	1374	1023-1045
AD-287924.1	AAAGCUUUAUUUCACAUUUUU	1075	1034-1054	AAAAAUGUGAAAUAAAGCUUUGC	1375	1032-1054
AD-287934.1	AAUUUGAAGCAGUGGUUGGCU	1076	928-948	AGCCAACCACUGCUUCAAAUUGA	1376	926-948
AD-287969.1	AAUGCUGCAAAGCUUUAUUUC	1077	1026-1046	GAAAUAAAGCUUUGCAGCAUUGA	1377	1024-1046
AD-287970.1	UGCUGCAAAGCUUUAUUUCAU	1078	1028-1048	AUGAAATAAAGCUUUGCAGCAUU	1378	1026-1048
AD-288005.1	AGAUUAAUUACCUGUCUUCCU	1080	1111-1131	AGGAAGACAGGUAAUUAAUCUUG	1380	1109-1131
AD-288006.1	AUUAAUUACCUGUCUUCCUGU	1081	1113-1133	ACAGGAAGACAGGUAAUUAAUCU	1381	1111-1133
AD-288008.1	UAAUUACCUGUCUUCCUGUUU	1082	1115-1135	AAACAGGAAGACAGGUAAUUAAU	1382	1113-1135
AD-288010.1	UACCUGUCUUCCUGUUUCUCA	1083	1119-1139	UGAGAAACAGGAAGACAGGUAAU	1383	1117-1139
AD-288011.1	ACCUGUCUUCCUGUUUCUCAA	1084	1120-1140	UUGAGAAACAGGAAGACAGGUAA	1384	1118-1140
AD-288015.1	UCUUCCUGUUUCUCAAGAAUA	1085	1125-1145	UAUUCUTGAGAAACAGGAAGACA	1385	1123-1145
AD-288046.1	UUUUCCUUUCAUGCCUCUUAA	1086	1171-1191	UUAAGAGGCAUGAAAGGAAAAAC	1386	1169-1191
AD-288049.1	UCCUUUCAUGCCUCUUAAAAA	1087	1174-1194	UUUUUAAGAGGCAUGAAAGGAAA	1387	1172-1194
AD-288050.1	CUUUCAUGCCUCUUAAAAACU	1088	1176-1196	AGUUUUTAAGAGGCAUGAAAGGA	1388	1174-1196
AD-288076.1	AAAACAUUGGUUUGGCACUAU	1089	1073-1093	AUAGUGCCAAACCAAUGUUUUUA	1389	1071-1093
AD-288092.1	GAUUAAUUACCUGUCUUCCUU	1090	1112-1132	AAGGAAGACAGGUAAUUAAUCUU	1390	1110-1132
AD-288094.1	UUACCUGUCUUCCUGUUUCUU	1091	1118-1138	AAGAAACAGGAAGACAGGUAAUU	1391	1116-1138
AD-288095.1	CCUGUCUUCCUGUUUCUCAAU	1092	1121-1141	AUUGAGAAACAGGAAGACAGGUA	1392	1119-1141
AD-288108.1	GGUCUGUUUUUCCUUUCAUGU	1093	1164-1184	ACAUGAAAGGAAAAACAGACCUA	1393	1162-1184
AD-288109.1	GUCUGUUUUUCCUUUCAUGCU	1094	1165-1185	AGCAUGAAAGGAAAAACAGACCU	1394	1163-1185
AD-288173.1	UUAUUUACACAGGGAAGGUUU	1095	1302-1322	AAACCUTCCCUGUGUAAAUAAGU	1395	1300-1322
AD-288174.1	UAUUUACACAGGGAAGGUUUA	1096	1303-1323	UAAACCTUCCCUGUGUAAAUAAG	1396	1301-1323

Duplex Name	Sense sequence 5' to 3'	SEQ ID NO:	Position in NM_178135.4	Antisense sequence 5' to 3'	SEQ ID NO:	Position in NM_178135.4
AD-288180.1	GGGAAGGUUUAAGACUGUUCA	1099	1313-1333	UGAACAGUCUUAAACCUUCCCUG	1399	1311-1333
AD-288181.1	GGAAGGUUUAAGACUGUUCAA	1100	1314-1334	UUGAACAGUCUUAAACCUUCCCU	1400	1312-1334
AD-288184.1	UUUAAGACUGUUCAAGUAGCA	1102	1320-1340	UGCUACTUGAACAGUCUUAAACC	1402	1318-1340
AD-288187.1	GACUGUUCAAGUAGCAUUCCA	1104	1325-1345	UGGAAUGCUACUUGAACAGUCUU	1404	1323-1345
AD-288188.1	ACUGUUCAAGUAGCAUUCCAA	1105	1326-1346	UUGGAATGCUACUUGAACAGUCU	1405	1324-1346
AD-288192.1	CAAGUAGCAUUCCAAUCUGUA	1108	1332-1352	UACAGATUGGAAUGCUACUUGAA	1408	1330-1352
AD-288227.1	AACUUAUUUACACAGGGAAGU	1111	1299-1319	ACUUCCCUGUGUAAAUAAGUUCU	1411	1297-1319
AD-288229.1	UACACAGGGAAGGUUUAAGAU	1112	1307-1327	AUCUUAAACCUUCCCUGUGUAAA	1412	1305-1327
AD-288230.1	CACAGGGAAGGUUUAAGACUU	1113	1309-1329	AAGUCUTAAACCUUCCCUGUGUA	1413	1307-1329
AD-288231.1	AGGGAAGGUUUAAGACUGUUU	1114	1312-1332	AAACAGTCUUAAACCUUCCCUGU	1414	1310-1332
AD-288232.1	GAAGGUUUAAGACUGUUCAAU	1115	1315-1335	AUUGAACAGUCUUAAACCUUCCC	1415	1313-1335
AD-288233.1	GGUUUAAGACUGUUCAAGUAU	1116	1318-1338	AUACUUGAACAGUCUUAAACCUU	1416	1316-1338
AD-288235.1	AAGACUGUUCAAGUAGCAUUU	1117	1323-1343	AAAUGCTACUUGAACAGUCUUAA	1417	1321-1343
AD-288236.1	AGACUGUUCAAGUAGCAUUCU	1118	1324-1344	AGAAUGCUACUUGAACAGUCUUA	1418	1322-1344
AD-288237.1	UGUUCAAGUAGCAUUCCAAUU	1119	1328-1348	AAUUGGAAUGCUACUUGAACAGU	1419	1326-1348
AD-288238.1	UUCAAGUAGCAUUCCAAUCUU	1120	1330-1350	AAGAUUGGAAUGCUACUUGAACA	1420	1328-1350
AD-288290.1	GCAGCUUUAUCUCAACCUGGA	1121	1419-1439	UCCAGGTUGAGAUAAAGCUGCCU	1421	1417-1439
AD-288316.1	AGCAUUUGAAAGAUUUCCCUA	1122	1455-1475	UAGGGAAAUCUUUCAAAUGCUGA	1422	1453-1475
AD-288318.1	UGAAAGAUUUCCCUAGCCUCU	1123	1461-1481	AGAGGCTAGGGAAAUCUUUCAAA	1423	1459-1481
AD-288324.1	UUCCCUAGCCUCUUCCUUUUU	1125	1469-1489	AAAAAGGAAGAGGCUAGGGAAAU	1425	1467-1489
AD-288337.1	AAGAACACAGAAUGAGUGCAU	1126	1374-1394	AUGCACTCAUUCUGUGUUCUUGU	1426	1372-1394
AD-288338.1	GAACACAGAAUGAGUGCACAU	1127	1376-1396	AUGUGCACUCAUUCUGUGUUCUU	1427	1374-1396
AD-288339.1	AACACAGAAUGAGUGCACAGU	1128	1377-1397	ACUGUGCACUCAUUCUGUGUUCU	1428	1375-1397
AD-288340.1	CAGAAUGAGUGCACAGCUAAU	1129	1381-1401	AUUAGCTGUGCACUCAUUCUGUG	1429	1379-1401
AD-288341.1	GAAUGAGUGCACAGCUAAGAU	1130	1383-1403	AUCUUAGCUGUGCACUCAUUCUG	1430	1381-1403
AD-288366.1	UUCAGCAUUUGAAAGAUUUCU	1131	1452-1472	AGAAAUCUUUCAAAUGCUGAAUC	1431	1450-1472
AD-288369.1	CAUUUGAAAGAUUUCCCUAGU	1132	1457-1477	ACUAGGGAAAUCUUUCAAAUGCU	1432	1455-1477
AD-288370.1	AUUUGAAAGAUUUCCCUAGCU	1133	1458-1478	AGCUAGGGAAAUCUUUCAAAUGC	1433	1456-1478
AD-288394.1	GUGCAACUCUAUUCUGGACUU	1136	1505-1525	AAGUCCAGAAUAGAGUUGCACCG	1436	1503-1525
AD-288396.1	GCAACUCUAUUCUGGACUUUA	1138	1507-1527	UAAAGUCCAGAAUAGAGUUGCAC	1438	1505-1527
AD-288397.1	CAACUCUAUUCUGGACUUUAU	1139	1508-1528	AUAAAGTCCAGAAUAGAGUUGCA	1439	1506-1528
AD-288427.1	AGUCCACCAAAAGUGGACCCU	1142	1559-1579	AGGGUCCACUUUUGGUGGACUUC	1442	1557-1579
AD-288466.1	AAACGGUGCAACUCUAUUCUU	1148	1500-1520	AAGAAUAGAGUUGCACCGUUUUG	1448	1498-1520

Duplex Name	Sense sequence 5' to 3'	SEQ ID NO:	Position in NM_178135.4	Antisense sequence 5' to 3'	SEQ ID NO:	Position in NM_178135.4
AD-288467.1	AACGGUGCAACUCUAUUCUGU	1149	1501-1521	ACAGAATAGAGUUGCACCGUUUU	1449	1499-1521
AD-288470.1	UAUUCUGGACUUUAUUACUUU	1150	1514-1534	AAAGUAAUAAAGUCCAGAAUAGA	1450	1512-1534
AD-288491.1	AAAGUGGACCCUCUAUAUUUC	1151	1568-1588	GAAAUATAGAGGGUCCACUUUUG	1451	1566-1588
AD-288492.1	AAGUGGACCCUCUAUAUUUCU	1152	1569-1589	AGAAAUAUAGAGGGUCCACUUUU	1452	1567-1589
AD-288561.1	AUGUUUAGACAAUUUUAGGCU	1153	1724-1744	AGCCUAAAAUUGUCUAAACAUCU	1453	1722-1744
AD-288562.1	GUUUAGACAAUUUUAGGCUCA	1154	1726-1746	UGAGCCTAAAAUUGUCUAAACAU	1454	1724-1746
AD-288567.1	GACAAUUUUAGGCUCAAAAAU	1159	1731-1751	AUUUUUGAGCCUAAAAUUGUCUA	1459	1729-1751
AD-288573.1	UAGGCUCAAAAAUUAAAGCUA	1161	1739-1759	UAGCUUTAAUUUUUGAGCCUAAA	1461	1737-1759
AD-288574.1	AGGCUCAAAAAUUAAAGCUAA	1162	1740-1760	UUAGCUTUAAUUUUUGAGCCUAA	1462	1738-1760
AD-288575.1	GCUCAAAAAUUAAAGCUAACA	1163	1742-1762	UGUUAGCUUUAAUUUUUGAGCCU	1463	1740-1762
AD-288576.1	UCAAAAAUUAAAGCUAACACA	1164	1744-1764	UGUGUUAGCUUUAAUUUUUGAGC	1464	1742-1764
AD-288613.1	UUCAUAUAUCCUUGGUCCCAU	1165	1701-1721	AUGGGACCAAGGAUAUAUGAAAG	1465	1699-1721
AD-288620.1	GAUGUUUAGACAAUUUUAGGU	1166	1723-1743	ACCUAAAAUUGUCUAAACAUCUC	1466	1721-1743
AD-288624.1	GGCUCAAAAAUUAAAGCUAAU	1167	1741-1761	AUUAGCTUUAAUUUUUGAGCCUA	1467	1739-1761
AD-288625.1	CUCAAAAAUUAAAGCUAACAU	1168	1743-1763	AUGUUAGCUUUAAUUUUUGAGCC	1468	1741-1763
AD-288626.1	CAAAAAUUAAAGCUAACACAU	1169	1745-1765	AUGUGUTAGCUUUAAUUUUUGAG	1469	1743-1765
AD-288628.1	AAAUUAAAGCUAACACAGGAA	1170	1748-1768	UUCCUGTGUUAGCUUUAAUUUUU	1470	1746-1768
AD-288634.1	UAACACAGGAAAAGGAACUGU	1171	1758-1778	ACAGUUCCUUUUCCUGUGUUAGC	1471	1756-1778
AD-288637.1	GGAAAAGGAACUGUACUGGCU	1172	1765-1785	AGCCAGTACAGUUCCUUUUCCUG	1472	1763-1785
AD-288696.1	CAGGAAAAGGAACUGUACUGU	1175	1763-1783	ACAGUACAGUUCCUUUUCCUGUG	1475	1761-1783
AD-288698.1	AGGAACUGUACUGGCUAUUAU	1176	1770-1790	AUAAUAGCCAGUACAGUUCCUUU	1476	1768-1790
AD-288912.1	CUCCCACUACAUCAAGACUAA	1177	2189-2209	UUAGUCTUGAUGUAGUGGGAGUC	1477	2187-2209
AD-288915.1	CACUACAUCAAGACUAAUCUU	1180	2193-2213	AAGAUUAGUCUUGAUGUAGUGGG	1480	2191-2213
AD-288916.1	CUACAUCAAGACUAAUCUUGU	1181	2195-2215	ACAAGATUAGUCUUGAUGUAGUG	1481	2193-2215
AD-288933.1	GUGUUUUUCACAUGUAUUAUA	1184	2221-2241	UAUAAUACAUGUGAAAAACACAC	1484	2219-2241
AD-288937.1	UCACAUGUAUUAUAGAAUGCU	1185	2228-2248	AGCAUUCUAUAAUACAUGUGAAA	1485	2226-2248
AD-288938.1	CACAUGUAUUAUAGAAUGCUU	1186	2229-2249	AAGCAUTCUAUAAUACAUGUGAA	1486	2227-2249
AD-288948.1	CUUUUGCAUGGACUAUCCUCU	1192	2247-2267	AGAGGATAGUCCAUGCAAAAGCA	1492	2245-2267
AD-288950.1	UUGCAUGGACUAUCCUCUUGU	1193	2250-2270	ACAAGAGGAUAGUCCAUGCAAAA	1493	2248-2270
AD-288956.1	GGACUAUCCUCUUGUUUUUAU	1196	2256-2276	AUAAAAACAAGAGGAUAGUCCAU	1496	2254-2276
AD-288957.1	GACUAUCCUCUUGUUUUUAUU	1197	2257-2277	AAUAAAAACAAGAGGAUAGUCCA	1497	2255-2277
AD-288959.1	CUAUCCUCUUGUUUUUAUUAA	1198	2259-2279	UUAAUAAAAACAAGAGGAUAGUC	1498	2257-2279
AD-288981.1	CCCACUACAUCAAGACUAAUU	1199	2191-2211	AAUUAGTCUUGAUGUAGUGGGAG	1499	2189-2211

Duplex Name	Sense sequence 5' to 3'	SEQ ID NO:	Position in NM_178135.4	Antisense sequence 5' to 3'	SEQ ID NO:	Position in NM_178135.4
AD-288982.1	ACUACAUCAAGACUAAUCUUU	1200	2194-2214	AAAGAUTAGUCUUGAUGUAGUGG	1500	2192-2214
AD-288996.1	AUGCUUUUGCAUGGACUAUCU	1201	2244-2264	AGAUAGTCCAUGCAAAAGCAUUC	1501	2242-2264

* Target: HSD17B13

Table 9. HSD17B13 ELF7 GNA7 *in vitro* 10nM screen in Cos-7 (Human Dual-Luciferase psiCHECK2 vector) and Primary Cynomolgus Hepatocytes

Duplex Name	% of Human Message Remaining 10nM	% of Human Message Remaining 0.1nM	% of Cyno Message remaining 10nM	% of Cyno Message remaining 0.1nM
AD-286958.1	108.7	111.4	84.5	99.1
AD-287001.1	84.8	98.4	14.7	81.4
AD-287012.1	88.6	110	97.1	88.8
AD-287014.1	95.2	105.8	116.5	102.3
AD-287015.1	65.4	93.8	14.5	80.3
AD-287017.1	98.5	94.9	91.6	96.2
AD-287026.1	31.9	91	44.8	73.6
AD-287059.1	76.9	117.2	70	94.4
AD-287060.1	101.6	97.9	71.1	97.8
AD-287061.1	94.6	92.8	60.5	96.4
AD-287062.1	90.8	97.7	67.1	113.1
AD-287064.1	97	92.5	75	98.2
AD-287065.1	92.2	98.2	74.4	98
AD-287066.1	98.5	96.4	27	99.3
AD-287126.1	95.6	99.9	19.1	93.5
AD-287200.1	98.7	126.7	91.5	95.3
AD-287201.1	38.7	101.6	88.6	100.6
AD-287202.1	74.5	97.2	88.7	100.7
AD-287203.1	72.9	98.7	50.3	87.1
AD-287205.1	72.8	98	40	96.9
AD-287206.1	62.7	112.9	19.6	88.4
AD-287227.1	64.3	95	34.2	95.1
AD-287246.1	58.1	97.5	20.8	72.4
AD-287247.1	76.2	95.9	84.8	115.1
AD-287248.1	65.5	110.9	55	92
AD-287249.1	90.1	107.8	126.6	113.4
AD-287250.1	76.9	113.2	96.2	95.6
AD-287251.1	35.8	92.3	53.5	93.7
AD-287252.1	57.7	89	32.7	101.4
AD-287253.1	76.1	95	74.1	92.6
AD-287254.1	104.7	124	89.5	100.5
AD-287258.1	91.4	107.8	44.9	98.1
AD-287287.1	55.2	96.5	65.7	104.4
AD-287288.1	53.1	96.9	36	108.3
AD-287289.1	77.3	98.1	57.5	97.8
AD-287290.1	23.5	103.2	55.3	82.8
AD-287293.1	46.6	89.5	88.6	102.2
AD-287316.1	78.6	82.4	34.1	92.4
AD-287320.1	86.2	88.8	105.8	97.9
AD-287321.1	86	108.2	81.3	91
AD-287324.1	72.7	113.6	34.3	107.8
AD-287325.1	78.4	104.6	85.2	86.2
AD-287326.1	39.2	95.1	17.3	73.3
AD-287327.1	91.7	95.2	99.6	90.4
AD-287344.1	13.6	81.4	14.4	58.3
AD-287346.1	115.2	122.2	96.5	103.1
AD-287347.1	43.3	89.6	26.3	86.7
AD-287366.1	53	98.4	36.1	90.1
AD-287367.1	102.8	99.3	98.4	93.3
AD-287370.1	107.7	106.7	102.1	93.8
AD-287371.1	79.2	107	81.6	93.5

Duplex Name	% of Human Message Remaining 10nM	% of Human Message Remaining 0.1nM	% of Cyno Message remaining 10nM	% of Cyno Message remaining 0.1nM
AD-287372.1	101.8	103.2	94.4	108.4
AD-287373.1	67.5	85.9	28.7	89.6
AD-287374.1	60.7	103.2	63.2	83.2
AD-287375.1	96	101	85.3	98
AD-287391.1	28.3	92	26.4	95.3
AD-287392.1	33.8	100.9	31.4	90.8
AD-287406.1	93.2	106.5	54.1	96.2
AD-287407.1	47.5	86.1	23.6	72.2
AD-287408.1	63.1	90.3	47.1	98.2
AD-287410.1	32.5	87.6	10.9	80.2
AD-287411.1	21.6	87.3	10	69.1
AD-287413.1	87.4	98.2	72.7	89.9
AD-287414.1	100.6	97.3	100.2	98.6
AD-287415.1	20.2	88.9	9.7	68.8
AD-287418.1	13.3	88.8	45.9	66.6
AD-287419.1	54.6	99.7	58.7	88
AD-287421.1	27.4	94.7	7.4	66.2
AD-287424.1	33.4	98	40.6	87.6
AD-287427.1	67.9	106.6	24.2	75.8
AD-287428.1	79.1	94.5	22.3	84.7
AD-287429.1	99.5	98.2	53.8	94.7
AD-287430.1	101.9	104	88.3	103.9
AD-287441.1	62.8	104	61.1	103.6
AD-287453.1	19.9	91.5	12.5	70.3
AD-287462.1	44.1	90.3	85.1	93.1
AD-287463.1	93.9	99.9	78.3	100.4
AD-287464.1	113	107.9	51.5	110.6
AD-287465.1	86.6	99	80.4	101.5
AD-287466.1	89.9	96.4	106.2	109.7
AD-287467.1	85.2	100.4	82.2	107.9
AD-287468.1	36.6	102.8	13.7	92.4
AD-287469.1	67.5	93.6	88.5	107.8
AD-287470.1	30	111.3	24.9	68.2
AD-287474.1	61.6	103.1	55.4	93.3
AD-287476.1	33.2	120.5	29.2	52
AD-287477.1	62.3	90.6	38.2	81.3
AD-287478.1	44	86.3	6.1	52.5
AD-287479.1	89.8	95.8	53	95.1
AD-287491.1	63.1	108.1	75.7	92.2
AD-287492.1	70.8	92.9	93.6	97.1
AD-287517.1	75.2	93.3	98	99.5
AD-287520.1	73.9	97.9	96.2	101.9
AD-287521.1	50.1	94.6	70.2	98.7
AD-287522.1	88.9	109.4	83.4	91.8
AD-287524.1	14.4	111.5	31.1	65.9
AD-287525.1	71.6	104.4	88.6	103.8
AD-287537.1	51.6	110.5	20.5	84.7
AD-287539.1	47.9	115.9	27.9	78.5
AD-287540.1	74.9	105.1	19.6	86.2
AD-287543.1	47.6	95.3	12.7	93.3
AD-287546.1	65.7	102.8	6.8	59
AD-287568.1	74.8	104.6	56.7	100.7
AD-287591.1	40	100.8	12.7	65.1
AD-287610.1	33.3	78.1	32.3	66.4

