PLASMINOGEN (PLG) iRNA COMPOSITIONS AND METHODS OF USE THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of priority to U.S. Provisional Application No. 63/378,731, filed on October 7, 2022, and claims the benefit of priority to U.S. Provisional Application No. 63/587,546, filed on October 3, 2023. The entire contents of the foregoing applications are hereby incorporated herein by reference.

REFERENCE TO A SEQUENCE LISTING

The official copy of the sequence listing is submitted electronically concurrently with the specification as an XML formatted sequence listing with a file name of ALN492WO_SeqList.xml, created on October 3, 2023, and having a size of 43,460,748 bytes. The sequence listing contained in this XML formatted document is part of the specification and is herein incorporated by reference in its entirety.

FIELD OF THE INVENTION

The instant disclosure relates generally to plasminogen (PLG)-targeting RNAi agents and methods.

BACKGROUND OF THE INVENTION

Plasminogen (PLG) is the precursor of the enzyme plasmin which is a serine protease that acts to break down fibrin and dissolve blood clots (fibrinolysis). PLG is primarily synthesized by the liver and released into the systemic circulation at a high plasma concentration (1.5-2μM). The two main physiological activators of plasminogen into plasmin are tissue plasminogen activator (tPA) and urokinase plasminogen activator (uPA). Plasminogen activator inhibitor (PAI-1), is an endogenous negative regulator that inhibits tPA and uPA activity, limiting plasminogen activation into plasmin and subsequent fibrinolysis.

Heavy menstrual bleeding (HMB) is excessive menstrual blood loss which interferes with a woman's physical, social, emotional and/or material quality of life. HMB affects ~30% of reproductive age women and is a significant burden for more than 10 million American women each year. HMB is associated with iron deficiency anemia, fatigue, and time lost from school/work/activities. Around 60-90% of women with a bleeding disorder suffer from HMB. Greater than $1 billion is spent every year for the treatment of HMB.

Current standard of care for HMB includes use of the anti-fibrinolytic plasminogen activation inhibitor small molecule tranexamic acid (TXA), oral contraceptive pills (OCP), and/or hormone releasing intrauterine devices (IUDs). However, side effects, high pill burden and lack of effectiveness commonly lead to discontinuation of these therapies. Therefore, there is a need for additional therapies for HMB.

Women with HMB have been shown to have higher uterine fibrinolytic activity including higher PLG levels, increased plasminogen activator t-PA levels and delayed PAI-1 levels.

Hereditary hemorrhagic telangiectasia (HHT) is a genetic blood vessel disorder which leads to excessive bleeding, affecting males and females of all ages and all ethnic backgrounds. Patients with HHT have abnormal fragile blood vessels that bleed easily and have locally increased fibrinolysis and vascular malformations, such as telangiectasia and arteriovenous malformations. About 90% of people with HHT have recurring nosebleeds and also may experience gastrointestinal bleeding, HMB, anemia, and frequent iron/blood transfusions. There are currently no FDA approved drugs for treating HHT and TXA is used off-label in HHT patients.

Given the central role of PLG in mediating fibrinolysis, inhibiting expression of the PLG gene is a potential target to reduce excessive mucocutaneous bleeding in disorders such as HHT and HMB as well as other types of bleeding associated with bleeding disorders, including nose bleeds and easy bruising.

BRIEF 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 Plasminogen (PLG) gene. The PLG 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 PLG gene and/or for treating a subject who would benefit from inhibiting or reducing the expression of a PLG gene, *e.g.*, a subject suffering or prone to suffering from a PLG-associated disease, for example, a bleeding disorder.

Accordingly, in one aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of Plasminogen (PLG) 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 3 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: 2 or 4. 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 3 and the antisense strand comprises at least 15 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 2 or 4.

In another aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of Plasminogen (PLG) 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 PLG 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 3, 4, 5, 6, 7, 8A, or 8B. 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 PLG which comprises at least 15 contiguous nucleotides from any one of the antisense sequences listed in any one of Tables 3, 4, 5, 6, 7, 8A, or 8B.