Duplex Name	% of Human Message Remaining 10nM	% of Human Message Remaining 0.1nM	% of Cyno Message remaining 10nM	% of Cyno Message remaining 0.1nM
AD-287615.1	24.4	104.8	12.5	68.7
AD-287616.1	15.7	102	16.1	63.6
AD-287627.1	81.3	92.3	111.8	94.5
AD-287632.1	93.9	93.1	88.9	106.9
AD-287633.1	106.4	91.9	68.4	122.6
AD-287634.1	82.3	114.7	78.7	94.5
AD-287636.1	21.8	97.7	18.9	56.5
AD-287637.1	27.6	92.3	22.8	91.4
AD-287638.1	99	101.2	101.6	98.1
AD-287647.1	74.2	108.2	74.5	94.3
AD-287648.1	12.9	92.8	29.8	61
AD-287651.1	66.5	100.6	92.8	106.4
AD-287652.1	12.8	79.5	11.5	66.2
AD-287653.1	18.9	69.8	17.9	87.7
AD-287654.1	87.5	101	75.4	91.4
AD-287655.1	61.6	101.7	88.3	98
AD-287656.1	91.7	122.5	86.4	97.9
AD-287658.1	78.1	118.7	45	89.4
AD-287659.1	37	100.9	22.1	87.2
AD-287679.1	55.4	93.6	24.4	85.1
AD-287680.1	14.3	114.1	17.4	35.8
AD-287683.1	59	94.1	33.3	87.5
AD-287690.1	81.2	144.4	49.9	93.5
AD-287693.1	68.7	125.5	85.8	100.5
AD-287694.1	100.2	111.7	87.8	101.8
AD-287695.1	88.4	110.2	89.2	106.1
AD-287696.1	13.8	78.3	12	63.6
AD-287700.1	15.6	97	22.9	82.3
AD-287701.1	46.1	95	108.7	109.1
AD-287702.1	80.1	112.2	80.1	93.9
AD-287703.1	70.1	102.6	92.2	105.5
AD-287704.1	38.2	113.8	25.4	95.5
AD-287706.1	94.3	105	96.1	97.8
AD-287707.1	82.6	114.2	103.2	106.7
AD-287709.1	78.2	93.8	89.9	103.9
AD-287711.1	23.1	76.9	15.5	88.1
AD-287724.1	54.2	94.9	100.4	97.6
AD-287725.1	83.1	116.3	61.8	101.3
AD-287726.1	20.8	77.6	15.5	70.6
AD-287727.1	33.6	111	27.9	57.1
AD-287728.1	28.8	107	11.2	76.6
AD-287735.1	13.2	92.7	9.6	25.6
AD-287736.1	60.7	111	26.9	83.8
AD-287737.1	71.3	98.7	42.5	105.1
AD-287738.1	31.3	114.3	21.8	87.8
AD-287739.1	22.5	101.9	55	72
AD-287740.1	16.3	73.5	19	55.7
AD-287778.1	82.4	113.7	66.4	90.9
AD-287793.1	47.8	91.5	84.1	92.9
AD-287795.1	32.9	99.6	54.4	102.2
AD-287798.1	48.8	98.3	18.5	90.5
AD-287800.1	59.4	96.3	58.7	95.1
AD-287801.1	17.7	140.3	16.1	71.4
AD-287802.1	5.6	82.9	17	27.8

Duplex Name	% of Human Message Remaining 10nM	% of Human Message Remaining 0.1nM	% of Cyno Message remaining 10nM	% of Cyno Message remaining 0.1nM
AD-287804.1	14.7	77.5	14.3	70.3
AD-287810.1	53.9	98.6	72.5	100.1
AD-287811.1	64.5	106	33.9	90.2
AD-287813.1	35.9	114.4	17.9	91.4
AD-287837.1	11.6	66	9.3	58
AD-287839.1	95.3	106.1	60	136.1
AD-287841.1	13.4	98.7	22.9	46.4
AD-287842.1	94.6	89.9	106.1	97.5
AD-287844.1	87.4	161.1	74	88.1
AD-287854.1	32.4	103.1	25.2	82.8
AD-287856.1	16.9	99.3	32.4	64.5
AD-287857.1	88	99.4	64.7	106.2
AD-287893.1	17.2	94.7	58.7	93.2
AD-287917.1	30.5	114.1	60	69.4
AD-287924.1	52.3	85.6	75.3	86.5
AD-287934.1	48.5	91.3	39.4	96.8
AD-287969.1	100.3	96.7	77.9	105.5
AD-287970.1	15.4	88.3	43	87.6
AD-287982.1	73.8	87.6	26.7	56.3
AD-288005.1	23.6	92.4	69.9	88.4
AD-288006.1	28.8	91.1	52.8	95.3
AD-288008.1	62.6	111.1	52	97.5
AD-288010.1	66.8	116.2	66.1	102
AD-288011.1	11.7	78	45.2	54.5
AD-288015.1	27.1	111.4	66.6	61
AD-288046.1	12.2	72.4	20.7	53.5
AD-288049.1	44.9	104.5	68.6	77.3
AD-288050.1	32.2	120.1	41.8	70.6
AD-288076.1	43.1	109.1	24.2	66.4
AD-288092.1	10.9	106.6	58.5	113.2
AD-288094.1	66.8	92.3	90.4	91.6
AD-288095.1	16.2	92.4	39	55.5
AD-288108.1	53.3	122.8	49.1	96.7
AD-288109.1	39.8	114.6	51	90.4
AD-288173.1	19.3	110.7	58.8	81.1
AD-288174.1	39	90.1	71.8	88.7
AD-288176.1	135.9	92.9	102.6	106
AD-288177.1	91.4	99.7	57.2	99.5
AD-288180.1	34.5	110	68	82
AD-288181.1	19.9	116.4	34.6	74.9
AD-288183.1	38.2	96.5	20.5	84.6
AD-288184.1	43.4	95	28.9	84.1
AD-288186.1	63.9	107.4	60.7	88
AD-288187.1	22.9	113.8	53	84.5
AD-288188.1	16.3	77.6	23.4	60.5
AD-288189.1	47.2	104.1	22.4	49.3
AD-288190.1	21.5	81.3	22.8	58.1
AD-288192.1	71.7	112.4	76.6	93.6
AD-288193.1	62.5	118.5	34	72.8
AD-288194.1	66.7	96.6	31.2	87.1
AD-288227.1	86.5	85.7	113.1	103.6
AD-288229.1	104.6	103.1	73.7	88.6
AD-288230.1	32.5	122.3	29.7	75.1
AD-288231.1	19	100.2	46.5	72.1

Duplex Name	% of Human Message Remaining 10nM	% of Human Message Remaining 0.1nM	% of Cyno Message remaining 10nM	% of Cyno Message remaining 0.1nM
AD-288232.1	66.9	95.5	97	95.2
AD-288233.1	26.2	108	21.1	68.6
AD-288235.1	7.4	79.8	39.3	52.6
AD-288236.1	18.1	78.8	21.5	51.6
AD-288237.1	59.8	133.8	37.3	72.6
AD-288238.1	10.4	57.4	21.3	58.1
AD-288290.1	68.9	108.4	29.8	90.7
AD-288316.1	38	98.2	42.2	61.8
AD-288318.1	37.6	99.4	25.3	66
AD-288319.1	23.7	93.5	44.4	90.4
AD-288324.1	56.4	146.7	51.7	81.8
AD-288337.1	24.7	94.5	30	78
AD-288338.1	34.8	95.6	46.9	68.3
AD-288339.1	67.3	86.5	78.5	94
AD-288340.1	19.5	114.6	29.5	51.7
AD-288341.1	23.1	88.9	48.8	75.7
AD-288366.1	34.6	160.9	42.9	91.4
AD-288369.1	16.4	120.9	28.2	77.4
AD-288370.1	15.1	73.8	26.8	89.1
AD-288391.1	30.1	84	21.2	64.5
AD-288393.1	56	96.6	41.8	101.9
AD-288394.1	20.1	107	48.5	75.6
AD-288395.1	64	94.8	53.7	101
AD-288396.1	86	94.3	100.2	90.7
AD-288397.1	28.3	83.9	33.9	83.9
AD-288398.1	63.4	108.8	87.6	91.7
AD-288402.1	60.1	103.7	37	89.3
AD-288427.1	110.8	95.6	89.8	97.2
AD-288430.1	94.7	118.3	85.2	92.7
AD-288431.1	87.4	94.7	106.5	94.5
AD-288432.1	39	112.5	81.6	88.7
AD-288433.1	100.7	113	107.9	92.4
AD-288434.1	104.8	99.6	87.5	102.3
AD-288466.1	65	99.1	77.1	100
AD-288467.1	99.4	99.8	64.9	98.6
AD-288470.1	30.7	97.7	82.9	83.8
AD-288491.1	82.6	98.5	69.8	90.6
AD-288492.1	77	98.1	84.5	106.6
AD-288561.1	54.5	92.2	102.4	103.6
AD-288562.1	35.9	91.8	32.2	89.5
AD-288563.1	18.7	79.9	29.9	69.1
AD-288564.1	24.5	68.1	38.3	80.9
AD-288565.1	47.1	97.6	53.9	83.8
AD-288566.1	33.7	89.8	30.5	64.6
AD-288567.1	75.7	92.5	101.7	99.7
AD-288572.1	93.2	97.6	92	110.6
AD-288573.1	51.9	95	46.3	86.1
AD-288574.1	12.6	79.8	25.8	54.3
AD-288575.1	51.2	116.2	61.7	76.2
AD-288576.1	26.9	98	51.7	75
AD-288613.1	36	92.1	103.9	113.2
AD-288620.1	62.8	94.8	107	88.5
AD-288624.1	26.8	101.4	32.2	66.8
AD-288625.1	16.4	99.3	40.5	73.2

Duplex Name	% of Human Message Remaining 10nM	% of Human Message Remaining 0.1nM	% of Cyno Message remaining 10nM	% of Cyno Message remaining 0.1nM
AD-288626.1	34.7	100.9	30.1	70.8
AD-288628.1	32.7	85.2	35.1	80.2
AD-288634.1	89.6	92.6	77	90.6
AD-288637.1	44.5	93.6	42.1	104
AD-288639.1	43.7	112	20.6	46.7
AD-288642.1	42.2	99.6	25.2	69.8
AD-288696.1	52.8	101.5	31.1	88
AD-288698.1	16.3	75.6	21	58.9
AD-288912.1	21.1	83.4	23.2	56.1
AD-288913.1	28.5	88	26.7	65.9
AD-288914.1	16.1	77.7	23.1	56.1
AD-288915.1	17.7	92.8	33.9	73.6
AD-288916.1	16.1	91.1	24	75.5
AD-288917.1	15.1	59.6	31	77
AD-288918.1	23.6	85.2	35.2	98.8
AD-288933.1	24.9	78.9	62.9	78.8
AD-288937.1	74.3	103.3	51.6	89.9
AD-288938.1	28.2	105.7	42.9	92.7
AD-288941.1	33.1	100	44.9	114.1
AD-288943.1	69.7	97.2	49.1	89
AD-288945.1	25.1	83.4	26.1	64.4
AD-288946.1	54	89.5	45.5	82.9
AD-288947.1	26.7	97.6	26.6	76.9
AD-288948.1	18.2	93.6	24.7	67.6
AD-288950.1	24.3	103.4	31.8	89.7
AD-288951.1	18.9	85.3	29.7	96.5
AD-288952.1	98.1	103.2	85.4	92.9
AD-288956.1	30.5	104	53	84.5
AD-288957.1	23.4	88.8	57.9	85.2
AD-288959.1	21.5	82.5	45.7	64.4
AD-288981.1	63.2	101.9	26.6	73.5
AD-288982.1	82.9	103.7	50.2	88.4
AD-288996.1	11.6	70.8	39.3	70.3

Table 10. HSD17B13 NonF DNA Modified Sequence*

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-291929.1	ascsacaaggdAcdTgaaccagaauL96	1502	asdTsucdTgdGuucadGudCcuugugusasg	1797	CUACACAAGGACUGAACCAGAAG	2092
AD-291931.1	ascsaaggacdTgdAaccagaaggaL96	1503	usdCscudTcdTgguudCadGuccuugusgsu	1798	ACACAAGGACUGAACCAGAAGGA	2093
AD-291988.1	uscscuucugdCudTcugaucaccaL96	1504	usdGsgudGadTcagadAgdCagaaggasusu	1799	AAUCCUUCUGCUUCUGAUCACCA	2094
AD-291993.1	csusgcuucudGadTcaccaucauuL96	1505	asdAsugdAudGgugadTcdAgaagcagsasa	1800	UUCUGCUUCUGAUCACCAUCAUC	2095
AD-291998.1	uscsugaucadCcdAucaucuacuuL96	1506	asdAsgudAgdAugaudGgdTgaucagasasg	1801	CUUCUGAUCACCAUCAUCUACUC	2096
AD-292005.1	ascscaucaudCudAcuccuacuuuL96	1507	asdAsagdTadGgagudAgdAugauggusgsa	1802	UCACCAUCAUCUACUCCUACUUG	2097
AD-292006.1	cscsaucaucdTadCuccuacuuguL96	1508	asdCsaadGudAggagdTadGaugauggsusg	1803	CACCAUCAUCUACUCCUACUUGG	2098
AD-292007.1	csasucaucudAcdTccuacuuggaL96	1509	usdCscadAgdTaggadGudAgaugaugsgsu	1804	ACCAUCAUCUACUCCUACUUGGA	2099
AD-292008.1	asuscaucuadCudCcuacuuggauL96	1510	asdTsccdAadGuaggdAgdTagaugausgsg	1805	CCAUCAUCUACUCCUACUUGGAG	2100
AD-292010.1	csasucuacudCcdTacuuggaguuL96	1511	asdAscudCcdAaguadGgdAguagaugsasu	1806	AUCAUCUACUCCUACUUGGAGUC	2101
AD-292012.1	uscsuacuccdTadCuuggagucguL96	1512	asdCsgadCudCcaagdTadGgaguagasusg	1807	CAUCUACUCCUACUUGGAGUCGU	2102
AD-292013.1	csusacuccudAcdTuggagucguuL96	1513	asdAscgdAcdTccaadGudAggaguagsasu	1808	AUCUACUCCUACUUGGAGUCGUU	2103
AD-292014.1	usascuccuadCudTggagucguuuL96	1514	asdAsacdGadCuccadAgdTaggaguasgsa	1809	UCUACUCCUACUUGGAGUCGUUG	2104
AD-292015.1	ascsuccuacdTudGgagucguuguL96	1515	asdCsaadCgdAcuccdAadGuaggagusasg	1810	CUACUCCUACUUGGAGUCGUUGG	2105
AD-292016.1	csusccuacudTgdGagucguugguL96	1516	asdCscadAcdGacucdCadAguaggagsusa	1811	UACUCCUACUUGGAGUCGUUGGU	2106
AD-292017.1	uscscuacuudGgdAgucguugguuL96	1517	asdAsccdAadCgacudCcdAaguaggasgsu	1812	ACUCCUACUUGGAGUCGUUGGUG	2107
AD-292028.1	gsuscguuggdTgdAaguuuuucauL96	1518	asdTsgadAadAacuudCadCcaacgacsusc	1813	GAGUCGUUGGUGAAGUUUUUCAU	2108
AD-292137.1	ususgguucudGudGggauauuaauL96	1519	asdTsuadAudAucccdAcdAgaaccaasusa	1814	UAUUGGUUCUGUGGGAUAUUAAU	2109
AD-292140.1	gsusucugugdGgdAuauuaauaauL96	1520	asdTsuadTudAauaudCcdCacagaacscsa	1815	UGGUUCUGUGGGAUAUUAAUAAG	2110
AD-292143.1	csusgugggadTadTuaauaagcguL96	1521	asdCsgcdTudAuuaadTadTcccacagsasa	1816	UUCUGUGGGAUAUUAAUAAGCGC	2111
AD-292182.1	gscsugagugdCcdGaaaacuagguL96	1522	asdCscudAgdTuuucdGgdCacucagcsusg	1817	CAGCUGAGUGCCGAAAACUAGGC	2112
AD-292183.1	csusgagugcdCgdAaaacuaggcuL96	1523	asdGsccdTadGuuuudCgdGcacucagscsu	1818	AGCUGAGUGCCGAAAACUAGGCG	2113
AD-292185.1	gsasgugccgdAadAacuaggcguuL96	1524	asdAscgdCcdTaguudTudCggcacucsasg	1819	CUGAGUGCCGAAAACUAGGCGUC	2114
AD-292186.1	asgsugccgadAadAcuaggcgucaL96	1525	usdGsacdGcdCuagudTudTcggcacuscsa	1820	UGAGUGCCGAAAACUAGGCGUCA	2115
AD-292187.1	gsusgccgaadAadCuaggcgucauL96	1526	asdTsgadCgdCcuagdTudTucggcacsusc	1821	GAGUGCCGAAAACUAGGCGUCAC	2116
AD-292188.1	usgsccgaaadAcdTaggcgucacuL96	1527	asdGsugdAcdGccuadGudTuucggcascsu	1822	AGUGCCGAAAACUAGGCGUCACU	2117
AD-292189.1	gscscgaaaadCudAggcgucacuuL96	1528	asdAsgudGadCgccudAgdTuuucggcsasc	1823	GUGCCGAAAACUAGGCGUCACUG	2118
AD-292190.1	cscsgaaaacdTadGgcgucacuguL96	1529	asdCsagdTgdAcgccdTadGuuuucggscsa	1824	UGCCGAAAACUAGGCGUCACUGC	2119
AD-292238.1	csasgagaagdAgdAucuaucgcuuL96	1530	asdAsgcdGadTagaudCudCuucucugsusu	1825	AACAGAGAAGAGAUCUAUCGCUC	2120
AD-292244.1	asgsagaucudAudCgcucucuaaaL96	1531	usdTsuadGadGagcgdAudAgaucucususc	1826	GAAGAGAUCUAUCGCUCUCUAAA	2121
AD-292245.1	gsasgaucuadTcdGcucucuaaauL96	1532	asdTsuudAgdAgagcdGadTagaucucsusu	1827	AAGAGAUCUAUCGCUCUCUAAAU	2122

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-292247.1	gsasucuaucdGcdTcucuaaaucaL96	1533	usdGsaudTudAgagadGcdGauagaucsusc	1828	GAGAUCUAUCGCUCUCUAAAUCA	2123
AD-292248.1	asuscuaucgdCudCucuaaaucauL96	1534	asdTsgadTudTagagdAgdCgauagauscsu	1829	AGAUCUAUCGCUCUCUAAAUCAG	2124
AD-292250.1	csusaucgcudCudCuaaaucagguL96	1535	asdCscudGadTuuagdAgdAgcgauagsasu	1830	AUCUAUCGCUCUCUAAAUCAGGU	2125
AD-292251.1	usasucgcucdTcdTaaaucagguuL96	1536	asdAsccdTgdAuuuadGadGagcgauasgsa	1831	UCUAUCGCUCUCUAAAUCAGGUG	2126
AD-292252.1	asuscgcucudCudAaaucaggugaL96	1537	usdCsacdCudGauuudAgdAgagcgausasg	1832	CUAUCGCUCUCUAAAUCAGGUGA	2127
AD-292253.1	uscsgcucucdTadAaucaggugaaL96	1538	usdTscadCcdTgauudTadGagagcgasusa	1833	UAUCGCUCUCUAAAUCAGGUGAA	2128
AD-292254.1	csgscucucudAadAucaggugaauL96	1539	asdTsucdAcdCugaudTudAgagagcgsasu	1834	AUCGCUCUCUAAAUCAGGUGAAG	2129
AD-292257.1	uscsucuaaadTcdAggugaagaaaL96	1540	usdTsucdTudCaccudGadTuuagagasgsc	1835	GCUCUCUAAAUCAGGUGAAGAAA	2130
AD-292309.1	asusgcugggdAcdAguauauccauL96	1541	asdTsggdAudAuacudGudCccagcaususa	1836	UAAUGCUGGGACAGUAUAUCCAG	2131
AD-292310.1	usgscugggadCadGuauauccaguL96	1542	asdCsugdGadTauacdTgdTcccagcasusu	1837	AAUGCUGGGACAGUAUAUCCAGC	2132
AD-292315.1	gsgsacaguadTadTccagccgauuL96	1543	asdAsucdGgdCuggadTadTacuguccscsa	1838	UGGGACAGUAUAUCCAGCCGAUC	2133
AD-292318.1	csasguauaudCcdAgccgaucuuuL96	1544	asdAsagdAudCggcudGgdAuauacugsusc	1839	GACAGUAUAUCCAGCCGAUCUUC	2134
AD-292344.1	ascscaaggadTgdAagagauuacuL96	1545	asdGsuadAudCucuudCadTccuuggusgsc	1840	GCACCAAGGAUGAAGAGAUUACC	2135
AD-292345.1	cscsaaggaudGadAgagauuaccaL96	1546	usdGsgudAadTcucudTcdAuccuuggsusg	1841	CACCAAGGAUGAAGAGAUUACCA	2136
AD-292346.1	csasaggaugdAadGagauuaccaaL96	1547	usdTsggdTadAucucdTudCauccuugsgsu	1842	ACCAAGGAUGAAGAGAUUACCAA	2137
AD-292363.1	cscsaagacadTudTgaggucaacaL96	1548	usdGsuudGadCcucadAadTgucuuggsusa	1843	UACCAAGACAUUUGAGGUCAACA	2138
AD-292366.1	asgsacauuudGadGgucaacaucuL96	1549	asdGsaudGudTgaccdTcdAaaugucususg	1844	CAAGACAUUUGAGGUCAACAUCC	2139
AD-292367.1	gsascauuugdAgdGucaacauccuL96	1550	asdGsgadTgdTugacdCudCaaaugucsusu	1845	AAGACAUUUGAGGUCAACAUCCU	2140
AD-292369.1	csasuuugagdGudCaacauccuauL96	1551	asdTsagdGadTguugdAcdCucaaaugsusc	1846	GACAUUUGAGGUCAACAUCCUAG	2141
AD-292370.1	asusuugaggdTcdAacauccuaguL96	1552	asdCsuadGgdAuguudGadCcucaaausgsu	1847	ACAUUUGAGGUCAACAUCCUAGG	2142
AD-292371.1	ususugaggudCadAcauccuaggaL96	1553	usdCscudAgdGaugudTgdAccucaaasusg	1848	CAUUUGAGGUCAACAUCCUAGGA	2143
AD-292373.1	usgsaggucadAcdAuccuaggacaL96	1554	usdGsucdCudAggaudGudTgaccucasasa	1849	UUUGAGGUCAACAUCCUAGGACA	2144
AD-292374.1	gsasggucaadCadTccuaggacauL96	1555	asdTsgudCcdTaggadTgdTugaccucsasa	1850	UUGAGGUCAACAUCCUAGGACAU	2145
AD-292376.1	gsgsucaacadTcdCuaggacauuuL96	1556	asdAsaudGudCcuagdGadTguugaccsusc	1851	GAGGUCAACAUCCUAGGACAUUU	2146
AD-292377.1	gsuscaacaudCcdTaggacauuuuL96	1557	asdAsaadTgdTccuadGgdAuguugacscsu	1852	AGGUCAACAUCCUAGGACAUUUU	2147
AD-292379.1	csasacauccdTadGgacauuuuugL96	1558	csdAsaadAadTguccdTadGgauguugsasc	1853	GUCAACAUCCUAGGACAUUUUUG	2148
AD-292380.1	asascauccudAgdGacauuuuuguL96	1559	asdCsaadAadAugucdCudAggauguusgsa	1854	UCAACAUCCUAGGACAUUUUUGG	2149
AD-292381.1	ascsauccuadGgdAcauuuuuggaL96	1560	usdCscadAadAaugudCcdTaggaugususg	1855	CAACAUCCUAGGACAUUUUUGGA	2150
AD-292382.1	csasuccuagdGadCauuuuuggauL96	1561	asdTsccdAadAaaugdTcdCuaggaugsusu	1856	AACAUCCUAGGACAUUUUUGGAU	2151
AD-292383.1	asusccuaggdAcdAuuuuuggauuL96	1562	asdAsucdCadAaaaudGudCcuaggausgsu	1857	ACAUCCUAGGACAUUUUUGGAUC	2152
AD-292384.1	uscscuaggadCadTuuuuggaucaL96	1563	usdGsaudCcdAaaaadTgdTccuaggasusg	1858	CAUCCUAGGACAUUUUUGGAUCA	2153
AD-292385.1	cscsuaggacdAudTuuuggaucauL96	1564	asdTsgadTcdCaaaadAudGuccuaggsasu	1859	AUCCUAGGACAUUUUUGGAUCAC	2154

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-292388.1	asgsgacauudTudTggaucacaaaL96	1565	usdTsugdTgdAuccadAadAauguccusasg	1860	CUAGGACAUUUUUGGAUCACAAA	2155
AD-292389.1	gsgsacauuudTudGgaucacaaaaL96	1566	usdTsuudGudGauccdAadAaauguccsusa	1861	UAGGACAUUUUUGGAUCACAAAA	2156
AD-292390.1	gsascauuuudTgdGaucacaaaauL96	1567	asdTsuudTgdTgaucdCadAaaaugucscsu	1862	AGGACAUUUUUGGAUCACAAAAG	2157
AD-292394.1	ususuuuggadTcdAcaaaagcacuL96	1568	asdGsugdCudTuugudGadTccaaaaasusg	1863	CAUUUUUGGAUCACAAAAGCACU	2158
AD-292397.1	ususggaucadCadAaagcacuucuL96	1569	asdGsaadGudGcuuudTgdTgauccaasasa	1864	UUUUGGAUCACAAAAGCACUUCU	2159
AD-292398.1	usgsgaucacdAadAagcacuucuuL96	1570	asdAsgadAgdTgcuudTudGugauccasasa	1865	UUUGGAUCACAAAAGCACUUCUU	2160
AD-292399.1	gsgsaucacadAadAgcacuucuuuL96	1571	asdAsagdAadGugcudTudTgugauccsasa	1866	UUGGAUCACAAAAGCACUUCUUC	2161
AD-292403.1	csascaaaagdCadCuucuuccauuL96	1572	asdAsugdGadAgaagdTgdCuuuugugsasu	1867	AUCACAAAAGCACUUCUUCCAUC	2162
AD-292404.1	ascsaaaagcdAcdTucuuccaucuL96	1573	asdGsaudGgdAagaadGudGcuuuugusgsa	1868	UCACAAAAGCACUUCUUCCAUCG	2163
AD-292405.1	csasaaagcadCudTcuuccaucgaL96	1574	usdCsgadTgdGaagadAgdTgcuuuugsusg	1869	CACAAAAGCACUUCUUCCAUCGA	2164
AD-292406.1	asasaagcacdTudCuuccaucgauL96	1575	asdTscgdAudGgaagdAadGugcuuuusgsu	1870	ACAAAAGCACUUCUUCCAUCGAU	2165
AD-292407.1	asasagcacudTcdTuccaucgauuL96	1576	asdAsucdGadTggaadGadAgugcuuususg	1871	CAAAAGCACUUCUUCCAUCGAUG	2166
AD-292408.1	asasgcacuudCudTccaucgaugaL96	1577	usdCsaudCgdAuggadAgdAagugcuususu	1872	AAAAGCACUUCUUCCAUCGAUGA	2167
AD-292409.1	asgscacuucdTudCcaucgaugauL96	1578	asdTscadTcdGauggdAadGaagugcususu	1873	AAAGCACUUCUUCCAUCGAUGAU	2168
AD-292410.1	gscsacuucudTcdCaucgaugauuL96	1579	asdAsucdAudCgaugdGadAgaagugcsusu	1874	AAGCACUUCUUCCAUCGAUGAUG	2169
AD-292434.1	asgsaaaucadTgdGccacaucguuL96	1580	asdAscgdAudGuggcdCadTgauuucuscsu	1875	AGAGAAAUCAUGGCCACAUCGUC	2170
AD-292486.1	ususccuuacdCudCaucccauauuL96	1581	asdAsuadTgdGgaugdAgdGuaaggaasusc	1876	GAUUCCUUACCUCAUCCCAUAUU	2171
AD-292487.1	uscscuuaccdTcdAucccauauuuL96	1582	asdAsaudAudGggaudGadGguaaggasasu	1877	AUUCCUUACCUCAUCCCAUAUUG	2172
AD-292492.1	ascscucaucdCcdAuauuguuccaL96	1583	usdGsgadAcdAauaudGgdGaugaggusasa	1878	UUACCUCAUCCCAUAUUGUUCCA	2173
AD-292495.1	uscsaucccadTadTuguuccagcaL96	1584	usdGscudGgdAacaadTadTgggaugasgsg	1879	CCUCAUCCCAUAUUGUUCCAGCA	2174
AD-292498.1	uscsccauaudTgdTuccagcaaauL96	1585	asdTsuudGcdTggaadCadAuaugggasusg	1880	CAUCCCAUAUUGUUCCAGCAAAU	2175
AD-292499.1	cscscauauudGudTccagcaaauuL96	1586	asdAsuudTgdCuggadAcdAauaugggsasu	1881	AUCCCAUAUUGUUCCAGCAAAUU	2176
AD-292526.1	usgsuuggcudTudCacagaggucuL96	1587	asdGsacdCudCugugdAadAgccaacasgsc	1882	GCUGUUGGCUUUCACAGAGGUCU	2177
AD-292531.1	gscsuuucacdAgdAggucugacauL96	1588	asdTsgudCadGaccudCudGugaaagcscsa	1883	UGGCUUUCACAGAGGUCUGACAU	2178
AD-292534.1	ususcacagadGgdTcugacaucauL96	1589	asdTsgadTgdTcagadCcdTcugugaasasg	1884	CUUUCACAGAGGUCUGACAUCAG	2179
AD-292536.1	csascagaggdTcdTgacaucagaaL96	1590	usdTscudGadTgucadGadCcucugugsasa	1885	UUCACAGAGGUCUGACAUCAGAA	2180
AD-292541.1	asgsgucugadCadTcagaacuucaL96	1591	usdGsaadGudTcugadTgdTcagaccuscsu	1886	AGAGGUCUGACAUCAGAACUUCA	2181
AD-292566.1	ususgggaaadAadCugguaucaaaL96	1592	usdTsugdAudAccagdTudTuucccaasgsg	1887	CCUUGGGAAAAACUGGUAUCAAA	2182
AD-292574.1	asascugguadTcdAaaaccucauuL96	1593	asdAsugdAgdGuuuudGadTaccaguususu	1888	AAAACUGGUAUCAAAACCUCAUG	2183
AD-292575.1	ascsugguaudCadAaaccucauguL96	1594	asdCsaudGadGguuudTgdAuaccagususu	1889	AAACUGGUAUCAAAACCUCAUGU	2184
AD-292576.1	csusgguaucdAadAaccucauguuL96	1595	asdAscadTgdAgguudTudGauaccagsusu	1890	AACUGGUAUCAAAACCUCAUGUC	2185
AD-292577.1	usgsguaucadAadAccucaugucuL96	1596	asdGsacdAudGaggudTudTgauaccasgsu	1891	ACUGGUAUCAAAACCUCAUGUCU	2186

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-292578.1	gsgsuaucaadAadCcucaugucuuL96	1597	asdAsgadCadTgaggdTudTugauaccsasg	1892	CUGGUAUCAAAACCUCAUGUCUC	2187
AD-292579.1	gsusaucaaadAcdCucaugucucuL96	1598	asdGsagdAcdAugagdGudTuugauacscsa	1893	UGGUAUCAAAACCUCAUGUCUCU	2188
AD-292582.1	uscsaaaaccdTcdAugucucugcuL96	1599	asdGscadGadGacaudGadGguuuugasusa	1894	UAUCAAAACCUCAUGUCUCUGCC	2189
AD-292596.1	csuscugcccdAgdTuuuugugaauL96	1600	asdTsucdAcdAaaaadCudGggcagagsasc	1895	GUCUCUGCCCAGUUUUUGUGAAU	2190
AD-292601.1	cscscaguuudTudGugaauacuguL96	1601	asdCsagdTadTucacdAadAaacugggscsa	1896	UGCCCAGUUUUUGUGAAUACUGG	2191
AD-292606.1	ususuuugugdAadTacuggguucaL96	1602	usdGsaadCcdCaguadTudCacaaaaascsu	1897	AGUUUUUGUGAAUACUGGGUUCA	2192
AD-292607.1	ususuugugadAudAcuggguucauL96	1603	asdTsgadAcdCcagudAudTcacaaaasasc	1898	GUUUUUGUGAAUACUGGGUUCAC	2193
AD-292610.1	usgsugaauadCudGgguucaccaaL96	1604	usdTsggdTgdAacccdAgdTauucacasasa	1899	UUUGUGAAUACUGGGUUCACCAA	2194
AD-292612.1	usgsaauacudGgdGuucaccaaaaL96	1605	usdTsuudGgdTgaacdCcdAguauucascsa	1900	UGUGAAUACUGGGUUCACCAAAA	2195
AD-292613.1	gsasauacugdGgdTucaccaaaaaL96	1606	usdTsuudTgdGugaadCcdCaguauucsasc	1901	GUGAAUACUGGGUUCACCAAAAA	2196
AD-292614.1	asasuacuggdGudTcaccaaaaauL96	1607	asdTsuudTudGgugadAcdCcaguauuscsa	1902	UGAAUACUGGGUUCACCAAAAAU	2197
AD-292615.1	asusacugggdTudCaccaaaaauuL96	1608	asdAsuudTudTggugdAadCccaguaususc	1903	GAAUACUGGGUUCACCAAAAAUC	2198
AD-292616.1	usascugggudTcdAccaaaaaucuL96	1609	asdGsaudTudTuggudGadAcccaguasusu	1904	AAUACUGGGUUCACCAAAAAUCC	2199
AD-292624.1	uscsaccaaadAadTccaagcacaaL96	1610	usdTsgudGcdTuggadTudTuuggugasasc	1905	GUUCACCAAAAAUCCAAGCACAA	2200
AD-292625.1	csasccaaaadAudCcaagcacaauL96	1611	asdTsugdTgdCuuggdAudTuuuggugsasa	1906	UUCACCAAAAAUCCAAGCACAAG	2201
AD-292629.1	asasaaauccdAadGcacaagauuaL96	1612	usdAsaudCudTgugcdTudGgauuuuusgsg	1907	CCAAAAAUCCAAGCACAAGAUUA	2202
AD-292630.1	asasaauccadAgdCacaagauuauL96	1613	asdTsaadTcdTugugdCudTggauuuususg	1908	CAAAAAUCCAAGCACAAGAUUAU	2203
AD-292631.1	asasauccaadGcdAcaagauuauuL96	1614	asdAsuadAudCuugudGcdTuggauuususu	1909	AAAAAUCCAAGCACAAGAUUAUG	2204
AD-292634.1	uscscaagcadCadAgauuauggcuL96	1615	asdGsccdAudAaucudTgdTgcuuggasusu	1910	AAUCCAAGCACAAGAUUAUGGCC	2205
AD-292638.1	asgscacaagdAudTauggccuguaL96	1616	usdAscadGgdCcauadAudCuugugcususg	1911	CAAGCACAAGAUUAUGGCCUGUA	2206
AD-292639.1	gscsacaagadTudAuggccuguauL96	1617	asdTsacdAgdGccaudAadTcuugugcsusu	1912	AAGCACAAGAUUAUGGCCUGUAU	2207
AD-292640.1	csascaagaudTadTggccuguauuL96	1618	asdAsuadCadGgccadTadAucuugugscsu	1913	AGCACAAGAUUAUGGCCUGUAUU	2208
AD-292641.1	ascsaagauudAudGgccuguauuuL96	1619	asdAsaudAcdAggccdAudAaucuugusgsc	1914	GCACAAGAUUAUGGCCUGUAUUG	2209
AD-292642.1	csasagauuadTgdGccuguauuguL96	1620	asdCsaadTadCaggcdCadTaaucuugsusg	1915	CACAAGAUUAUGGCCUGUAUUGG	2210
AD-292646.1	asusuauggcdCudGuauuggagauL96	1621	asdTscudCcdAauacdAgdGccauaauscsu	1916	AGAUUAUGGCCUGUAUUGGAGAC	2211
AD-292650.1	usgsgccugudAudTggagacagauL96	1622	asdTscudGudCuccadAudAcaggccasusa	1917	UAUGGCCUGUAUUGGAGACAGAU	2212
AD-292651.1	gsgsccuguadTudGgagacagauuL96	1623	asdAsucdTgdTcuccdAadTacaggccsasu	1918	AUGGCCUGUAUUGGAGACAGAUG	2213
AD-292652.1	gscscuguaudTgdGagacagaugaL96	1624	usdCsaudCudGucucdCadAuacaggcscsa	1919	UGGCCUGUAUUGGAGACAGAUGA	2214
AD-292667.1	asgsaugaagdTcdGuaagaagucuL96	1625	asdGsacdTudCuuacdGadCuucaucusgsu	1920	ACAGAUGAAGUCGUAAGAAGUCU	2215
AD-292668.1	gsasugaagudCgdTaagaagucuuL96	1626	asdAsgadCudTcuuadCgdAcuucaucsusg	1921	CAGAUGAAGUCGUAAGAAGUCUG	2216
AD-292671.1	gsasagucgudAadGaagucugauaL96	1627	usdAsucdAgdAcuucdTudAcgacuucsasu	1922	AUGAAGUCGUAAGAAGUCUGAUA	2217
AD-292673.1	asgsucguaadGadAgucugauagaL96	1628	usdCsuadTcdAgacudTcdTuacgacususc	1923	GAAGUCGUAAGAAGUCUGAUAGA	2218

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-292677.1	gsusaagaagdTcdTgauagauggaL96	1629	usdCscadTcdTaucadGadCuucuuacsgsa	1924	UCGUAAGAAGUCUGAUAGAUGGA	2219
AD-292678.1	usasagaagudCudGauagauggaaL96	1630	usdTsccdAudCuaucdAgdAcuucuuascsg	1925	CGUAAGAAGUCUGAUAGAUGGAA	2220
AD-292679.1	asasgaagucdTgdAuagauggaauL96	1631	asdTsucdCadTcuaudCadGacuucuusasc	1926	GUAAGAAGUCUGAUAGAUGGAAU	2221
AD-292680.1	asgsaagucudGadTagauggaauaL96	1632	usdAsuudCcdAucuadTcdAgacuucususa	1927	UAAGAAGUCUGAUAGAUGGAAUA	2222
AD-292681.1	gsasagucugdAudAgauggaauauL96	1633	asdTsaudTcdCaucudAudCagacuucsusu	1928	AAGAAGUCUGAUAGAUGGAAUAC	2223
AD-292682.1	asasgucugadTadGauggaauacuL96	1634	asdGsuadTudCcaucdTadTcagacuuscsu	1929	AGAAGUCUGAUAGAUGGAAUACU	2224
AD-292684.1	gsuscugauadGadTggaauacuuaL96	1635	usdAsagdTadTuccadTcdTaucagacsusu	1930	AAGUCUGAUAGAUGGAAUACUUA	2225
AD-292685.1	uscsugauagdAudGgaauacuuauL96	1636	asdTsaadGudAuuccdAudCuaucagascsu	1931	AGUCUGAUAGAUGGAAUACUUAC	2226
AD-292691.1	asgsauggaadTadCuuaccaauaaL96	1637	usdTsaudTgdGuaagdTadTuccaucusasu	1932	AUAGAUGGAAUACUUACCAAUAA	2227
AD-292692.1	gsasuggaaudAcdTuaccaauaauL96	1638	asdTsuadTudGguaadGudAuuccaucsusa	1933	UAGAUGGAAUACUUACCAAUAAG	2228
AD-292693.1	asusggaauadCudTaccaauaagaL96	1639	usdCsuudAudTgguadAgdTauuccauscsu	1934	AGAUGGAAUACUUACCAAUAAGA	2229
AD-292694.1	usgsgaauacdTudAccaauaagaaL96	1640	usdTscudTadTuggudAadGuauuccasusc	1935	GAUGGAAUACUUACCAAUAAGAA	2230
AD-292695.1	gsgsaauacudTadCcaauaagaaaL96	1641	usdTsucdTudAuuggdTadAguauuccsasu	1936	AUGGAAUACUUACCAAUAAGAAA	2231
AD-292696.1	gsasauacuudAcdCaauaagaaaaL96	1642	usdTsuudCudTauugdGudAaguauucscsa	1937	UGGAAUACUUACCAAUAAGAAAA	2232
AD-292697.1	asasuacuuadCcdAauaagaaaauL96	1643	asdTsuudTcdTuauudGgdTaaguauuscsc	1938	GGAAUACUUACCAAUAAGAAAAU	2233
AD-292725.1	gsusuccaucdGudAuaucaauauuL96	1644	asdAsuadTudGauaudAcdGauggaacsasa	1939	UUGUUCCAUCGUAUAUCAAUAUC	2234
AD-292726.1	ususccaucgdTadTaucaauaucuL96	1645	asdGsaudAudTgauadTadCgauggaascsa	1940	UGUUCCAUCGUAUAUCAAUAUCU	2235
AD-292727.1	uscscaucgudAudAucaauaucuuL96	1646	asdAsgadTadTugaudAudAcgauggasasc	1941	GUUCCAUCGUAUAUCAAUAUCUU	2236
AD-292728.1	cscsaucguadTadTcaauaucuuuL96	1647	asdAsagdAudAuugadTadTacgauggsasa	1942	UUCCAUCGUAUAUCAAUAUCUUU	2237
AD-292757.1	ascsagaagudTudCuuccugaacuL96	1648	asdGsuudCadGgaagdAadAcuucugusasg	1943	CUACAGAAGUUUCUUCCUGAACG	2238
AD-292759.1	asgsaaguuudCudTccugaacgcuL96	1649	asdGscgdTudCaggadAgdAaacuucusgsu	1944	ACAGAAGUUUCUUCCUGAACGCG	2239
AD-292761.1	asasguuucudTcdCugaacgcgcuL96	1650	asdGscgdCgdTucagdGadAgaaacuuscsu	1945	AGAAGUUUCUUCCUGAACGCGCC	2240
AD-292766.1	uscsuuccugdAadCgcgccucaguL96	1651	asdCsugdAgdGcgcgdTudCaggaagasasa	1946	UUUCUUCCUGAACGCGCCUCAGC	2241
AD-292787.1	gsasuuuuaadAudCguaugcagaaL96	1652	usdTscudGcdAuacgdAudTuaaaaucsgsc	1947	GCGAUUUUAAAUCGUAUGCAGAA	2242
AD-292788.1	asususuuaaadTcdGuaugcagaauL96	1653	asdTsucdTgdCauacdGadTuuaaaausesg	1948	CGAUUUUAAAUCGUAUGCAGAAU	2243
AD-292789.1	ususuuaaaudCgdTaugcagaauaL96	1654	usdAsuudCudGcauadCgdAuuuaaaasusc	1949	GAUUUUAAAUCGUAUGCAGAAUA	2244
AD-292793.1	asasaucguadTgdCagaauauucaL96	1655	usdGsaadTadTucugdCadTacgauuusasa	1950	UUAAAUCGUAUGCAGAAUAUUCA	2245
AD-292795.1	asuscguaugdCadGaauauucaauL96	1656	asdTsugdAadTauucdTgdCauacgaususu	1951	AAAUCGUAUGCAGAAUAUUCAAU	2246
AD-292796.1	uscsguaugcdAgdAauauucaauuL96	1657	asdAsuudGadAuauudCudGcauacgasusu	1952	AAUCGUAUGCAGAAUAUUCAAUU	2247
AD-292797.1	csgsuaugcadGadAuauucaauuuL96	1658	asdAsaudTgdAauaudTcdTgcauacgsasu	1953	AUCGUAUGCAGAAUAUUCAAUUU	2248
AD-292800.1	asusgcagaadTadTucaauuugaaL96	1659	usdTscadAadTugaadTadTucugcausasc	1954	GUAUGCAGAAUAUUCAAUUUGAA	2249
AD-292802.1	gscsagaauadTudCaauuugaaguL96	1660	asdCsuudCadAauugdAadTauucugcsasu	1955	AUGCAGAAUAUUCAAUUUGAAGC	2250