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 3-25, 90-112, 126-148, 153-175, 185-207, 202-224, 221-243, 247-269, 267-289, 287-309, 303-325, 323-345, 353-375, 372-394, 396-418, 460-482, 513-535, 550-572, 575-597, 592-614, 607-629, 623-645, 642-664, 703-725, 718-740, 740-762, 787-809, 818-840, 850-872, 870-892, 885-907, 910-932, 982-1004, 1012-1034, 1029-1051, 1061-1083, 1094-1116, 1239-1261, 1254-1276, 1313-1335, 1339-1361, 1364-1386, 1396-1418, 1426-1448, 1452-1474, 1469-1491, 1489-1511, 1592-1614, 1607-1629, 1651-1673, 1685-1707, 1700-1722, 1716-1738, 1841-1863, 1856-1878, 1919-1941, 1978-2000, 1998-2020, 2047-2069, 2062-2084, 2086-2108, 2150-2172, 2173-2195, 2223-2245, 2248-2270, 2263-2285, 2343-2365, 2433-2455, 2473-2495, 2511-2533, 2553-2575, 2578-2600, 2605-2627, 2621-2643, 2646-2668, 2661-2683, 2701-2723, 2727-2749, 2742-2764, 2771-2793, 2804-2826, 2826-2848, 2874-2896, 2890-2912, 2914-2936, 2929-2951, 2947-2969, 2962-2984, 2987-3009, 3006-3028, 3025-3047, 3068-3090, 3097-3119, 3116-3138, 3143-3165, 3168-3190, 3183-3205, 3209-3231, 3236-3258, 3269-3291, 3289-3311, 3310-3332, 3330-3352, 3391-3413, 3407-3429, 3422-3444, 3447-3469, 3468-3490, 3485-3507 of SEQ ID NO: 1; or 8-30, 45-67, 519-541, 534-556, 617-639, 653-675, 669-691, 702-724, 717-739, 760-782, 776-798, 798-820, 851-873, 870-892, 885-907, 904-926, 929-951, 962-984, 984-1006, 1000-1022, 1016-1038, 1055-1077, 1070-1092, 1113-1135, 1128-1150, or 1159-1181 of SEQ ID NO: 3. In some embodiments, the region of complementarity comprises at least 15 contiguous nucleotides from any one of nucleotides 3-25, 90-112, 126-148, 153-175, 185-207, 202-224, 221-243, 247-269, 267-289, 287-309, 303-325, 323-345, 353-375, 372-394, 396-418, 460-482, 513-535, 550-572, 575-597, 592-614, 607-629, 623-645, 642-664, 703-725, 718-740, 740-762, 787-809, 818-840, 850-872, 870-892, 885-907, 910-932, 982-1004, 1012-1034, 1029-1051, 1061-1083, 1094-1116, 1239-1261, 1254-1276, 1313-1335, 1339-1361, 1364-1386, 1396-1418, 1426-1448, 1452-1474, 1469-1491, 1489-1511, 1592-1614, 1607-1629, 1651-1673, 1685-1707, 1700-1722, 1716-1738, 1841-1863, 1856-1878, 1919-1941, 1978-2000, 1998-2020, 2047-2069, 2062-2084, 2086-2108, 2150-2172, 2173-2195, 2223-2245, 2248-2270, 2263-2285, 2343-2365, 2433-2455, 2473-2495, 2511-2533, 2553-2575, 2578-2600, 2605-2627, 2621-2643, 2646-2668, 2661-2683, 2701-2723, 2727-2749, 2742-2764, 2771-2793, 2804-2826, 2826-2848, 2874-2896, 2890-2912, 2914-2936, 2929-2951, 2947-2969, 2962-2984, 2987-3009, 3006-3028, 3025-3047, 3068-3090, 3097-3119, 3116-3138, 3143-3165, 3168-3190, 3183-3205, 3209-3231, 3236-3258, 3269-3291, 3289-3311, 3310-3332, 3330-3352, 3391-3413, 3407-3429, 3422-3444, 3447-3469, 3468-3490, 3485-3507 of SEQ ID NO: 1; or 8-30, 45-67, 519-541, 534-556, 617-639, 653-675, 669-691, 702-724, 717-739, 760-782, 776-798, 798-820, 851-873, 870-892, 885-907, 904-926, 929-951, 962-984, 984-1006, 1000-1022, 1016-1038, 1055-1077, 1070-1092, 1113-1135, 1128-1150, or 1159-1181 of SEQ ID NO: 3.