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-292806.1	asasuauucadAudTugaagcaguuL96	1661	asdAscudGcdTucaadAudTgaauauuscsu	1956	AGAAUAUUCAAUUUGAAGCAGUG	2251
AD-292808.1	usasuucaaudTudGaagcagugguL96	1662	asdCscadCudGcuucdAadAuugaauasusu	1957	AAUAUUCAAUUUGAAGCAGUGGU	2252
AD-292870.1	gsasuguaugdCadTgauaaugauaL96	1663	usdAsucdAudTaucadTgdCauacaucsusc	1958	GAGAUGUAUGCAUGAUAAUGAUA	2253
AD-292893.1	asasuaguuudCgdAaucaaugcuuL96	1664	asdAsgcdAudTgauudCgdAaacuauuscsa	1959	UGAAUAGUUUCGAAUCAAUGCUG	2254
AD-292906.1	csasaugcugdCadAagcuuuauuuL96	1665	asdAsaudAadAgcuudTgdCagcauugsasu	1960	AUCAAUGCUGCAAAGCUUUAUUU	2255
AD-292915.1	asasagcuuudAudTucacauuuuuL96	1666	asdAsaadAudGugaadAudAaagcuuusgsc	1961	GCAAAGCUUUAUUUCACAUUUUU	2256
AD-292935.1	asasaaacaudTgdGuuuggcacuaL96	1667	usdAsgudGcdCaaacdCadAuguuuuusasa	1962	UUAAAAACAUUGGUUUGGCACUA	2257
AD-292936.1	asasaacauudGgdTuuggcacuauL96	1668	asdTsagdTgdCcaaadCcdAauguuuususa	1963	UAAAAACAUUGGUUUGGCACUAG	2258
AD-292967.1	ascsgaacaadGadTuaauuaccuuL96	1669	asdAsggdTadAuuaadTcdTuguucgususu	1964	AAACGAACAAGAUUAAUUACCUG	2259
AD-292970.1	asascaagaudTadAuuaccugucuL96	1670	asdGsacdAgdGuaaudTadAucuuguuscsg	1965	CGAACAAGAUUAAUUACCUGUCU	2260
AD-292974.1	asgsauuaaudTadCcugucuuccuL96	1671	asdGsgadAgdAcaggdTadAuuaaucususg	1966	CAAGAUUAAUUACCUGUCUUCCU	2261
AD-292975.1	gsasuuaauudAcdCugucuuccuuL96	1672	asdAsggdAadGacagdGudAauuaaucsusu	1967	AAGAUUAAUUACCUGUCUUCCUG	2262
AD-292978.1	usasauuaccdTgdTcuuccuguuuL96	1673	asdAsacdAgdGaagadCadGguaauuasasu	1968	AUUAAUUACCUGUCUUCCUGUUU	2263
AD-292979.1	asasuuaccudGudCuuccuguuucL96	1674	gsdAsaadCadGgaagdAcdAgguaauusasa	1969	UUAAUUACCUGUCUUCCUGUUUC	2264
AD-292980.1	asusuaccugdTcdTuccuguuucuL96	1675	asdGsaadAcdAggaadGadCagguaaususa	1970	UAAUUACCUGUCUUCCUGUUUCU	2265
AD-292981.1	ususaccugudCudTccuguuucuuL96	1676	asdAsgadAadCaggadAgdAcagguaasusu	1971	AAUUACCUGUCUUCCUGUUUCUC	2266
AD-292982.1	usasccugucdTudCcuguuucucaL96	1677	usdGsagdAadAcaggdAadGacagguasasu	1972	AUUACCUGUCUUCCUGUUUCUCA	2267
AD-292983.1	ascscugucudTcdCuguuucucaaL96	1678	usdTsgadGadAacagdGadAgacaggusasa	1973	UUACCUGUCUUCCUGUUUCUCAA	2268
AD-292984.1	cscsugucuudCcdTguuucucaauL96	1679	asdTsugdAgdAaacadGgdAagacaggsusa	1974	UACCUGUCUUCCUGUUUCUCAAG	2269
AD-293027.1	gsgsucuguudTudTccuuucauguL96	1680	asdCsaudGadAaggadAadAacagaccsusa	1975	UAGGUCUGUUUUUCCUUUCAUGC	2270
AD-293028.1	gsuscuguuudTudCcuuucaugcuL96	1681	asdGscadTgdAaaggdAadAaacagacscsu	1976	AGGUCUGUUUUUCCUUUCAUGCC	2271
AD-293034.1	ususuuccuudTcdAugccucuuaaL96	1682	usdTsaadGadGgcaudGadAaggaaaasasc	1977	GUUUUUCCUUUCAUGCCUCUUAA	2272
AD-293037.1	uscscuuucadTgdCcucuuaaaaaL96	1683	usdTsuudTadAgaggdCadTgaaaggasasa	1978	UUUCCUUUCAUGCCUCUUAAAAA	2273
AD-293039.1	csusuucaugdCcdTcuuaaaaacuL96	1684	asdGsuudTudTaagadGgdCaugaaagsgsa	1979	UCCUUUCAUGCCUCUUAAAAACU	2274
AD-293099.1	ususuuuccadTudTaaagguggauL96	1685	asdTsccdAcdCuuuadAadTggaaaaasusa	1980	UAUUUUUCCAUUUAAAGGUGGAC	2275
AD-293153.1	asascuuauudTadCacagggaaguL96	1686	asdCsuudCcdCugugdTadAauaaguuscsu	1981	AGAACUUAUUUACACAGGGAAGG	2276
AD-293156.1	ususauuuacdAcdAgggaagguuuL96	1687	asdAsacdCudTcccudGudGuaaauaasgsu	1982	ACUUAUUUACACAGGGAAGGUUU	2277
AD-293162.1	ascsacagggdAadGguuuaagacuL96	1688	asdGsucdTudAaaccdTudCccugugusasa	1983	UUACACAGGGAAGGUUUAAGACU	2278
AD-293163.1	csascagggadAgdGuuuaagacuuL96	1689	asdAsgudCudTaaacdCudTcccugugsusa	1984	UACACAGGGAAGGUUUAAGACUG	2279
AD-293166.1	asgsggaaggdTudTaagacuguuuL96	1690	asdAsacdAgdTcuuadAadCcuucccusgsu	1985	ACAGGGAAGGUUUAAGACUGUUC	2280
AD-293167.1	gsgsgaaggudTudAagacuguucaL96	1691	usdGsaadCadGucuudAadAccuucccsusg	1986	CAGGGAAGGUUUAAGACUGUUCA	2281
AD-293168.1	gsgsaagguudTadAgacuguucaaL96	1692	usdTsgadAcdAgucudTadAaccuuccscsu	1987	AGGGAAGGUUUAAGACUGUUCAA	2282

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-293169.1	gsasagguuudAadGacuguucaauL96	1693	asdTsugdAadCagucdTudAaaccuucscsc	1988	GGGAAGGUUUAAGACUGUUCAAG	2283
AD-293170.1	asasgguuuadAgdAcuguucaaguL96	1694	asdCsuudGadAcagudCudTaaaccuuscsc	1989	GGAAGGUUUAAGACUGUUCAAGU	2284
AD-293171.1	asgsguuuaadGadCuguucaaguaL96	1695	usdAscudTgdAacagdTcdTuaaaccususc	1990	GAAGGUUUAAGACUGUUCAAGUA	2285
AD-293172.1	gsgsuuuaagdAcdTguucaaguauL96	1696	asdTsacdTudGaacadGudCuuaaaccsusu	1991	AAGGUUUAAGACUGUUCAAGUAG	2286
AD-293174.1	ususuaagacdTgdTucaaguagcaL96	1697	usdGscudAcdTugaadCadGucuuaaascsc	1992	GGUUUAAGACUGUUCAAGUAGCA	2287
AD-293176.1	usasagacugdTudCaaguagcauuL96	1698	asdAsugdCudAcuugdAadCagucuuasasa	1993	UUUAAGACUGUUCAAGUAGCAUU	2288
AD-293177.1	asasgacugudTcdAaguagcauuuL96	1699	asdAsaudGcdTacuudGadAcagucuusasa	1994	UUAAGACUGUUCAAGUAGCAUUC	2289
AD-293178.1	asgsacuguudCadAguagcauucuL96	1700	asdGsaadTgdCuacudTgdAacagucususa	1995	UAAGACUGUUCAAGUAGCAUUCC	2290
AD-293179.1	gsascuguucdAadGuagcauuccaL96	1701	usdGsgadAudGcuacdTudGaacagucsusu	1996	AAGACUGUUCAAGUAGCAUUCCA	2291
AD-293180.1	ascsuguucadAgdTagcauuccaaL96	1702	usdTsggdAadTgcuadCudTgaacaguscsu	1997	AGACUGUUCAAGUAGCAUUCCAA	2292
AD-293181.1	csusguucaadGudAgcauuccaauL96	1703	asdTsugdGadAugcudAcdTugaacagsusc	1998	GACUGUUCAAGUAGCAUUCCAAU	2293
AD-293182.1	usgsuucaagdTadGcauuccaauuL96	1704	asdAsuudGgdAaugcdTadCuugaacasgsu	1999	ACUGUUCAAGUAGCAUUCCAAUC	2294
AD-293183.1	gsusucaagudAgdCauuccaaucuL96	1705	asdGsaudTgdGaaugdCudAcuugaacsasg	2000	CUGUUCAAGUAGCAUUCCAAUCU	2295
AD-293184.1	ususcaaguadGcdAuuccaaucuuL96	1706	asdAsgadTudGgaaudGcdTacuugaascsa	2001	UGUUCAAGUAGCAUUCCAAUCUG	2296
AD-293186.1	csasaguagcdAudTccaaucuguaL96	1707	usdAscadGadTuggadAudGcuacuugsasa	2002	UUCAAGUAGCAUUCCAAUCUGUA	2297
AD-293187.1	asasguagcadTudCcaaucuguauL96	1708	asdTsacdAgdAuuggdAadTgcuacuusgsa	2003	UCAAGUAGCAUUCCAAUCUGUAG	2298
AD-293191.1	asgscauuccdAadTcuguagccauL96	1709	asdTsggdCudAcagadTudGgaaugcusasc	2004	GUAGCAUUCCAAUCUGUAGCCAU	2299
AD-293218.1	gsasauaucadAcdAagaacacagaL96	1710	usdCsugdTgdTucuudGudTgauauucsusg	2005	CAGAAUAUCAACAAGAACACAGA	2300
AD-293228.1	asasgaacacdAgdAaugagugcauL96	1711	asdTsgcdAcdTcauudCudGuguucuusgsu	2006	ACAAGAACACAGAAUGAGUGCAC	2301
AD-293230.1	gsasacacagdAadTgagugcacauL96	1712	asdTsgudGcdAcucadTudCuguguucsusu	2007	AAGAACACAGAAUGAGUGCACAG	2302
AD-293231.1	asascacagadAudGagugcacaguL96	1713	asdCsugdTgdCacucdAudTcuguguuscsu	2008	AGAACACAGAAUGAGUGCACAGC	2303
AD-293235.1	csasgaaugadGudGcacagcuaauL96	1714	asdTsuadGcdTgugcdAcdTcauucugsusg	2009	CACAGAAUGAGUGCACAGCUAAG	2304
AD-293271.1	asgsgcagcudTudAucucaaccuuL96	1715	asdAsggdTudGagaudAadAgcugccusgsc	2010	GCAGGCAGCUUUAUCUCAACCUG	2305
AD-293273.1	gscsagcuuudAudCucaaccuggaL96	1716	usdCscadGgdTugagdAudAaagcugcscsu	2011	AGGCAGCUUUAUCUCAACCUGGA	2306
AD-293306.1	ususcagcaudTudGaaagauuucuL96	1717	asdGsaadAudCuuucdAadAugcugaasusc	2012	GAUUCAGCAUUUGAAAGAUUUCC	2307
AD-293309.1	asgscauuugdAadAgauuucccuaL96	1718	usdAsggdGadAaucudTudCaaaugcusgsa	2013	UCAGCAUUUGAAAGAUUUCCCUA	2308
AD-293311.1	csasuuugaadAgdAuuucccuaguL96	1719	asdCsuadGgdGaaaudCudTucaaaugscsu	2014	AGCAUUUGAAAGAUUUCCCUAGC	2309
AD-293312.1	asususugaaadGadTuucccuagcuL96	1720	asdGscudAgdGgaaadTcdTuucaaausgsc	2015	GCAUUUGAAAGAUUUCCCUAGCC	2310
AD-293315.1	usgsaaagaudTudCccuagccucuL96	1721	asdGsagdGcdTagggdAadAucuuucasasa	2016	UUUGAAAGAUUUCCCUAGCCUCU	2311
AD-293316.1	gsasaagauudTcdCcuagccucuuL96	1722	asdAsgadGgdCuaggdGadAaucuuucsasa	2017	UUGAAAGAUUUCCCUAGCCUCUU	2312
AD-293323.1	ususcccuagdCcdTcuuccuuuuuL96	1723	asdAsaadAgdGaagadGgdCuagggaasasu	2018	AUUUCCCUAGCCUCUUCCUUUUU	2313
AD-293353.1	asasaacggudGcdAacucuauucuL96	1724	asdGsaadTadGaguudGcdAccguuuusgsg	2019	CCAAAACGGUGCAACUCUAUUCU	2314

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-293354.1	asasacggugdCadAcucuauucuuL96	1725	asdAsgadAudAgagudTgdCaccguuususg	2020	CAAAACGGUGCAACUCUAUUCUG	2315
AD-293355.1	asascggugcdAadCucuauucuguL96	1726	asdCsagdAadTagagdTudGcaccguususu	2021	AAAACGGUGCAACUCUAUUCUGG	2316
AD-293358.1	gsgsugcaacdTcdTauucuggacuL96	1727	asdGsucdCadGaauadGadGuugcaccsgsu	2022	ACGGUGCAACUCUAUUCUGGACU	2317
AD-293359.1	gsusgcaacudCudAuucuggacuuL96	1728	asdAsgudCcdAgaaudAgdAguugcacscsg	2023	CGGUGCAACUCUAUUCUGGACUU	2318
AD-293360.1	usgscaacucdTadTucuggacuuuL96	1729	asdAsagdTcdCagaadTadGaguugcascsc	2024	GGUGCAACUCUAUUCUGGACUUU	2319
AD-293361.1	gscsaacucudAudTcuggacuuuaL96	1730	usdAsaadGudCcagadAudAgaguugcsasc	2025	GUGCAACUCUAUUCUGGACUUUA	2320
AD-293362.1	csasacucuadTudCuggacuuuauL96	1731	asdTsaadAgdTccagdAadTagaguugscsa	2026	UGCAACUCUAUUCUGGACUUUAU	2321
AD-293363.1	asascucuaudTcdTggacuuuauuL96	1732	asdAsuadAadGuccadGadAuagaguusgsc	2027	GCAACUCUAUUCUGGACUUUAUU	2322
AD-293364.1	ascsucuauudCudGgacuuuauuaL96	1733	usdAsaudAadAgucdAgdAauagagususg	2028	CAACUCUAUUCUGGACUUUAUUA	2323
AD-293365.1	csuscuauucdTgdGacuuuauuauL96	1734	asdTsaadTadAagucdCadGaauagagsusu	2029	AACUCUAUUCUGGACUUUAUUAC	2324
AD-293368.1	usasuucuggdAcdTuuauuacuuuL96	1735	asdAsagdTadAuaaadGudCcagaauasgsa	2030	UCUAUUCUGGACUUUAUUACUUG	2325
AD-293369.1	asusucuggadCudTuauuacuugaL96	1736	usdCsaadGudAauaadAgdTccagaausasg	2031	CUAUUCUGGACUUUAUUACUUGA	2326
AD-293370.1	ususcuggacdTudTauuacuugauL96	1737	asdTscadAgdTaauadAadGuccagaasusa	2032	UAUUCUGGACUUUAUUACUUGAU	2327
AD-293410.1	usgsaaguccdAcdCaaaaguggauL96	1738	asdTsccdAcdTuuugdGudGgacuucasgsa	2033	UCUGAAGUCCACCAAAAGUGGAC	2328
AD-293419.1	cscsaaaagudGgdAcccucuauauL96	1739	asdTsaudAgdAgggudCcdAcuuuuggsusg	2034	CACCAAAAGUGGACCCUCUAUAU	2329
AD-293420.1	csasaaagugdGadCccucuauauuL96	1740	asdAsuadTadGagggdTcdCacuuuugsgsu	2035	ACCAAAAGUGGACCCUCUAUAUU	2330
AD-293422.1	asasaguggadCcdCucuauauuucL96	1741	gsdAsaadTadTagagdGgdTccacuuususg	2036	CAAAAGUGGACCCUCUAUAUUUC	2331
AD-293423.1	asasguggacdCcdTcuauauuucuL96	1742	asdGsaadAudAuagadGgdGuccacuususu	2037	AAAAGUGGACCCUCUAUAUUUCC	2332
AD-293530.1	csusuucauadTadTccuugguccuL96	1743	asdGsgadCcdAaggadTadTaugaaagscsa	2038	UGCUUUCAUAUAUCCUUGGUCCC	2333
AD-293532.1	ususcauauadTcdCuuggucccauL96	1744	asdTsggdGadCcaagdGadTauaugaasasg	2039	CUUUCAUAUAUCCUUGGUCCCAG	2334
AD-293554.1	gsasuguuuadGadCaauuuuagguL96	1745	asdCscudAadAauugdTcdTaaacaucsusc	2040	GAGAUGUUUAGACAAUUUUAGGC	2335
AD-293555.1	asusguuuagdAcdAauuuuaggcuL96	1746	asdGsccdTadAaauudGudCuaaacauscsu	2041	AGAUGUUUAGACAAUUUUAGGCU	2336
AD-293557.1	gsusuuagacdAadTuuuaggcucaL96	1747	usdGsagdCcdTaaaadTudGucuaaacsasu	2042	AUGUUUAGACAAUUUUAGGCUCA	2337
AD-293558.1	ususuagacadAudTuuaggcucaaL96	1748	usdTsgadGcdCuaaadAudTgucuaaascsa	2043	UGUUUAGACAAUUUUAGGCUCAA	2338
AD-293559.1	ususagacaadTudTuaggcucaaaL96	1749	usdTsugdAgdCcuaadAadTugucuaasasc	2044	GUUUAGACAAUUUUAGGCUCAAA	2339
AD-293560.1	usasgacaaudTudTaggcucaaaaL96	1750	usdTsuudGadGccuadAadAuugucuasasa	2045	UUUAGACAAUUUUAGGCUCAAAA	2340
AD-293562.1	gsascaauuudTadGgcucaaaaauL96	1751	asdTsuudTudGagccdTadAaauugucsusa	2046	UAGACAAUUUUAGGCUCAAAAAU	2341
AD-293569.1	ususaggcucdAadAaauuaaagcuL96	1752	asdGscudTudAauuudTudGagccuaasasa	2047	UUUUAGGCUCAAAAAUUAAAGCU	2342
AD-293570.1	usasggcucadAadAauuaaagcuaL96	1753	usdAsgcdTudTaauudTudTgagccuasasa	2048	UUUAGGCUCAAAAAUUAAAGCUA	2343
AD-293571.1	asgsgcucaadAadAuuaaagcuaaL96	1754	usdTsagdCudTuaaudTudTugagccusasa	2049	UUAGGCUCAAAAAUUAAAGCUAA	2344
AD-293572.1	gsgscucaaadAadTuaaagcuaauL96	1755	asdTsuadGcdTuuaadTudTuugagccsusa	2050	UAGGCUCAAAAAUUAAAGCUAAC	2345
AD-293573.1	gscsucaaaadAudTaaagcuaacaL96	1756	usdGsuudAgdCuuuadAudTuuugagcscsu	2051	AGGCUCAAAAAUUAAAGCUAACA	2346

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-293574.1	csuscaaaaadTudAaagcuaacauL96	1757	asdTsgudTadGcuuudAadTuuuugagscsc	2052	GGCUCAAAAAUUAAAGCUAACAC	2347
AD-293575.1	uscsaaaaaudTadAagcuaacacaL96	1758	usdGsugdTudAgcuudTadAuuuuugasgsc	2053	GCUCAAAAAUUAAAGCUAACACA	2348
AD-293576.1	csasaaaauudAadAgcuaacacauL96	1759	asdTsgudGudTagcudTudAauuuuugsasg	2054	CUCAAAAAUUAAAGCUAACACAG	2349
AD-293579.1	asasauuaaadGcdTaacacaggaaL96	1760	usdTsccdTgdTguuadGcdTuuaauuususu	2055	AAAAAUUAAAGCUAACACAGGAA	2350
AD-293586.1	asgscuaacadCadGgaaaaggaauL96	1761	asdTsucdCudTuuccdTgdTguuagcususu	2056	AAAGCUAACACAGGAAAAGGAAC	2351
AD-293589.1	usasacacagdGadAaaggaacuguL96	1762	asdCsagdTudCcuuudTcdCuguguuasgsc	2057	GCUAACACAGGAAAAGGAACUGU	2352
AD-293592.1	csascaggaadAadGgaacuguacuL96	1763	asdGsuadCadGuuccdTudTuccugugsusu	2058	AACACAGGAAAAGGAACUGUACU	2353
AD-293594.1	csasggaaaadGgdAacuguacuguL96	1764	asdCsagdTadCaguudCcdTuuuccugsusg	2059	CACAGGAAAAGGAACUGUACUGG	2354
AD-293601.1	asgsgaacugdTadCuggcuauuauL96	1765	asdTsaadTadGccagdTadCaguuccususu	2060	AAAGGAACUGUACUGGCUAUUAC	2355
AD-293602.1	gsgsaacugudAcdTggcuauuacaL96	1766	usdGsuadAudAgccadGudAcaguuccsusu	2061	AAGGAACUGUACUGGCUAUUACA	2356
AD-293872.1	csgsacucccdAcdTacaucaagauL96	1767	asdTscudTgdAuguadGudGggagucgsgsa	2062	UCCGACUCCCACUACAUCAAGAC	2357
AD-293875.1	csuscccacudAcdAucaagacuaaL96	1768	usdTsagdTcdTugaudGudAgugggagsusc	2063	GACUCCCACUACAUCAAGACUAA	2358
AD-293876.1	uscsccacuadCadTcaagacuaauL96	1769	asdTsuadGudCuugadTgdTagugggasgsu	2064	ACUCCCACUACAUCAAGACUAAU	2359
AD-293877.1	cscscacuacdAudCaagacuaauuL96	1770	asdAsuudAgdTcuugdAudGuagugggsasg	2065	CUCCCACUACAUCAAGACUAAUC	2360
AD-293878.1	cscsacuacadTcdAagacuaaucuL96	1771	asdGsaudTadGucuudGadTguaguggsgsa	2066	UCCCACUACAUCAAGACUAAUCU	2361
AD-293879.1	csascuacaudCadAgacuaaucuuL96	1772	asdAsgadTudAgucudTgdAuguagugsgsg	2067	CCCACUACAUCAAGACUAAUCUU	2362
AD-293880.1	ascsuacaucdAadGacuaaucuuuL96	1773	asdAsagdAudTagucdTudGauguagusgsg	2068	CCACUACAUCAAGACUAAUCUUG	2363
AD-293881.1	csusacaucadAgdAcuaaucuuguL96	1774	asdCsaadGadTuagudCudTgauguagsusg	2069	CACUACAUCAAGACUAAUCUUGU	2364
AD-293882.1	usascaucaadGadCuaaucuuguuL96	1775	asdAscadAgdAuuagdTcdTugauguasgsu	2070	ACUACAUCAAGACUAAUCUUGUU	2365
AD-293883.1	ascsaucaagdAcdTaaucuuguuuL96	1776	asdAsacdAadGauuadGudCuugaugusasg	2071	CUACAUCAAGACUAAUCUUGUUU	2366
AD-293898.1	ususgugugudTudTucacauguauL96	1777	asdTsacdAudGugaadAadAcacacaasasa	2072	UUUUGUGUGUUUUUCACAUGUAU	2367
AD-293902.1	gsusguuuuudCadCauguauuauaL96	1778	usdAsuadAudAcaugdTgdAaaaacacsasc	2073	GUGUGUUUUUCACAUGUAUUAUA	2368
AD-293909.1	uscsacaugudAudTauagaaugcuL96	1779	asdGscadTudCuauadAudAcaugugasasa	2074	UUUCACAUGUAUUAUAGAAUGCU	2369
AD-293910.1	csascauguadTudAuagaaugcuuL96	1780	asdAsgcdAudTcuaudAadTacaugugsasa	2075	UUCACAUGUAUUAUAGAAUGCUU	2370
AD-293914.1	usgsuauuaudAgdAaugcuuuuguL96	1781	asdCsaadAadGcauudCudAuaauacasusg	2076	CAUGUAUUAUAGAAUGCUUUUGC	2371
AD-293915.1	gsusauuauadGadAugcuuuugcaL96	1782	usdGscadAadAgcaudTcdTauaauacsasu	2077	AUGUAUUAUAGAAUGCUUUUGCA	2372
AD-293919.1	usasuagaaudGcdTuuugcauggaL96	1783	usdCscadTgdCaaaadGcdAuucuauasasu	2078	AUUAUAGAAUGCUUUUGCAUGGA	2373
AD-293922.1	asgsaaugcudTudTgcauggacuaL96	1784	usdAsgudCcdAugcadAadAgcauucusasu	2079	AUAGAAUGCUUUUGCAUGGACUA	2374
AD-293923.1	gsasaugcuudTudGcauggacuauL96	1785	asdTsagdTcdCaugcdAadAagcauucsusa	2080	UAGAAUGCUUUUGCAUGGACUAU	2375
AD-293925.1	asusgcuuuudGcdAuggacuaucuL96	1786	asdGsaudAgdTccaudGcdAaaagcaususc	2081	GAAUGCUUUUGCAUGGACUAUCC	2376
AD-293928.1	csusuuugcadTgdGacuauccucuL96	1787	asdGsagdGadTagucdCadTgcaaaagscsa	2082	UGCUUUUGCAUGGACUAUCCUCU	2377
AD-293931.1	ususgcauggdAcdTauccucuuguL96	1788	asdCsaadGadGgauadGudCcaugcaasasa	2083	UUUUGCAUGGACUAUCCUCUUGU	2378

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-293932.1	usgscauggadCudAuccucuuguuL96	1789	asdAscadAgdAggaudAgdTccaugcasasa	2084	UUUGCAUGGACUAUCCUCUUGUU	2379
AD-293933.1	gscsauggacdTadTccucuuguuuL96	1790	asdAsacdAadGaggadTadGuccaugcsasa	2085	UUGCAUGGACUAUCCUCUUGUUU	2380
AD-293934.1	csasuggacudAudCcucuuguuuuL96	1791	asdAsaadCadAgaggdAudAguccaugscsa	2086	UGCAUGGACUAUCCUCUUGUUUU	2381
AD-293935.1	asusggacuadTcdCucuuguuuuuL96	1792	asdAsaadAcdAagagdGadTaguccausgsc	2087	GCAUGGACUAUCCUCUUGUUUUU	2382
AD-293936.1	usgsgacuaudCcdTcuuguuuuuaL96	1793	usdAsaadAadCaagadGgdAuaguccasusg	2088	CAUGGACUAUCCUCUUGUUUUUA	2383
AD-293937.1	gsgsacuaucdCudCuuguuuuuauL96	1794	asdTsaadAadAcaagdAgdGauaguccsasu	2089	AUGGACUAUCCUCUUGUUUUUAU	2384
AD-293938.1	gsascuauccdTcdTuguuuuuauuL96	1795	asdAsuadAadAacaadGadGgauagucscsa	2090	UGGACUAUCCUCUUGUUUUUAUU	2385
AD-293940.1	csusauccucdTudGuuuuuauuaaL96	1796	usdTsaadTadAaaacdAadGaggauagsusc	2091	GACUAUCCUCUUGUUUUUAUUAA	2386

* Target: HSD17B13

Table 11. HSD17B13 NonF DNA Unmodified Sequence*

Duplex Name	Sense sequence 5' to 3'	SEQ ID NO:	Position in NM_178135.4	Antisense sequence 5' to 3'	SEQ ID NO:	Range in NM_178135.4
AD-291929.1	ACACAAGGACTGAACCAGAAU	2387	25-45	ATUCTGGUUCAGUCCUUGUGUAG	2682	23-45
AD-291931.1	ACAAGGACTGAACCAGAAGGA	2388	27-47	UCCUTCTGGUUCAGUCCUUGUGU	2683	25-47
AD-291988.1	UCCUUCUGCUTCUGAUCACCA	2389	85-105	UGGUGATCAGAAGCAGAAGGAUU	2684	83-105
AD-291993.1	CUGCUUCUGATCACCAUCAUU	2390	90-110	AAUGAUGGUGATCAGAAGCAGAA	2685	88-110
AD-291998.1	UCUGAUCACCAUCAUCUACUU	2391	95-115	AAGUAGAUGAUGGTGAUCAGAAG	2686	93-115
AD-292005.1	ACCAUCAUCUACUCCUACUUU	2392	102-122	AAAGTAGGAGUAGAUGAUGGUGA	2687	100-122
AD-292006.1	CCAUCAUCTACUCCUACUUGU	2393	103-123	ACAAGUAGGAGTAGAUGAUGGUG	2688	101-123
AD-292007.1	CAUCAUCUACTCCUACUUGGA	2394	104-124	UCCAAGTAGGAGUAGAUGAUGGU	2689	102-124
AD-292008.1	AUCAUCUACUCCUACUUGGAU	2395	105-125	ATCCAAGUAGGAGTAGAUGAUGG	2690	103-125
AD-292010.1	CAUCUACUCCTACUUGGAGUU	2396	107-127	AACUCCAAGUAGGAGUAGAUGAU	2691	105-127
AD-292012.1	UCUACUCCTACUUGGAGUCGU	2397	109-129	ACGACUCCAAGTAGGAGUAGAUG	2692	107-129
AD-292013.1	CUACUCCUACTUGGAGUCGUU	2398	110-130	AACGACTCCAAGUAGGAGUAGAU	2693	108-130
AD-292014.1	UACUCCUACUTGGAGUCGUUU	2399	111-131	AAACGACUCCAAGTAGGAGUAGA	2694	109-131
AD-292015.1	ACUCCUACTUGGAGUCGUUGU	2400	112-132	ACAACGACUCCAAGUAGGAGUAG	2695	110-132
AD-292017.1	UCCUACUUGGAGUCGUUGGUU	2402	114-134	AACCAACGACUCCAAGUAGGAGU	2697	112-134
AD-292028.1	GUCGUUGGTGAAGUUUUUCAU	2403	125-145	ATGAAAAACUUCACCAACGACUC	2698	123-145
AD-292137.1	UUGGUUCUGUGGGAUAUUAAU	2404	252-272	ATUAAUAUCCCACAGAACCAAUA	2699	250-272
AD-292140.1	GUUCUGUGGGAUAUUAAUAAU	2405	255-275	ATUATUAAUAUCCCACAGAACCA	2700	253-275
AD-292143.1	CUGUGGGATATUAAUAAGCGU	2406	258-278	ACGCTUAUUAATATCCCACAGAA	2701	256-278
AD-292182.1	GCUGAGUGCCGAAAACUAGGU	2407	297-317	ACCUAGTUUUCGGCACUCAGCUG	2702	295-317
AD-292183.1	CUGAGUGCCGAAAACUAGGCU	2408	298-318	AGCCTAGUUUUCGGCACUCAGCU	2703	296-318
AD-292185.1	GAGUGCCGAAAACUAGGCGUU	2409	300-320	AACGCCTAGUUTUCGGCACUCAG	2704	298-320
AD-292186.1	AGUGCCGAAAACUAGGCGUCA	2410	301-321	UGACGCCUAGUTUTCGGCACUCA	2705	299-321
AD-292187.1	GUGCCGAAAACUAGGCGUCAU	2411	302-322	ATGACGCCUAGTUTUCGGCACUC	2706	300-322
AD-292188.1	UGCCGAAAACTAGGCGUCACU	2412	303-323	AGUGACGCCUAGUTUUCGGCACU	2707	301-323
AD-292189.1	GCCGAAAACUAGGCGUCACUU	2413	304-324	AAGUGACGCCUAGTUUUCGGCAC	2708	302-324
AD-292190.1	CCGAAAACTAGGCGUCACUGU	2414	305-325	ACAGTGACGCCTAGUUUUCGGCA	2709	303-325
AD-292238.1	CAGAGAAGAGAUCUAUCGCUU	2415	353-373	AAGCGATAGAUCUCUUCUCUGUU	2710	351-373
AD-292244.1	AGAGAUCUAUCGCUCUCUAAA	2416	359-379	UTUAGAGAGCGAUAGAUCUCUUC	2711	357-379

Duplex Name	Sense sequence 5' to 3'	SEQ ID NO:	Position in NM_178135.4	Antisense sequence 5' to 3'	SEQ ID NO:	Range in NM_178135.4
AD-292245.1	GAGAUCUATCGCUCUCUAAAU	2417	360-380	ATUUAGAGAGCGATAGAUCUCUU	2712	358-380
AD-292247.1	GAUCUAUCGCTCUCUAAAUCA	2418	362-382	UGAUTUAGAGAGCGAUAGAUCUC	2713	360-382
AD-292248.1	AUCUAUCGCUCUCUAAAUCAU	2419	363-383	ATGATUTAGAGAGCGAUAGAUCU	2714	361-383
AD-292250.1	CUAUCGCUCUCUAAAUCAGGU	2420	365-385	ACCUGATUUAGAGAGCGAUAGAU	2715	363-385
AD-292251.1	UAUCGCUCTCTAAAUCAGGUU	2421	366-386	AACCTGAUUUAGAGAGCGAUAGA	2716	364-386
AD-292253.1	UCGCUCUCTAAAUCAGGUGAA	2423	368-388	UTCACCTGAUUTAGAGAGCGAUA	2718	366-388
AD-292254.1	CGCUCUCUAAAUCAGGUGAAU	2424	369-389	ATUCACCUGAUTUAGAGAGCGAU	2719	367-389
AD-292257.1	UCUCUAAATCAGGUGAAGAAA	2425	372-392	UTUCTUCACCUGATUUAGAGAGC	2720	370-392
AD-292309.1	AUGCUGGGACAGUAUAUCCAU	2426	424-444	ATGGAUAUACUGUCCCAGCAUUA	2721	422-444
AD-292310.1	UGCUGGGACAGUAUAUCCAGU	2427	425-445	ACUGGATAUACTGTCCCAGCAUU	2722	423-445
AD-292315.1	GGACAGUATATCCAGCCGAUU	2428	430-450	AAUCGGCUGGATATACUGUCCCA	2723	428-450
AD-292318.1	CAGUAUAUCCAGCCGAUCUUU	2429	433-453	AAAGAUCGGCUGGAUAUACUGUC	2724	431-453
AD-292344.1	ACCAAGGATGAAGAGAUUACU	2430	459-479	AGUAAUCUCUUCATCCUUGGUGC	2725	457-479
AD-292345.1	CCAAGGAUGAAGAGAUUACCA	2431	460-480	UGGUAATCUCUTCAUCCUUGGUG	2726	458-480
AD-292346.1	CAAGGAUGAAGAGAUUACCAA	2432	461-481	UTGGTAAUCUCTUCAUCCUUGGU	2727	459-481
AD-292363.1	CCAAGACATUTGAGGUCAACA	2433	478-498	UGUUGACCUCAAATGUCUUGGUA	2728	476-498
AD-292366.1	AGACAUUUGAGGUCAACAUCU	2434	481-501	AGAUGUTGACCTCAAAUGUCUUG	2729	479-501
AD-292367.1	GACAUUUGAGGUCAACAUCCU	2435	482-502	AGGATGTUGACCUCAAAUGUCUU	2730	480-502
AD-292369.1	CAUUUGAGGUCAACAUCCUAU	2436	484-504	ATAGGATGUUGACCUCAAAUGUC	2731	482-504
AD-292370.1	AUUUGAGGTCAACAUCCUAGU	2437	485-505	ACUAGGAUGUUGACCUCAAAUGU	2732	483-505
AD-292371.1	UUUGAGGUCAACAUCCUAGGA	2438	486-506	UCCUAGGAUGUTGACCUCAAAUG	2733	484-506
AD-292373.1	UGAGGUCAACAUCCUAGGACA	2439	488-508	UGUCCUAGGAUGUTGACCUCAAA	2734	486-508
AD-292374.1	GAGGUCAACATCCUAGGACAU	2440	489-509	ATGUCCTAGGATGTUGACCUCAA	2735	487-509
AD-292376.1	GGUCAACATCCUAGGACAUUU	2441	491-511	AAAUGUCCUAGGATGUUGACCUC	2736	489-511
AD-292377.1	GUCAACAUCCTAGGACAUUUU	2442	492-512	AAAATGTCCUAGGAUGUUGACCU	2737	490-512
AD-292379.1	CAACAUCCTAGGACAUUUUUG	2443	494-514	CAAAAATGUCCTAGGAUGUUGAC	2738	492-514
AD-292380.1	AACAUCCUAGGACAUUUUUGU	2444	495-515	ACAAAAAUGUCCUAGGAUGUUGA	2739	493-515
AD-292381.1	ACAUCCUAGGACAUUUUUGGA	2445	496-516	UCCAAAAAUGUCCTAGGAUGUUG	2740	494-516
AD-292382.1	CAUCCUAGGACAUUUUUGGAU	2446	497-517	ATCCAAAAAUGTCCUAGGAUGUU	2741	495-517
AD-292383.1	AUCCUAGGACAUUUUUGGAUU	2447	498-518	AAUCCAAAAAUGUCCUAGGAUGU	2742	496-518
AD-292384.1	UCCUAGGACATUUUUGGAUCA	2448	499-519	UGAUCCAAAAATGTCCUAGGAUG	2743	497-519
AD-292385.1	CCUAGGACAUTUUUGGAUCAU	2449	500-520	ATGATCCAAAAAUGUCCUAGGAU	2744	498-520

Duplex Name	Sense sequence 5' to 3'	SEQ ID NO:	Position in NM_178135.4	Antisense sequence 5' to 3'	SEQ ID NO:	Range in NM_178135.4
AD-292388.1	AGGACAUUTUTGGAUCACAAA	2450	503-523	UTUGTGAUCCAAAAAUGUCCUAG	2745	501-523
AD-292389.1	GGACAUUUTUGGAUCACAAAA	2451	504-524	UTUUGUGAUCCAAAAAUGUCCUA	2746	502-524
AD-292390.1	GACAUUUUTGGAUCACAAAAU	2452	505-525	ATUUTGTGAUCCAAAAAUGUCCU	2747	503-525
AD-292394.1	UUUUUGGATCACAAAAGCACU	2453	509-529	AGUGCUTUUGUGATCCAAAAAUG	2748	507-529
AD-292397.1	UUGGAUCACAAAAGCACUUCU	2454	512-532	AGAAGUGCUUUTGTGAUCCAAAA	2749	510-532
AD-292398.1	UGGAUCACAAAAGCACUUCUU	2455	513-533	AAGAAGTGCUUTUGUGAUCCAAA	2750	511-533
AD-292399.1	GGAUCACAAAAGCACUUCUUU	2456	514-534	AAAGAAGUGCUTUTGUGAUCCAA	2751	512-534
AD-292403.1	CACAAAAGCACUUCUUCCAUU	2457	518-538	AAUGGAAGAAGTGCUUUUGUGAU	2752	516-538
AD-292404.1	ACAAAAGCACTUCUUCCAUCU	2458	519-539	AGAUGGAAGAAGUGCUUUUGUGA	2753	517-539
AD-292405.1	CAAAAGCACUTCUUCCAUCGA	2459	520-540	UCGATGGAAGAAGTGCUUUUGUG	2754	518-540
AD-292406.1	AAAAGCACTUCUUCCAUCGAU	2460	521-541	ATCGAUGGAAGAAGUGCUUUUGU	2755	519-541
AD-292407.1	AAAGCACUTCTUCCAUCGAUU	2461	522-542	AAUCGATGGAAGAAGUGCUUUUG	2756	520-542
AD-292409.1	AGCACUUCTUCCAUCGAUGAU	2463	524-544	ATCATCGAUGGAAGAAGUGCUUU	2758	522-544
AD-292410.1	GCACUUCUTCCAUCGAUGAUU	2464	525-545	AAUCAUCGAUGGAAGAAGUGCUU	2759	523-545
AD-292434.1	AGAAAUCATGGCCACAUCGUU	2465	549-569	AACGAUGUGGCCATGAUUUCUCU	2760	547-569
AD-292486.1	UUCCUUACCUCAUCCCAUAUU	2466	601-621	AAUATGGGAUGAGGUAAGGAAUC	2761	599-621
AD-292487.1	UCCUUACCTCAUCCCAUAUUU	2467	602-622	AAAUAUGGGAUGAGGUAAGGAAU	2762	600-622
AD-292492.1	ACCUCAUCCCAUAUUGUUCCA	2468	607-627	UGGAACAAUAUGGGAUGAGGUAA	2763	605-627
AD-292495.1	UCAUCCCATATUGUUCCAGCA	2469	610-630	UGCUGGAACAATATGGGAUGAGG	2764	608-630
AD-292498.1	UCCCAUAUTGTUCCAGCAAAU	2470	613-633	ATUUGCTGGAACAAUAUGGGAUG	2765	611-633
AD-292499.1	CCCAUAUUGUTCCAGCAAAUU	2471	614-634	AAUUTGCUGGAACAAUAUGGGAU	2766	612-634
AD-292526.1	UGUUGGCUTUCACAGAGGUCU	2472	641-661	AGACCUCUGUGAAAGCCAACAGC	2767	639-661
AD-292531.1	GCUUUCACAGAGGUCUGACAU	2473	646-666	ATGUCAGACCUCUGUGAAAGCCA	2768	644-666
AD-292534.1	UUCACAGAGGTCUGACAUCAU	2474	649-669	ATGATGTCAGACCTCUGUGAAAG	2769	647-669
AD-292536.1	CACAGAGGTCTGACAUCAGAA	2475	651-671	UTCUGATGUCAGACCUCUGUGAA	2770	649-671
AD-292541.1	AGGUCUGACATCAGAACUUCA	2476	656-676	UGAAGUTCUGATGTCAGACCUCU	2771	654-676
AD-292566.1	UUGGGAAAAACUGGUAUCAAA	2477	681-701	UTUGAUACCAGTUTUUCCCAAGG	2772	679-701
AD-292574.1	AACUGGUATCAAAACCUCAUU	2478	689-709	AAUGAGGUUUUGATACCAGUUUU	2773	687-709
AD-292575.1	ACUGGUAUCAAAACCUCAUGU	2479	690-710	ACAUGAGGUUUTGAUACCAGUUU	2774	688-710
AD-292576.1	CUGGUAUCAAAACCUCAUGUU	2480	691-711	AACATGAGGUUTUGAUACCAGUU	2775	689-711
AD-292577.1	UGGUAUCAAAACCUCAUGUCU	2481	692-712	AGACAUGAGGUTUTGAUACCAGU	2776	690-712
AD-292578.1	GGUAUCAAAACCUCAUGUCUU	2482	693-713	AAGACATGAGGTUTUGAUACCAG	2777	691-713