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

In one embodiment, substantially all of the nucleotides of the sense strand 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 embodiment, the antisense strand of the dsRNA agent is chosen from the antisense strands of AD-2315878 (SEQ ID NO:1291), AD-2315874 (SEQ ID NO:1287), or AD-2315875 (SEQ ID NO:1288). In another embodiment, the sense strand is chosen from the sense strands of AD-2315878 (SEQ ID NO:1277), AD-2315874 (SEQ ID NO:1273), or AD-2315875 (SEQ ID NO:1274). In a further embodiment, the dsRNA agent is AD-2315878, AD-2315874, or AD-2315875.

In one embodiment, (a) the sense strand of the dsRNA agent comprises the sequence and all of the modifications of SEQ ID NO: 881, and the antisense strand of the dsRNA agent comprises the sequence and all the modifications of SEQ ID NO:1265; (b) the sense strand of the dsRNA agent comprises the sequence and all of the modifications of SEQ ID NO: 914, and the antisense strand of the dsRNA agent comprises the sequence and all the modifications of SEQ ID NO:1266; or (c) the sense strand of the dsRNA agent comprises the sequence and all of the modifications of SEQ ID NO: 907, and the antisense strand of the dsRNA agent comprises the sequence and all the modifications of SEQ ID NO:1272.

In one aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of Plasminogen (PLG) 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 3 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:2 or 4, wherein substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand are modified nucleotides, and wherein 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 3 and the antisense strand comprises at least 15 contiguous nucleotides from the nucleotide sequence of SEQ ID NO:2 or 4, wherein substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand are modified nucleotides, and wherein 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, a 2-O-(N-methylacetamide) modified nucleotide, a nucleotide comprising vinyl phosphonate, a nucleotide comprising a glycol nucleic acid (GNA) (e.g., an adenosine-glycol nucleic acid), a nucleotide comprising a glycol nucleic acid S-Isomer (S-GNA) (e.g., a thymidine-glycol nucleic acid S-Isomer), a nucleotide comprising 2-hydroxymethyl-tetrahydrofuran-5-phosphate, a nucleotide comprising 2'-deoxythymidine-3'phosphate, a nucleotide comprising 2'-deoxyguanosine-3'-phosphate, a 2′-5′-linked ribonucleotide (3′-RNA), and a terminal nucleotide linked to a cholesteryl derivative and a dodecanoic acid bisdecylamide group; 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.

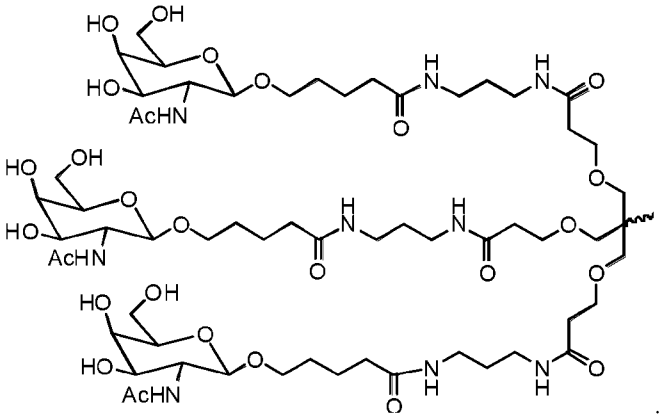
The dsRNA may include at least one strand that comprises a 3' overhang of at least 1 nucleotide; or at least one strand that comprises a 3' overhang of at least 2 nucleotides.

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

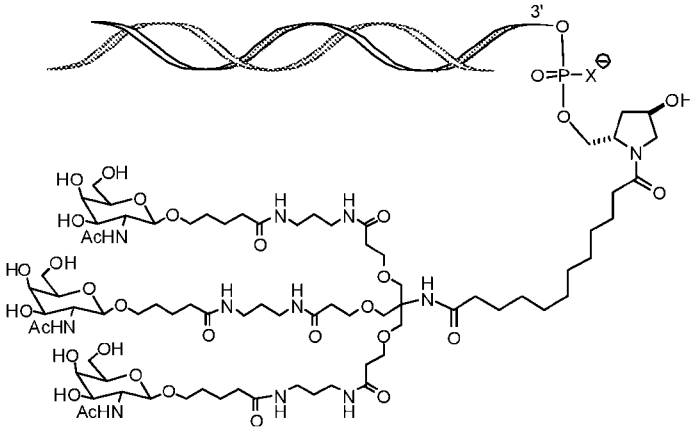
In one embodiment, the ligand is conjugated to the 3' end of the sense strand of the dsRNA agent.