Duplex Name	Sense sequence 5' to 3'	SEQ ID NO:	Position in NM_178135.4	Antisense sequence 5' to 3'	SEQ ID NO:	Range in NM_178135.4
AD-292579.1	GUAUCAAAACCUCAUGUCUCU	2483	694-714	AGAGACAUGAGGUTUUGAUACCA	2778	692-714
AD-292582.1	UCAAAACCTCAUGUCUCUGCU	2484	697-717	AGCAGAGACAUGAGGUUUUGAUA	2779	695-717
AD-292596.1	CUCUGCCCAGTUUUUGUGAAU	2485	711-731	ATUCACAAAAACUGGGCAGAGAC	2780	709-731
AD-292601.1	CCCAGUUUTUGUGAAUACUGU	2486	716-736	ACAGTATUCACAAAAACUGGGCA	2781	714-736
AD-292606.1	UUUUUGUGAATACUGGGUUCA	2487	721-741	UGAACCCAGUATUCACAAAAACU	2782	719-741
AD-292607.1	UUUUGUGAAUACUGGGUUCAU	2488	722-742	ATGAACCCAGUAUTCACAAAAAC	2783	720-742
AD-292610.1	UGUGAAUACUGGGUUCACCAA	2489	725-745	UTGGTGAACCCAGTAUUCACAAA	2784	723-745
AD-292612.1	UGAAUACUGGGUUCACCAAAA	2490	727-747	UTUUGGTGAACCCAGUAUUCACA	2785	725-747
AD-292613.1	GAAUACUGGGTUCACCAAAAA	2491	728-748	UTUUTGGUGAACCCAGUAUUCAC	2786	726-748
AD-292614.1	AAUACUGGGUTCACCAAAAAU	2492	729-749	ATUUTUGGUGAACCCAGUAUUCA	2787	727-749
AD-292615.1	AUACUGGGTUCACCAAAAAUU	2493	730-750	AAUUTUTGGUGAACCCAGUAUUC	2788	728-750
AD-292616.1	UACUGGGUTCACCAAAAAUCU	2494	731-751	AGAUTUTUGGUGAACCCAGUAUU	2789	729-751
AD-292624.1	UCACCAAAAATCCAAGCACAA	2495	739-759	UTGUGCTUGGATUTUUGGUGAAC	2790	737-759
AD-292625.1	CACCAAAAAUCCAAGCACAAU	2496	740-760	ATUGTGCUUGGAUTUUUGGUGAA	2791	738-760
AD-292629.1	AAAAAUCCAAGCACAAGAUUA	2497	744-764	UAAUCUTGUGCTUGGAUUUUUGG	2792	742-764
AD-292630.1	AAAAUCCAAGCACAAGAUUAU	2498	745-765	ATAATCTUGUGCUTGGAUUUUUG	2793	743-765
AD-292631.1	AAAUCCAAGCACAAGAUUAUU	2499	746-766	AAUAAUCUUGUGCTUGGAUUUUU	2794	744-766
AD-292634.1	UCCAAGCACAAGAUUAUGGCU	2500	749-769	AGCCAUAAUCUTGTGCUUGGAUU	2795	747-769
AD-292639.1	GCACAAGATUAUGGCCUGUAU	2502	754-774	ATACAGGCCAUAATCUUGUGCUU	2797	752-774
AD-292640.1	CACAAGAUTATGGCCUGUAUU	2503	755-775	AAUACAGGCCATAAUCUUGUGCU	2798	753-775
AD-292641.1	ACAAGAUUAUGGCCUGUAUUU	2504	756-776	AAAUACAGGCCAUAAUCUUGUGC	2799	754-776
AD-292642.1	CAAGAUUATGGCCUGUAUUGU	2505	757-777	ACAATACAGGCCATAAUCUUGUG	2800	755-777
AD-292646.1	AUUAUGGCCUGUAUUGGAGAU	2506	761-781	ATCUCCAAUACAGGCCAUAAUCU	2801	759-781
AD-292650.1	UGGCCUGUAUTGGAGACAGAU	2507	765-785	ATCUGUCUCCAAUACAGGCCAUA	2802	763-785
AD-292651.1	GGCCUGUATUGGAGACAGAUU	2508	766-786	AAUCTGTCUCCAATACAGGCCAU	2803	764-786
AD-292652.1	GCCUGUAUTGGAGACAGAUGA	2509	767-787	UCAUCUGUCUCCAAUACAGGCCA	2804	765-787
AD-292667.1	AGAUGAAGTCGUAAGAAGUCU	2510	782-802	AGACTUCUUACGACUUCAUCUGU	2805	780-802
AD-292668.1	GAUGAAGUCGTAAGAAGUCUU	2511	783-803	AAGACUTCUUACGACUUCAUCUG	2806	781-803
AD-292671.1	GAAGUCGUAAGAAGUCUGAUA	2512	786-806	UAUCAGACUUCTUACGACUUCAU	2807	784-806
AD-292673.1	AGUCGUAAGAAGUCUGAUAGA	2513	788-808	UCUATCAGACUTCTUACGACUUC	2808	786-808
AD-292677.1	GUAAGAAGTCTGAUAGAUGGA	2514	792-812	UCCATCTAUCAGACUUCUUACGA	2809	790-812
AD-292678.1	UAAGAAGUCUGAUAGAUGGAA	2515	793-813	UTCCAUCUAUCAGACUUCUUACG	2810	791-813

Duplex Name	Sense sequence 5' to 3'	SEQ ID NO:	Position in NM_178135.4	Antisense sequence 5' to 3'	SEQ ID NO:	Range in NM_178135.4
AD-292679.1	AAGAAGUCTGAUAGAUGGAAU	2516	794-814	ATUCCATCUAUCAGACUUCUUAC	2811	792-814
AD-292680.1	AGAAGUCUGATAGAUGGAAUA	2517	795-815	UAUUCCAUCUATCAGACUUCUUA	2812	793-815
AD-292681.1	GAAGUCUGAUAGAUGGAAUAU	2518	796-816	ATAUTCCAUCUAUCAGACUUCUU	2813	794-816
AD-292682.1	AAGUCUGATAGAUGGAAUACU	2519	797-817	AGUATUCCAUCTATCAGACUUCU	2814	795-817
AD-292684.1	GUCUGAUAGATGGAAUACUUA	2520	799-819	UAAGTATUCCATCTAUCAGACUU	2815	797-819
AD-292685.1	UCUGAUAGAUGGAAUACUUAU	2521	800-820	ATAAGUAUUCCAUCUAUCAGACU	2816	798-820
AD-292691.1	AGAUGGAATACUUACCAAUAA	2522	806-826	UTAUTGGUAAGTATUCCAUCUAU	2817	804-826
AD-292692.1	GAUGGAAUACTUACCAAUAAU	2523	807-827	ATUATUGGUAAGUAUUCCAUCUA	2818	805-827
AD-292693.1	AUGGAAUACUTACCAAUAAGA	2524	808-828	UCUUAUTGGUAAGTAUUCCAUCU	2819	806-828
AD-292694.1	UGGAAUACTUACCAAUAAGAA	2525	809-829	UTCUTATUGGUAAGUAUUCCAUC	2820	807-829
AD-292695.1	GGAAUACUTACCAAUAAGAAA	2526	810-830	UTUCTUAUUGGTAAGUAUUCCAU	2821	808-830
AD-292696.1	GAAUACUUACCAAUAAGAAAA	2527	811-831	UTUUCUTAUUGGUAAGUAUUCCA	2822	809-831
AD-292697.1	AAUACUUACCAAUAAGAAAAU	2528	812-832	ATUUTCTUAUUGGTAAGUAUUCC	2823	810-832
AD-292725.1	GUUCCAUCGUAUAUCAAUAUU	2529	840-860	AAUATUGAUAUACGAUGGAACAA	2824	838-860
AD-292726.1	UUCCAUCGTATAUCAAUAUCU	2530	841-861	AGAUAUTGAUATACGAUGGAACA	2825	839-861
AD-292727.1	UCCAUCGUAUAUCAAUAUCUU	2531	842-862	AAGATATUGAUAUACGAUGGAAC	2826	840-862
AD-292728.1	CCAUCGUATATCAAUAUCUUU	2532	843-863	AAAGAUAUUGATATACGAUGGAA	2827	841-863
AD-292757.1	ACAGAAGUTUCUUCCUGAACU	2533	872-892	AGUUCAGGAAGAAACUUCUGUAG	2828	870-892
AD-292759.1	AGAAGUUUCUTCCUGAACGCU	2534	874-894	AGCGTUCAGGAAGAAACUUCUGU	2829	872-894
AD-292761.1	AAGUUUCUTCCUGAACGCGCU	2535	876-896	AGCGCGTUCAGGAAGAAACUUCU	2830	874-896
AD-292766.1	UCUUCCUGAACGCGCCUCAGU	2536	881-901	ACUGAGGCGCGTUCAGGAAGAAA	2831	879-901
AD-292787.1	GAUUUUAAAUCGUAUGCAGAA	2537	902-922	UTCUGCAUACGAUTUAAAAUCGC	2832	900-922
AD-292788.1	AUUUUAAATCGUAUGCAGAAU	2538	903-923	ATUCTGCAUACGATUUAAAAUCG	2833	901-923
AD-292793.1	AAAUCGUATGCAGAAUAUUCA	2540	908-928	UGAATATUCUGCATACGAUUUAA	2835	906-928
AD-292795.1	AUCGUAUGCAGAAUAUUCAAU	2541	910-930	ATUGAATAUUCTGCAUACGAUUU	2836	908-930
AD-292796.1	UCGUAUGCAGAAUAUUCAAUU	2542	911-931	AAUUGAAUAUUCUGCAUACGAUU	2837	909-931
AD-292797.1	CGUAUGCAGAAUAUUCAAUUU	2543	912-932	AAAUTGAAUAUTCTGCAUACGAU	2838	910-932
AD-292800.1	AUGCAGAATATUCAAUUUGAA	2544	915-935	UTCAAATUGAATATUCUGCAUAC	2839	913-935
AD-292802.1	GCAGAAUATUCAAUUUGAAGU	2545	917-937	ACUUCAAAUUGAATAUUCUGCAU	2840	915-937
AD-292806.1	AAUAUUCAAUTUGAAGCAGUU	2546	921-941	AACUGCTUCAAAUTGAAUAUUCU	2841	919-941
AD-292870.1	GAUGUAUGCATGAUAAUGAUA	2548	989-1009	UAUCAUTAUCATGCAUACAUCUC	2843	987-1009
AD-292893.1	AAUAGUUUCGAAUCAAUGCUU	2549	1012-1032	AAGCAUTGAUUCGAAACUAUUCA	2844	1010-1032

Duplex Name	Sense sequence 5' to 3'	SEQ ID NO:	Position in NM_178135.4	Antisense sequence 5' to 3'	SEQ ID NO:	Range in NM_178135.4
AD-292906.1	CAAUGCUGCAAAGCUUUAUUU	2550	1025-1045	AAAUAAAGCUUTGCAGCAUUGAU	2845	1023-1045
AD-292915.1	AAAGCUUUAUTUCACAUUUUU	2551	1034-1054	AAAAAUGUGAAAUAAAGCUUUGC	2846	1032-1054
AD-292936.1	AAAACAUUGGTUUGGCACUAU	2553	1073-1093	ATAGTGCCAAACCAAUGUUUUUA	2848	1071-1093
AD-292967.1	ACGAACAAGATUAAUUACCUU	2554	1104-1124	AAGGTAAUUAATCTUGUUCGUUU	2849	1102-1124
AD-292970.1	AACAAGAUTAAUUACCUGUCU	2555	1107-1127	AGACAGGUAAUTAAUCUUGUUCG	2850	1105-1127
AD-292974.1	AGAUUAAUTACCUGUCUUCCU	2556	1111-1131	AGGAAGACAGGTAAUUAAUCUUG	2851	1109-1131
AD-292975.1	GAUUAAUUACCUGUCUUCCUU	2557	1112-1132	AAGGAAGACAGGUAAUUAAUCUU	2852	1110-1132
AD-292978.1	UAAUUACCTGTCUUCCUGUUU	2558	1115-1135	AAACAGGAAGACAGGUAAUUAAU	2853	1113-1135
AD-292979.1	AAUUACCUGUCUUCCUGUUUC	2559	1116-1136	GAAACAGGAAGACAGGUAAUUAA	2854	1114-1136
AD-292980.1	AUUACCUGTCTUCCUGUUUCU	2560	1117-1137	AGAAACAGGAAGACAGGUAAUUA	2855	1115-1137
AD-292981.1	UUACCUGUCUTCCUGUUUCUU	2561	1118-1138	AAGAAACAGGAAGACAGGUAAUU	2856	1116-1138
AD-292982.1	UACCUGUCTUCCUGUUUCUCA	2562	1119-1139	UGAGAAACAGGAAGACAGGUAAU	2857	1117-1139
AD-292983.1	ACCUGUCUTCCUGUUUCUCAA	2563	1120-1140	UTGAGAAACAGGAAGACAGGUAA	2858	1118-1140
AD-292984.1	CCUGUCUUCCTGUUUCUCAAU	2564	1121-1141	ATUGAGAAACAGGAAGACAGGUA	2859	1119-1141
AD-293027.1	GGUCUGUUTUTCCUUUCAUGU	2565	1164-1184	ACAUGAAAGGAAAAACAGACCUA	2860	1162-1184
AD-293028.1	GUCUGUUUTUCCUUUCAUGCU	2566	1165-1185	AGCATGAAAGGAAAAACAGACCU	2861	1163-1185
AD-293034.1	UUUUCCUUTCAUGCCUCUUAA	2567	1171-1191	UTAAGAGGCAUGAAAGGAAAAAC	2862	1169-1191
AD-293037.1	UCCUUUCATGCCUCUUAAAAA	2568	1174-1194	UTUUTAAGAGGCATGAAAGGAAA	2863	1172-1194
AD-293039.1	CUUUCAUGCCTCUUAAAAACU	2569	1176-1196	AGUUTUTAAGAGGCAUGAAAGGA	2864	1174-1196
AD-293099.1	UUUUUCCATUTAAAGGUGGAU	2570	1245-1265	ATCCACCUUUAAATGGAAAAAUA	2865	1243-1265
AD-293153.1	AACUUAUUTACACAGGGAAGU	2571	1299-1319	ACUUCCCUGUGTAAAUAAGUUCU	2866	1297-1319
AD-293156.1	UUAUUUACACAGGGAAGGUUU	2572	1302-1322	AAACCUTCCCUGUGUAAAUAAGU	2867	1300-1322
AD-293162.1	ACACAGGGAAGGUUUAAGACU	2573	1308-1328	AGUCTUAAACCTUCCCUGUGUAA	2868	1306-1328
AD-293163.1	CACAGGGAAGGUUUAAGACUU	2574	1309-1329	AAGUCUTAAACCUTCCCUGUGUA	2869	1307-1329
AD-293166.1	AGGGAAGGTUTAAGACUGUUU	2575	1312-1332	AAACAGTCUUAAACCUUCCCUGU	2870	1310-1332
AD-293167.1	GGGAAGGUTUAAGACUGUUCA	2576	1313-1333	UGAACAGUCUUAAACCUUCCCUG	2871	1311-1333
AD-293168.1	GGAAGGUUTAAGACUGUUCAA	2577	1314-1334	UTGAACAGUCUTAAACCUUCCCU	2872	1312-1334
AD-293169.1	GAAGGUUUAAGACUGUUCAAU	2578	1315-1335	ATUGAACAGUCTUAAACCUUCCC	2873	1313-1335
AD-293170.1	AAGGUUUAAGACUGUUCAAGU	2579	1316-1336	ACUUGAACAGUCUTAAACCUUCC	2874	1314-1336
AD-293171.1	AGGUUUAAGACUGUUCAAGUA	2580	1317-1337	UACUTGAACAGTCTUAAACCUUC	2875	1315-1337
AD-293172.1	GGUUUAAGACTGUUCAAGUAU	2581	1318-1338	ATACTUGAACAGUCUUAAACCUU	2876	1316-1338
AD-293174.1	UUUAAGACTGTUCAAGUAGCA	2582	1320-1340	UGCUACTUGAACAGUCUUAAACC	2877	1318-1340

Duplex Name	Sense sequence 5' to 3'	SEQ ID NO:	Position in NM_178135.4	Antisense sequence 5' to 3'	SEQ ID NO:	Range in NM_178135.4
AD-293177.1	AAGACUGUTCAAGUAGCAUUU	2584	1323-1343	AAAUGCTACUUGAACAGUCUUAA	2879	1321-1343
AD-293178.1	AGACUGUUCAAGUAGCAUUCU	2585	1324-1344	AGAATGCUACUTGAACAGUCUUA	2880	1322-1344
AD-293179.1	GACUGUUCAAGUAGCAUUCCA	2586	1325-1345	UGGAAUGCUACTUGAACAGUCUU	2881	1323-1345
AD-293180.1	ACUGUUCAAGTAGCAUUCCAA	2587	1326-1346	UTGGAATGCUACUTGAACAGUCU	2882	1324-1346
AD-293181.1	CUGUUCAAGUAGCAUUCCAAU	2588	1327-1347	ATUGGAAUGCUACTUGAACAGUC	2883	1325-1347
AD-293182.1	UGUUCAAGTAGCAUUCCAAUU	2589	1328-1348	AAUUGGAAUGCTACUUGAACAGU	2884	1326-1348
AD-293183.1	GUUCAAGUAGCAUUCCAAUCU	2590	1329-1349	AGAUTGGAAUGCUACUUGAACAG	2885	1327-1349
AD-293184.1	UUCAAGUAGCAUUCCAAUCUU	2591	1330-1350	AAGATUGGAAUGCTACUUGAACA	2886	1328-1350
AD-293186.1	CAAGUAGCAUTCCAAUCUGUA	2592	1332-1352	UACAGATUGGAAUGCUACUUGAA	2887	1330-1352
AD-293187.1	AAGUAGCATUCCAAUCUGUAU	2593	1333-1353	ATACAGAUUGGAATGCUACUUGA	2888	1331-1353
AD-293191.1	AGCAUUCCAATCUGUAGCCAU	2594	1337-1357	ATGGCUACAGATUGGAAUGCUAC	2889	1335-1357
AD-293218.1	GAAUAUCAACAAGAACACAGA	2595	1364-1384	UCUGTGTUCUUGUTGAUAUUCUG	2890	1362-1384
AD-293228.1	AAGAACACAGAAUGAGUGCAU	2596	1374-1394	ATGCACTCAUUCUGUGUUCUUGU	2891	1372-1394
AD-293230.1	GAACACAGAATGAGUGCACAU	2597	1376-1396	ATGUGCACUCATUCUGUGUUCUU	2892	1374-1396
AD-293231.1	AACACAGAAUGAGUGCACAGU	2598	1377-1397	ACUGTGCACUCAUTCUGUGUUCU	2893	1375-1397
AD-293235.1	CAGAAUGAGUGCACAGCUAAU	2599	1381-1401	ATUAGCTGUGCACTCAUUCUGUG	2894	1379-1401
AD-293271.1	AGGCAGCUTUAUCUCAACCUU	2600	1417-1437	AAGGTUGAGAUAAAGCUGCCUGC	2895	1415-1437
AD-293273.1	GCAGCUUUAUCUCAACCUGGA	2601	1419-1439	UCCAGGTUGAGAUAAAGCUGCCU	2896	1417-1439
AD-293306.1	UUCAGCAUTUGAAAGAUUUCU	2602	1452-1472	AGAAAUCUUUCAAAUGCUGAAUC	2897	1450-1472
AD-293309.1	AGCAUUUGAAAGAUUUCCCUA	2603	1455-1475	UAGGGAAAUCUTUCAAAUGCUGA	2898	1453-1475
AD-293311.1	CAUUUGAAAGAUUUCCCUAGU	2604	1457-1477	ACUAGGGAAAUCUTUCAAAUGCU	2899	1455-1477
AD-293312.1	AUUUGAAAGATUUCCCUAGCU	2605	1458-1478	AGCUAGGGAAATCTUUCAAAUGC	2900	1456-1478
AD-293315.1	UGAAAGAUTUCCCUAGCCUCU	2606	1461-1481	AGAGGCTAGGGAAAUCUUUCAAA	2901	1459-1481
AD-293323.1	UUCCCUAGCCTCUUCCUUUUU	2608	1469-1489	AAAAAGGAAGAGGCUAGGGAAAU	2903	1467-1489
AD-293353.1	AAAACGGUGCAACUCUAUUCU	2609	1499-1519	AGAATAGAGUUGCACCGUUUUGG	2904	1497-1519
AD-293354.1	AAACGGUGCAACUCUAUUCUU	2610	1500-1520	AAGAAUAGAGUTGCACCGUUUUG	2905	1498-1520
AD-293355.1	AACGGUGCAACUCUAUUCUGU	2611	1501-1521	ACAGAATAGAGTUGCACCGUUUU	2906	1499-1521
AD-293359.1	GUGCAACUCUAUUCUGGACUU	2613	1505-1525	AAGUCCAGAAUAGAGUUGCACCG	2908	1503-1525
AD-293360.1	UGCAACUCTATUCUGGACUUU	2614	1506-1526	AAAGTCCAGAATAGAGUUGCACC	2909	1504-1526
AD-293361.1	GCAACUCUAUTCUGGACUUUA	2615	1507-1527	UAAAGUCCAGAAUAGAGUUGCAC	2910	1505-1527
AD-293362.1	CAACUCUATUCUGGACUUUAU	2616	1508-1528	ATAAAGTCCAGAATAGAGUUGCA	2911	1506-1528
AD-293364.1	ACUCUAUUCUGGACUUUAUUA	2618	1510-1530	UAAUAAAGUCCAGAAUAGAGUUG	2913	1508-1530

Duplex Name	Sense sequence 5' to 3'	SEQ ID NO:	Position in NM_178135.4	Antisense sequence 5' to 3'	SEQ ID NO:	Range in NM_178135.4
AD-293365.1	CUCUAUUCTGGACUUUAUUAU	2619	1511-1531	ATAATAAAGUCCAGAAUAGAGUU	2914	1509-1531
AD-293368.1	UAUUCUGGACTUUAUUACUUU	2620	1514-1534	AAAGTAAUAAAGUCCAGAAUAGA	2915	1512-1534
AD-293369.1	AUUCUGGACUTUAUUACUUGA	2621	1515-1535	UCAAGUAAUAAAGTCCAGAAUAG	2916	1513-1535
AD-293370.1	UUCUGGACTUTAUUACUUGAU	2622	1516-1536	ATCAAGTAAUAAAGUCCAGAAUA	2917	1514-1536
AD-293410.1	UGAAGUCCACCAAAAGUGGAU	2623	1556-1576	ATCCACTUUUGGUGGACUUCAGA	2918	1554-1576
AD-293419.1	CCAAAAGUGGACCCUCUAUAU	2624	1565-1585	ATAUAGAGGGUCCACUUUUGGUG	2919	1563-1585
AD-293420.1	CAAAAGUGGACCCUCUAUAUU	2625	1566-1586	AAUATAGAGGGTCCACUUUUGGU	2920	1564-1586
AD-293422.1	AAAGUGGACCCUCUAUAUUUC	2626	1568-1588	GAAATATAGAGGGTCCACUUUUG	2921	1566-1588
AD-293423.1	AAGUGGACCCTCUAUAUUUCU	2627	1569-1589	AGAAAUAUAGAGGGUCCACUUUU	2922	1567-1589
AD-293530.1	CUUUCAUATATCCUUGGUCCU	2628	1699-1719	AGGACCAAGGATATAUGAAAGCA	2923	1697-1719
AD-293532.1	UUCAUAUATCCUUGGUCCCAU	2629	1701-1721	ATGGGACCAAGGATAUAUGAAAG	2924	1699-1721
AD-293554.1	GAUGUUUAGACAAUUUUAGGU	2630	1723-1743	ACCUAAAAUUGTCTAAACAUCUC	2925	1721-1743
AD-293555.1	AUGUUUAGACAAUUUUAGGCU	2631	1724-1744	AGCCTAAAAUUGUCUAAACAUCU	2926	1722-1744
AD-293557.1	GUUUAGACAATUUUAGGCUCA	2632	1726-1746	UGAGCCTAAAATUGUCUAAACAU	2927	1724-1746
AD-293558.1	UUUAGACAAUTUUAGGCUCAA	2633	1727-1747	UTGAGCCUAAAAUTGUCUAAACA	2928	1725-1747
AD-293559.1	UUAGACAATUTUAGGCUCAAA	2634	1728-1748	UTUGAGCCUAAAATUGUCUAAAC	2929	1726-1748
AD-293560.1	UAGACAAUTUTAGGCUCAAAA	2635	1729-1749	UTUUGAGCCUAAAAUUGUCUAAA	2930	1727-1749
AD-293562.1	GACAAUUUTAGGCUCAAAAAU	2636	1731-1751	ATUUTUGAGCCTAAAAUUGUCUA	2931	1729-1751
AD-293569.1	UUAGGCUCAAAAAUUAAAGCU	2637	1738-1758	AGCUTUAAUUUTUGAGCCUAAAA	2932	1736-1758
AD-293570.1	UAGGCUCAAAAAUUAAAGCUA	2638	1739-1759	UAGCTUTAAUUTUTGAGCCUAAA	2933	1737-1759
AD-293571.1	AGGCUCAAAAAUUAAAGCUAA	2639	1740-1760	UTAGCUTUAAUTUTUGAGCCUAA	2934	1738-1760
AD-293572.1	GGCUCAAAAATUAAAGCUAAU	2640	1741-1761	ATUAGCTUUAATUTUUGAGCCUA	2935	1739-1761
AD-293573.1	GCUCAAAAAUTAAAGCUAACA	2641	1742-1762	UGUUAGCUUUAAUTUUUGAGCCU	2936	1740-1762
AD-293574.1	CUCAAAAATUAAAGCUAACAU	2642	1743-1763	ATGUTAGCUUUAATUUUUGAGCC	2937	1741-1763
AD-293575.1	UCAAAAAUTAAAGCUAACACA	2643	1744-1764	UGUGTUAGCUUTAAUUUUUGAGC	2938	1742-1764
AD-293576.1	CAAAAAUUAAAGCUAACACAU	2644	1745-1765	ATGUGUTAGCUTUAAUUUUUGAG	2939	1743-1765
AD-293579.1	AAAUUAAAGCTAACACAGGAA	2645	1748-1768	UTCCTGTGUUAGCTUUAAUUUUU	2940	1746-1768
AD-293586.1	AGCUAACACAGGAAAAGGAAU	2646	1755-1775	ATUCCUTUUCCTGTGUUAGCUUU	2941	1753-1775
AD-293589.1	UAACACAGGAAAAGGAACUGU	2647	1758-1778	ACAGTUCCUUUTCCUGUGUUAGC	2942	1756-1778
AD-293592.1	CACAGGAAAAGGAACUGUACU	2648	1761-1781	AGUACAGUUCCTUTUCCUGUGUU	2943	1759-1781
AD-293594.1	CAGGAAAAGGAACUGUACUGU	2649	1763-1783	ACAGTACAGUUCCTUUUCCUGUG	2944	1761-1783
AD-293601.1	AGGAACUGTACUGGCUAUUAU	2650	1770-1790	ATAATAGCCAGTACAGUUCCUUU	2945	1768-1790

Duplex Name	Sense sequence 5' to 3'	SEQ ID NO:	Position in NM_178135.4	Antisense sequence 5' to 3'	SEQ ID NO:	Range in NM_178135.4
AD-293872.1	CGACUCCCACTACAUCAAGAU	2652	2186-2206	ATCUTGAUGUAGUGGGAGUCGGA	2947	2184-2206
AD-293875.1	CUCCCACUACAUCAAGACUAA	2653	2189-2209	UTAGTCTUGAUGUAGUGGGAGUC	2948	2187-2209
AD-293876.1	UCCCACUACATCAAGACUAAU	2654	2190-2210	ATUAGUCUUGATGTAGUGGGAGU	2949	2188-2210
AD-293877.1	CCCACUACAUCAAGACUAAUU	2655	2191-2211	AAUUAGTCUUGAUGUAGUGGGAG	2950	2189-2211
AD-293878.1	CCACUACATCAAGACUAAUCU	2656	2192-2212	AGAUTAGUCUUGATGUAGUGGGA	2951	2190-2212
AD-293879.1	CACUACAUCAAGACUAAUCUU	2657	2193-2213	AAGATUAGUCUTGAUGUAGUGGG	2952	2191-2213
AD-293880.1	ACUACAUCAAGACUAAUCUUU	2658	2194-2214	AAAGAUTAGUCTUGAUGUAGUGG	2953	2192-2214
AD-293881.1	CUACAUCAAGACUAAUCUUGU	2659	2195-2215	ACAAGATUAGUCUTGAUGUAGUG	2954	2193-2215
AD-293882.1	UACAUCAAGACUAAUCUUGUU	2660	2196-2216	AACAAGAUUAGTCTUGAUGUAGU	2955	2194-2216
AD-293898.1	UUGUGUGUTUTUCACAUGUAU	2662	2217-2237	ATACAUGUGAAAAACACACAAAA	2957	2215-2237
AD-293902.1	GUGUUUUUCACAUGUAUUAUA	2663	2221-2241	UAUAAUACAUGTGAAAAACACAC	2958	2219-2241
AD-293909.1	UCACAUGUAUTAUAGAAUGCU	2664	2228-2248	AGCATUCUAUAAUACAUGUGAAA	2959	2226-2248
AD-293910.1	CACAUGUATUAUAGAAUGCUU	2665	2229-2249	AAGCAUTCUAUAATACAUGUGAA	2960	2227-2249
AD-293914.1	UGUAUUAUAGAAUGCUUUUGU	2666	2233-2253	ACAAAAGCAUUCUAUAAUACAUG	2961	2231-2253
AD-293915.1	GUAUUAUAGAAUGCUUUUGCA	2667	2234-2254	UGCAAAAGCAUTCTAUAAUACAU	2962	2232-2254
AD-293919.1	UAUAGAAUGCTUUUGCAUGGA	2668	2238-2258	UCCATGCAAAAGCAUUCUAUAAU	2963	2236-2258
AD-293923.1	GAAUGCUUTUGCAUGGACUAU	2670	2242-2262	ATAGTCCAUGCAAAAGCAUUCUA	2965	2240-2262
AD-293925.1	AUGCUUUUGCAUGGACUAUCU	2671	2244-2264	AGAUAGTCCAUGCAAAAGCAUUC	2966	2242-2264
AD-293928.1	CUUUUGCATGGACUAUCCUCU	2672	2247-2267	AGAGGATAGUCCATGCAAAAGCA	2967	2245-2267
AD-293931.1	UUGCAUGGACTAUCCUCUUGU	2673	2250-2270	ACAAGAGGAUAGUCCAUGCAAAA	2968	2248-2270
AD-293932.1	UGCAUGGACUAUCCUCUUGUU	2674	2251-2271	AACAAGAGGAUAGTCCAUGCAAA	2969	2249-2271
AD-293933.1	GCAUGGACTATCCUCUUGUUU	2675	2252-2272	AAACAAGAGGATAGUCCAUGCAA	2970	2250-2272
AD-293934.1	CAUGGACUAUCCUCUUGUUUU	2676	2253-2273	AAAACAAGAGGAUAGUCCAUGCA	2971	2251-2273
AD-293935.1	AUGGACUATCCUCUUGUUUUU	2677	2254-2274	AAAAACAAGAGGATAGUCCAUGC	2972	2252-2274
AD-293936.1	UGGACUAUCCTCUUGUUUUUA	2678	2255-2275	UAAAAACAAGAGGAUAGUCCAUG	2973	2253-2275
AD-293937.1	GGACUAUCCUCUUGUUUUUAU	2679	2256-2276	ATAAAAACAAGAGGAUAGUCCAU	2974	2254-2276
AD-293938.1	GACUAUCCTCTUGUUUUUAUU	2680	2257-2277	AAUAAAAACAAGAGGAUAGUCCA	2975	2255-2277
AD-293940.1	CUAUCCUCTUGUUUUUAUUAA	2681	2259-2279	UTAATAAAAACAAGAGGAUAGUC	2976	2257-2279

* Target: HSD17B13

Table 12. HSD17B13 NonF DNA in vitro 10nM screen in Cos-7 (Human Dual-Luciferase psiCHECK2 vector) and Primary Cynomolgus Hepatocytes

Duplex Name	% of Human Message Remaining 10nM	%of Human Message Remaining 0.1nM	%of Cyno Message remaining 10nM	%of Cyno Message remaining 0.1nM
AD-291929.1	71.9	80.9	83.6	83.4
AD-291931.1	110.8	84.8	100.1	97.8
AD-291988.1	78.0	104.0	65.3	97.3
AD-291993.1	102.1	100.5	78.9	69.1
AD-291998.1	81.6	97.4	26.3	60.9
AD-292005.1	101.3	93.7	69.2	74.9
AD-292006.1	45.7	93.2	58.7	81.7
AD-292007.1	130.7	101.5	62.4	100.0
AD-292008.1	99.4	102.4	63.7	91.3
AD-292010.1	72.6	87.1	49.5	95.8
AD-292012.1	79.5	83.6	86.8	86.3
AD-292013.1	61.3	94.1	45.2	83.9
AD-292014.1	50.0	87.4	40.0	40.1
AD-292015.1	44.9	88.2	31.6	78.8
AD-292016.1	52.6	84.2	48.2	90.8
AD-292017.1	43.8	86.8	54.8	96.7
AD-292028.1	77.4	88.2	107.2	91.5
AD-292137.1	96.9	83.6	105.7	103.9
AD-292140.1	30.6	95.0	26.3	59.0
AD-292143.1	38.4	79.3	33.9	85.3
AD-292182.1	127.2	99.8	91.8	71.1
AD-292183.1	95.2	91.8	102.5	87.6
AD-292185.1	50.6	91.7	74.5	93.3
AD-292186.1	48.6	95.0	81.3	85.6
AD-292187.1	90.1	89.5	82.7	95.5
AD-292188.1	53.1	99.0	42.5	81.8
AD-292189.1	103.9	78.7	73.2	104.0
AD-292190.1	67.5	81.6	105.5	81.9
AD-292238.1	40.6	86.1	71.7	86.6
AD-292244.1	92.8	78.7	116.0	91.8

Duplex Name	% of Human Message Remaining 10nM	%of Human Message Remaining 0.1nM	%of Cyno Message remaining 10nM	%of Cyno Message remaining 0.1nM
AD-292245.1	62.2	75.2	55.5	97.0
AD-292247.1	51.0	84.4	63.4	87.5
AD-292248.1	77.4	104.3	51.0	94.8
AD-292250.1	31.0	85.4	44.9	92.2
AD-292251.1	45.7	91.0	74.1	90.6
AD-292252.1	60.0	83.4	88.6	102.1
AD-292253.1	29.1	121.4	35.3	75.7
AD-292254.1	50.1	94.7	32.3	62.3
AD-292257.1	54.9	96.3	57.6	84.8
AD-292309.1	93.2	108.1	93.4	87.1
AD-292310.1	94.4	101.0	87.9	101.6
AD-292315.1	86.1	88.8	62.9	90.8
AD-292318.1	67.1	105.0	85.3	85.5
AD-292344.1	36.1	91.7	33.0	53.0
AD-292345.1	68.5	88.1	81.9	106.0
AD-292346.1	38.8	80.4	63.7	66.2
AD-292363.1	85.2	76.8	96.0	101.8
AD-292366.1	75.3	82.9	100.2	107.5
AD-292367.1	86.9	70.2	97.0	113.8
AD-292369.1	96.6	88.6	91.3	91.6
AD-292370.1	44.8	84.8	59.7	88.9
AD-292371.1	47.1	76.8	78.3	96.3
AD-292373.1	83.4	79.9	32.3	128.5
AD-292374.1	126.7	92.9	78.8	98.5
AD-292376.1	63.8	89.3	73.9	87.3
AD-292377.1	47.5	79.9	49.7	77.6
AD-292379.1	92.9	99.8	99.0	86.5
AD-292380.1	69.1	82.6	46.5	70.2
AD-292381.1	30.1	73.4	58.1	95.4
AD-292382.1	42.1	86.7	87.3	97.4
AD-292383.1	18.7	69.7	47.1	41.7
AD-292384.1	27.4	83.2	36.6	83.8
AD-292385.1	59.5	107.0	51.1	115.1

Duplex Name	% of Human Message Remaining 10nM	%of Human Message Remaining 0.1nM	%of Cyno Message remaining 10nM	%of Cyno Message remaining 0.1nM
AD-292388.1	33.9	80.2	37.4	51.4
AD-292389.1	54.9	90.8	79.0	92.4
AD-292390.1	43.4	81.4	49.8	82.4
AD-292394.1	20.8	74.8	56.3	57.0
AD-292397.1	87.6	80.3	56.8	79.6
AD-292398.1	25.3	84.3	21.9	56.5
AD-292399.1	43.1	84.4	26.6	61.1
AD-292403.1	75.2	91.7	19.6	59.7
AD-292404.1	99.9	89.7	68.5	70.8
AD-292405.1	65.8	93.2	39.0	49.5
AD-292406.1	77.3	70.4	89.7	96.8
AD-292407.1	47.4	91.5	64.1	50.3
AD-292408.1	67.3	102.5	72.1	89.8
AD-292409.1	47.3	84.2	88.6	91.7
AD-292410.1	90.3	89.2	50.5	94.3
AD-292434.1	109.2	85.6	97.7	118.1
AD-292486.1	87.6	93.4	81.4	70.9
AD-292487.1	71.1	91.4	83.5	101.3
AD-292492.1	55.7	89.0	83.1	104.7
AD-292495.1	74.2	87.6	39.8	89.4
AD-292498.1	59.5	94.1	48.3	102.0
AD-292499.1	40.6	95.4	36.7	69.9
AD-292526.1	82.6	90.8	66.4	71.7
AD-292531.1	95.5	81.2	100.4	110.5
AD-292534.1	78.2	88.3	60.2	76.1
AD-292536.1	55.9	90.9	43.0	82.7
AD-292541.1	88.3	74.4	27.8	41.9
AD-292566.1	19.9	72.5	13.2	52.6
AD-292574.1	24.4	71.6	26.1	73.5
AD-292575.1	65.6	81.9	77.2	81.2
AD-292576.1	16.5	80.7	28.5	43.3
AD-292577.1	43.3	95.8	25.8	68.5
AD-292578.1	23.4	58.8	15.6	68.8

Duplex Name	% of Human Message Remaining 10nM	%of Human Message Remaining 0.1nM	%of Cyno Message remaining 10nM	%of Cyno Message remaining 0.1nM
AD-292579.1	39.4	80.5	18.5	81.3
AD-292582.1	53.7	89.0	56.3	96.1
AD-292596.1	71.7	90.7	34.6	78.4
AD-292601.1	80.9	103.8	83.1	101.7
AD-292606.1	72.8	93.1	71.1	110.5
AD-292607.1	64.0	94.9	96.3	81.4
AD-292610.1	76.6	83.1	88.3	90.3
AD-292612.1	52.9	81.4	66.2	81.5
AD-292613.1	27.9	79.6	53.3	96.2
AD-292614.1	51.4	92.8	87.1	96.4
AD-292615.1	75.1	88.2	92.9	108.1
AD-292616.1	73.9	90.6	90.3	85.7
AD-292624.1	54.2	97.1	59.3	99.4
AD-292625.1	28.1	83.1	22.7	73.4
AD-292629.1	25.7	80.1	49.1	63.6
AD-292630.1	26.4	99.1	31.1	47.4
AD-292631.1	53.9	70.9	84.9	103.8
AD-292634.1	74.5	92.9	89.3	82.6
AD-292638.1	50.1	88.5	74.8	79.7
AD-292639.1	73.9	86.3	62.4	85.5
AD-292640.1	17.0	71.2	49.7	48.3
AD-292641.1	55.1	100.4	70.5	92.6
AD-292642.1	29.7	93.0	50.8	81.0
AD-292646.1	41.7	95.5	79.8	92.7
AD-292650.1	85.5	84.2	104.5	95.4
AD-292651.1	44.4	94.8	72.9	84.0
AD-292652.1	78.7	85.1	73.9	97.5
AD-292667.1	91.8	83.0	108.4	95.8
AD-292668.1	24.5	61.0	95.9	83.9
AD-292671.1	18.8	61.8	42.5	93.0
AD-292673.1	41.0	77.7	35.8	79.4
AD-292677.1	73.0	74.0	111.0	90.7
AD-292678.1	60.3	90.4	56.9	95.8

Duplex Name	% of Human Message Remaining 10nM	%of Human Message Remaining 0.1nM	%of Cyno Message remaining 10nM	%of Cyno Message remaining 0.1nM
AD-292679.1	45.0	74.8	45.1	72.5
AD-292680.1	42.9	89.4	22.9	44.0
AD-292681.1	56.4	99.9	94.6	105.1
AD-292682.1	63.9	84.7	64.0	64.5
AD-292684.1	24.2	81.8	16.2	88.1
AD-292685.1	55.6	89.3	40.6	81.3
AD-292691.1	27.0	82.0	27.8	59.7
AD-292692.1	56.9	76.9	57.8	85.9
AD-292693.1	24.3	76.9	16.6	47.8
AD-292694.1	26.5	84.2	61.0	91.0
AD-292695.1	35.8	82.1	24.0	62.8
AD-292696.1	32.5	87.4	27.5	60.8
AD-292697.1	51.8	79.1	33.8	57.3
AD-292725.1	49.1	61.8	101.5	90.3
AD-292726.1	41.3	71.5	81.7	90.6
AD-292727.1	64.4	82.9	78.5	96.0
AD-292728.1	54.9	65.4	96.9	121.5
AD-292757.1	38.0	71.0	53.7	72.0
AD-292759.1	93.8	89.4	89.7	82.5
AD-292761.1	47.1	97.8	29.0	84.6
AD-292766.1	139.5	89.6	92.1	105.5
AD-292787.1	57.9	77.4	79.6	95.3
AD-292788.1	23.2	88.1	75.5	85.9
AD-292789.1	14.8	78.8	47.7	73.0
AD-292793.1	16.8	62.8	16.1	33.1
AD-292795.1	14.3	57.5	53.5	43.0
AD-292796.1	22.7	56.2	18.2	71.8
AD-292797.1	5.6	28.2	10.4	17.0
AD-292800.1	9.6	58.3	12.8	25.3
AD-292802.1	13.0	70.4	18.8	60.5
AD-292806.1	14.9	63.8	9.9	39.7
AD-292808.1	76.4	90.2	64.5	85.2
AD-292870.1	11.8	42.5	33.1	50.4

Duplex Name	% of Human Message Remaining 10nM	%of Human Message Remaining 0.1nM	%of Cyno Message remaining 10nM	%of Cyno Message remaining 0.1nM
AD-292893.1	19.5	60.5	126.3	95.7
AD-292906.1	26.3	32.8	39.7	80.9
AD-292915.1	19.4	49.0	41.4	38.1
AD-292935.1	73.8	82.0	42.3	64.3
AD-292936.1	60.6	74.3	51.1	53.1
AD-292967.1	11.4	46.8	51.2	89.8
AD-292970.1	17.0	58.6	48.2	87.4
AD-292974.1	23.3	72.1	68.3	78.4
AD-292975.1	22.3	80.7	52.6	79.2
AD-292978.1	23.6	77.6	29.9	74.0
AD-292979.1	50.5	84.9	54.2	97.1
AD-292980.1	36.4	107.7	42.5	91.0
AD-292981.1	67.7	79.8	76.1	107.9
AD-292982.1	27.1	76.5	42.7	74.1
AD-292983.1	21.5	71.3	39.1	77.3
AD-292984.1	24.2	73.5	36.2	69.6
AD-293027.1	37.3	82.5	41.7	86.2
AD-293028.1	59.8	81.3	64.4	92.3
AD-293034.1	30.5	89.4	40.2	54.5
AD-293037.1	45.8	77.7	42.3	81.9
AD-293039.1	25.3	76.7	37.8	49.6
AD-293099.1	47.1	87.8	50.8	77.5
AD-293153.1	71.0	85.3	75.2	104.1
AD-293156.1	38.3	93.0	46.6	131.7
AD-293162.1	53.5	82.3	65.5	99.4
AD-293163.1	36.1	84.2	74.8	96.1
AD-293166.1	55.4	86.7	56.3	79.2
AD-293167.1	69.9	94.9	52.4	63.0
AD-293168.1	68.5	77.5	62.5	74.1
AD-293169.1	62.0	89.4	51.6	98.0
AD-293170.1	27.7	93.7	39.6	64.8
AD-293171.1	14.1	67.7	42.0	36.4
AD-293172.1	63.2	82.8	64.9	88.2

Duplex Name	% of Human Message Remaining 10nM	%of Human Message Remaining 0.1nM	%of Cyno Message remaining 10nM	%of Cyno Message remaining 0.1nM
AD-293174.1	19.3	95.6	50.2	68.6
AD-293176.1	20.5	63.7	36.4	40.1
AD-293177.1	21.4	93.0	31.5	44.8
AD-293178.1	24.3	73.6	70.8	75.4
AD-293179.1	52.5	78.7	51.1	85.3
AD-293180.1	34.0	91.7	60.7	71.5
AD-293181.1	58.7	107.6	35.6	78.0
AD-293182.1	16.9	60.5	39.5	45.0
AD-293183.1	31.4	78.1	74.7	83.4
AD-293184.1	25.6	58.7	59.7	50.9
AD-293186.1	48.4	78.2	41.4	73.5
AD-293187.1	41.7	78.8	50.4	84.9
AD-293191.1	56.1	103.5	72.3	84.1
AD-293218.1	36.6	67.3	44.9	69.3
AD-293228.1	83.7	92.4	84.0	74.2
AD-293230.1	76.4	95.3	76.2	67.1
AD-293231.1	57.6	83.2	56.3	101.8
AD-293235.1	56.7	97.6	99.6	86.3
AD-293271.1	112.7	85.7	85.7	110.6
AD-293273.1	60.2	92.6	38.6	89.9
AD-293306.1	33.9	90.2	42.6	70.4
AD-293309.1	28.6	68.9	33.4	58.9
AD-293311.1	13.4	66.4	28.2	41.2
AD-293312.1	21.7	88.7	46.9	92.5
AD-293315.1	29.4	88.6	50.1	82.0
AD-293316.1	32.7	75.3	40.2	67.0
AD-293323.1	85.3	103.1	49.1	91.3
AD-293353.1	64.0	76.6	83.0	84.7
AD-293354.1	50.9	79.2	64.5	84.5
AD-293355.1	78.0	110.8	76.0	88.7
AD-293358.1	46.0	106.3	91.5	98.3
AD-293359.1	77.0	73.5	74.2	82.4
AD-293360.1	75.9	104.8	56.5	88.2

Duplex Name	% of Human Message Remaining 10nM	%of Human Message Remaining 0.1nM	%of Cyno Message remaining 10nM	%of Cyno Message remaining 0.1nM
AD-293361.1	73.4	87.3	72.7	86.0
AD-293362.1	38.3	81.1	75.0	84.3
AD-293363.1	35.2	72.6	78.9	79.4
AD-293364.1	83.5	86.1	80.9	74.2
AD-293365.1	55.0	88.5	69.3	114.8
AD-293368.1	19.6	50.5	40.7	66.8
AD-293369.1	14.3	63.5	38.5	63.5
AD-293370.1	93.8	84.2	99.4	112.0
AD-293410.1	99.6	81.5	111.6	112.2
AD-293419.1	84.8	89.5	88.7	66.7
AD-293420.1	65.4	89.3	72.7	75.8
AD-293422.1	55.1	104.1	99.0	97.0
AD-293423.1	58.8	75.0	82.0	101.6
AD-293530.1	33.5	86.1	54.2	103.1
AD-293532.1	42.7	95.8	84.4	91.4
AD-293554.1	63.0	84.0	106.1	100.8
AD-293555.1	49.0	87.7	85.4	110.5
AD-293557.1	34.8	90.9	42.7	71.2
AD-293558.1	34.0	63.5	56.9	62.9
AD-293559.1	23.4	53.8	52.4	48.2
AD-293560.1	23.8	75.6	45.8	46.4
AD-293562.1	54.3	67.3	45.0	68.8
AD-293569.1	54.2	99.4	144.4	123.6
AD-293570.1	43.8	106.2	66.9	67.3
AD-293571.1	17.8	67.2	45.3	58.4
AD-293572.1	25.4	78.2	43.2	52.5
AD-293573.1	33.1	88.7	43.2	61.4
AD-293574.1	89.3	84.3	70.6	94.1
AD-293575.1	50.3	80.2	50.3	73.4
AD-293576.1	47.3	88.6	42.2	69.7
AD-293579.1	37.0	88.6	43.0	78.7
AD-293586.1	109.6	101.6	69.8	111.1
AD-293589.1	66.1	82.7	86.4	104.3

Duplex Name	% of Human Message Remaining 10nM	%of Human Message Remaining 0.1nM	%of Cyno Message remaining 10nM	%of Cyno Message remaining 0.1nM
AD-293592.1	54.7	84.6	63.6	95.7
AD-293594.1	41.8	82.8	53.7	80.9
AD-293601.1	40.1	80.8	69.9	68.9
AD-293602.1	78.8	77.2	75.2	72.3
AD-293872.1	89.1	88.4	106.8	116.8
AD-293875.1	74.4	78.5	78.7	84.3
AD-293876.1	25.1	68.3	70.4	61.4
AD-293877.1	26.8	77.7	35.9	50.4
AD-293878.1	13.3	80.2	75.0	64.2
AD-293879.1	34.1	59.4	45.2	54.3
AD-293880.1	19.0	80.8	59.2	55.4
AD-293881.1	16.3	78.2	38.7	49.0
AD-293882.1	11.9	39.5	33.7	47.3
AD-293883.1	8.9	58.7	50.9	34.1
AD-293898.1	23.0	64.6	41.5	76.4
AD-293902.1	16.0	53.9	43.3	56.9
AD-293909.1	75.9	112.6	74.2	91.0
AD-293910.1	32.6	89.6	54.3	79.9
AD-293914.1	35.0	88.0	52.9	72.0
AD-293915.1	22.7	87.0	39.4	82.5
AD-293919.1	31.8	79.6	59.5	84.2
AD-293922.1	53.2	96.2	37.0	65.9
AD-293923.1	48.5	76.0	77.7	99.7
AD-293925.1	31.1	81.9	53.0	87.7
AD-293928.1	29.4	73.5	68.8	95.5
AD-293931.1	27.5	85.4	52.5	79.1
AD-293932.1	14.2	61.7	55.5	65.7
AD-293933.1	49.1	80.3	42.1	74.9
AD-293934.1	30.9	79.7	46.1	87.7
AD-293935.1	48.7	79.1	68.3	70.8
AD-293936.1	55.0	84.6	45.8	90.3
AD-293937.1	29.6	80.1	58.5	83.9
AD-293938.1	24.7	67.9	58.4	94.8

Duplex Name	% of Human Message Remaining 10nM	%of Human Message Remaining 0.1nM	%of Cyno Message remaining 10nM	%of Cyno Message remaining 0.1nM
AD-293940.1	17.7	61.9	51.9	69.0

EXAMPLE 3: Identification of a Loss-Of-Function Mutation That Protects Agains NASH

Non-alcoholic steatohepatitis (NASH) is a progressive disease characterized by hepatic fat build-up and inflammation that may lead to cirrhosis. NASH is predicted to be the major driver for liver transplantation by 2020. Liver-related mortality increases exponentially with fibrosis progression.

A splice variant (rs72613567:TA) in HSD17B13 results in an unstable and truncated protein with reduced enzymatic activity against steroid substrates and, thus, represents a loss-of function variant in HSD17B13. HSD17B13:rs72613567:TA was reproducibly associated with reduced serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and as depicted in Figure 1, this variant is associated with siginifcantly reduced risk of alcoholic and nonalcoholic liver disease, cirrhosis and hepatocellular carcinoma in an allele dosage-dependent manner.

HSD17B13, expressed in hepatocytes, is, thus, an attractive target for the treatment of NASH and other chronic liver diseases using dsRNA agents that inhibit the expression of HSD17B13 and mimic the loss-of-function variant rs72613567:TA.

EXAMPLE 4: *In Vivo* Efficacy of dsRNA Agents Targeting HSD17B13

A. Human/NHP cross-reactive siRNA efficacy against ectopically expressed human HSD17B13 in mice

Mice (n=3/group) were injected with an adeno-associated virus (AAV) expressing human HSD17B13. Fourteen days after AAV injection, mice were subcutaneously administered a single 3 mg/kg dose of AD-288917. Ten days after administration, human HSD17B13 expression in liver was determined by RT-qPCR and normalized against human HSD17B13 expression of control animals injected with PBS. As depicted in Figure 2A, a single dose of AD-288917 effectively inhibits the expression of human HSD17B13.

B. Human/NHP cross-reactive siRNA efficacy against endogenous HSD17B13 in non-human primates

Cynomolgus monkeys (n=3/group) were subcutaneously administered a single 3 mg/kg dose of AD-288917. Twenty-one days after duplex 1 administration, endogenous HSD17B13 expression was determined in liver biopsies by RT-qPCR and normalized against endogenous HSD17B13 expression of control animals injected with PBS. As depicted in Figure 2B, a single dose of AD-288917 effectively inhibits the expression of endogenous HSD17B13.

EXAMPLE 5: *In Vivo* Efficacy of dsRNA Agents Targeting HSD17B13

Cynomolgus monkeys (n=3/group) were subcutaneously administered a single 3 mg/kg dose or a single 10 mg/kg dose of an agent listed in Table 13. Twenty-one days after duplex administration, endogenous HSD17B13 expression was determined in liver biopsies (left and right lobes) by RT-qPCR and normalized against endogenous HSD17B13 expression of control animals

injected with PBS. As shown in Table 14, a single 3 mg/kg or 10 mg/kg dose of all of the agents tested effectively inhibited the expression of endogenous HSD17B13.

Table 14.

Groups (n=3/group)	3 mg/kg			10 mg/kg		
	Left lobe	Right lobe	Average L+R	Left lobe	Right lobe	Average L+R
AD-288917 AVG	0.58	0.58	0.58	0.25	0.26	0.25
AD-288917 SEM	0.26	0.26	0.26	0.01	0.05	0.03
AD-288996 AVG	0.28	0.18	0.23	0.11	0.11	0.11
AD-288996 SEM	0.08	0.09	0.07	0.06	0.05	0.05
AD-413639 AVG	0.35	0.34	0.34	0.14	0.13	0.13
AD-413639 SEM	0.16	0.11	0.13	0.07	0.06	0.06
AD-413644 AVG	0.33	0.30	0.32	0.10	0.11	0.11
AD-413644 SEM	0.13	0.09	0.10	0.02	0.03	0.02
AD-413669 AVG	0.33	0.23	0.28	0.23	0.20	0.21
AD-413669 SEM	0.09	0.07	0.08	0.11	0.10	0.10
PBS (control) AVG	1.06	1.02	1.04			
PBS (control) SEM	0.26	0.20	0.23			
Results represent HSD17B13 expression (fold change versus PBS-control group)						

Table 13.

Duplex ID	Strand	Modified Sequence (5'-3')	SEQ ID NO:	Unmodified Sequenceq (5'-3')	SEQ ID NO:
AD-288917	sense	usascaucAfaGfAfCfuaaucuuguuL96	4486	UACAUCAAGACUAAUCUUGUU	4496
	antisense	asAfscaag(Agn)uuagucUfuGfauguasgsu	4487	AACAAGAUUAGUCUUGAUGUAGU	4497
AD-288996	sense	asusgcuuUfuGfCfAfuggacuaucuL96	4488	AUGCUUUUGCAUGGACUAUCU	4498
	antisense	asGfsauag(Tgn)ccaugcAfaAfagcaususc	4489	AGAUAGTCCAUGCAAAAGCAUUC	4499
AD-413639	sense	csgsuaugCfaGfAfAfuauucaauuuL96	4490	CGUAUGCAGAAUAUUCAAUUU	4500
	antisense	asAfsauuGf(Agn)auauucUfgCfauacgsasu	4491	AAAUUGAAUAUUCUGCAUACGAU	4501
AD-413644	sense	csgsuaugCfaGfAfAfuauucaauuuL96	4492	CGUAUGCAGAAUAUUCAAUUU	4502
	antisense	asAfsaUfuGf(Agn)auauUfcUfgCfaUfaCfgsasu	4493	AAAUUGAAUAUUCUGCAUACGAU	4503
AD-413669	sense	csusacauCfaAfGfAfcuaaucuuguL96	4494	CUACAUCAAGACUAAUCUUGU	4504
	antisense	asCfsaaga(Tgn)uaguCfuUfgAfuguagsusg	4495	ACAAGATUAGUCUUGAUGUAGUG	4505

We claim:

1. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of 17β-hydroxysteroid dehydrogenase type 13 (HSD17B13) in a cell, comprising a sense strand and an antisense strand forming a double stranded region,

wherein the sense strand comprises at least 15 contiguous nucleotides which differ by no more than three nucleotides from SEQ ID NO: 4498, and the antisense strand comprises a region of complementarity to at least 15 contiguous nucleotides differing by no more than three nucleotides from nucleotides 2242-2264 of SEQ ID NO: 1,

wherein at least one of the nucleotides of the sense strand and at least one of the nucleotides of the antisense strand comprises a modification selected from the group consisting of a 2′-O-methyl modification and a 2′-fluoro modification.

2. The dsRNA agent of claim 1, wherein all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand are modified.

3. The dsRNA agent of claim 1, wherein the sense strand comprises no more than four 2′-fluoro modified nucleotides.

4. The dsRNA agent of claim 1, wherein the antisense strand comprises no more than six 2′-fluoro modified nucleotides.

5. The dsRNA agent of claim 1, wherein the antisense strand comprises at least one glycol-modified nucleotide.

6. The dsRNA agent of claim 5, wherein the antisense strand comprises a glycol modified nucleotide at position 7, counting from the 5′-end.

7. The dsRNA agent of claim 1, wherein the sense strand comprises four 2′-fluoro modified nucleotides at nucleotides 7 and 9-11, counting from the 5′-end, and

wherein the antisense strand comprises three 2′-fluoro modified nucleotides at nucleotides 2, 14, and 16, counting from the 5′-end, and one glycol modified nucleotide at nucleotide 7, counting from the 5′-end.

8. The dsRNA agent of claim 1, wherein: (a) the sense strand comprises at least one phosphorothioate or methylphosphonate internucleotide linkage; (b) the antisense strand comprises at least one phosphorothioate or methylphosphonate internucleotide linkage; or (c) both the sense strand and the antisense strand each comprise at least one phosphorothioate or methylphosphonate internucleotide linkage.

9. The dsRNA agent of claim 8, wherein the sense strand comprises two phosphorothioate or methylphosphonate internucleotide linkages at the 5′-terminus.

10. The dsRNA agent of claim 8, wherein the antisense strand comprises two phosphorothioate or methylphosphonate internucleotide linkages at each of the 5′-terminus and the 3′-terminus.

11. The dsRNA agent of claim 8, wherein the sense strand comprises two phosphorothioate or methylphosphonate internucleotide linkages at the 5′-terminus and the antisense strand comprises two phosphorothioate or methylphosphonate internucleotide linkages at each of the 5′-terminus and the 3′-terminus.

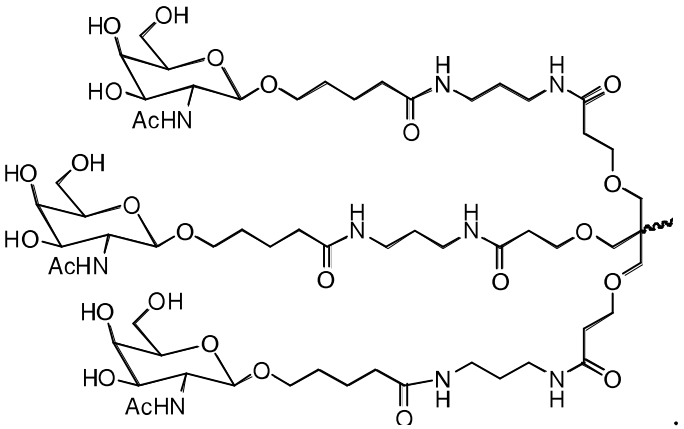
12. The dsRNA agent of claim 1, wherein at least one strand is conjugated to a ligand.

13. The dsRNA agent of claim 12, wherein the ligand is conjugated to the 3′-end of the sense strand.

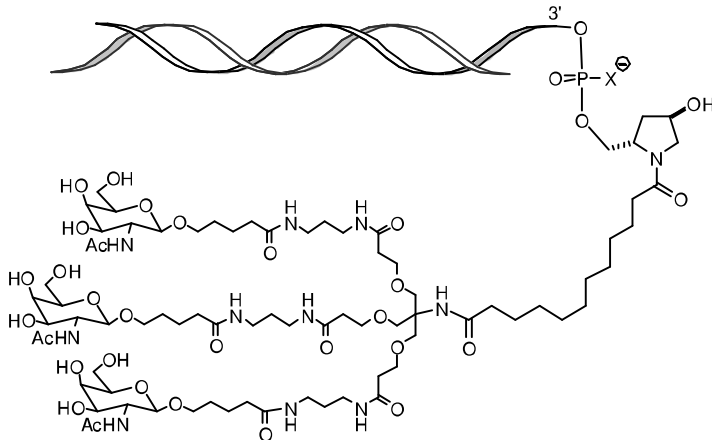
14. The dsRNA agent of claim 1, wherein the ligand comprises an N-acetylgalactosamine (GalNAc) derivative.

15. The dsRNA agent of claim 14, wherein the ligand comprises one or more GalNAc derivatives attached through a monovalent linker, a bivalent branched linker, or a trivalent branched linker.

16. The dsRNA agent of claim 15, wherein the ligand comprises:



17. The dsRNA agent of claim 16, wherein the dsRNA agent is conjugated to the ligand as shown in the following schematic:



and, wherein X is O.

18. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of 17β-hydroxysteroid dehydrogenase type 13 (HSD17B13) in a cell, comprising a sense strand and an antisense strand,

wherein the nucleotide sequence of the sense strand consists of the nucleotide sequence of SEQ ID NO: 4498 and the nucleotide sequence of the antisense strand consists of the nucleotide sequence of SEQ ID NO: 4499, and

wherein at least one of the nucleotides of the sense strand and at least one of nucleotides of the antisense strand comprises a modification selected from the group consisting of a 2′-O-methyl modification and a 2′-fluoro modification.

19. The dsRNA agent of claim 18, wherein all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand are modified.

20. The dsRNA agent of claim 19, wherein the sense strand and the antisense strand each contain at least one 2′-O-methyl modification and at least one 2′-fluoro modification.

21. The dsRNA agent of claim 20, wherein the sense strand and/or the antisense strand each independently contain 1-2 phosphorothioate or methylphosphonate internucleotide linkages at their 5′-termini and/or 3′-termini.

22. The dsRNA agent of claim 21, wherein:

(a) the sense strand comprises:

(i) four 2′-fluoro modified nucleotides at nucleotides 7 and 9-11, counting from the 5′-end;

(ii) seventeen 2′-O-methyl modified nucleotides at nucleotides 1-6, 8, and 12-21, counting from the 5′-end; and

(iii) phosphorothioate linkages between nucleotides 1 and 2 and between nucleotides 2 and 3, counting from the 5′-end; and

(b) the antisense strand comprises:

(i) three 2′-fluoro modified nucleotides at nucleotides 2, 14, and 16, counting from the 5′-end;

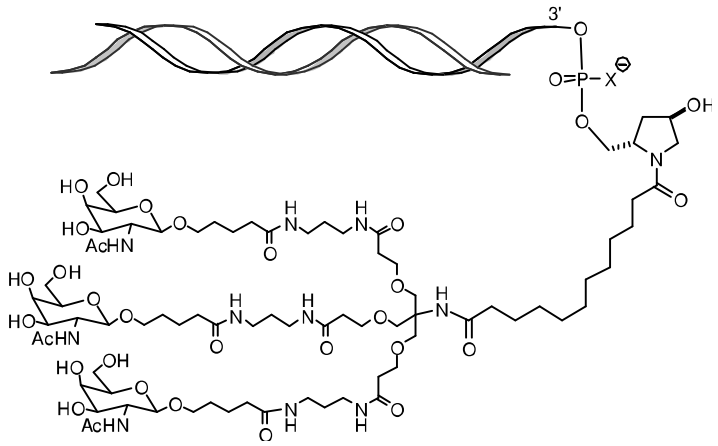
(ii) nineteen 2′-O-methyl modified nucleotides at nucleotides 1, 3-6, 8-13, 15, and 17-23, counting from the 5′-end;

(iii) one glycol modified nucleotide at nucleotide 7, counting from the 5′-end; and

(iv) phosphorothioate linkages between nucleotides 1 and 2, between nucleotides 2 and 3, between nucleotides 21 and 22, and between nucleotides 22 and 23, counting from the 5′-end.

23. The dsRNA agent of claim 22, wherein the sense strand is conjugated to a ligand, wherein the ligand comprises a multivalent galactose, an N-acetylgalactosamine, an N-acetylgalactosamine derivative, a divalent N-acetylgalactosamine, or a trivalent N-acetylgalactosamine.

24. The dsRNA agent of claim 23, wherein the dsRNA agent is conjugated to the ligand as shown in the following schematic:



and, wherein X is O.

25. A pharmaceutical composition for inhibiting expression of a gene encoding 17β-hydroxysteroid dehydrogenase type 13 (HSD17B13) comprising the dsRNA agent of claim 1.

26. The pharmaceutical composition of claim 25, wherein the dsRNA agent is in a buffered solution.

27. The pharmaceutical composition of claim 26, wherein the buffered solution comprises acetate, citrate, prolamine, carbonate, phosphate, phosphate buffered saline, or any combination thereof.

28. A pharmaceutical composition for inhibiting expression of a gene encoding 17β-hydroxysteroid dehydrogenase type 13 (HSD17B13) comprising the dsRNA agent of claim 24.

29. The pharmaceutical composition of claim 28, wherein the dsRNA agent is in a buffered solution.

30. The pharmaceutical composition of claim 29, wherein the buffered solution comprises acetate, citrate, prolamine, carbonate, phosphate, phosphate buffered saline, or any combination thereof.