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 3, 4, 5, 6, 7, 8A, or 8B.

In one aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of Plasminogen (PLG) 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 PLG, wherein each strand is about 14 to about 30 nucleotides in length, wherein said dsRNA agent is represented by formula (III):

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

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;

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 another 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 another 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.

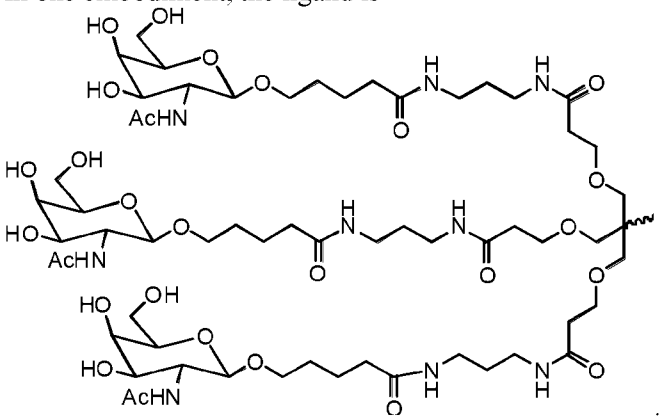
In one embodiment, at least one n_p' is linked to a neighboring nucleotide via a phosphorothioate linkage. In another embodiment, wherein all n_p' are linked to neighboring nucleotides via phosphorothioate linkages.

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

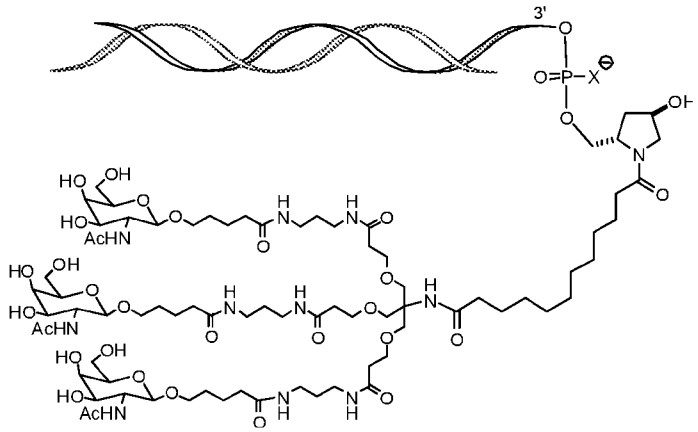
In one embodiment, the ligand is conjugated to the 3' end of the sense strand of the dsRNA agent.

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 plasminogen (PLG) 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 PLG, 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;

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 plasminogen (PLG) 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 PLG, 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.

In one aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting the expression of plasminogen (PLG) 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 PLG, 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, 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 plasminogen (PLG) 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 PLG, 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 plasminogen (PLG) 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 PLG, wherein each strand is about 14 to about 30 nucleotides in length, wherein the dsRNA agent is represented by formula (III):

sense: $5' n_p\text{-}N_a\text{-}Y\ Y\ Y\text{-}N_a\text{-}n_q\ 3'$

antisense: $3' n_p'\text{-}N_a'\text{-}Y'Y'Y'\text{-}N_a'\text{-}n_q'\ 5'$ (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 plasminogen (PLG) 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 3 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:2 or 4, 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 3 and the antisense strand comprises at least 15 contiguous nucleotides from the nucleotide sequence of SEQ ID NO:2 or 4, 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 3, 4, 5, 6, 7, 8A, or 8B.

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 3, 4, 5, 6, 7, 8A, or 8B.

In another aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of plasminogen (PLG) in a cell, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region. The sense strand comprises a nucleotide sequence of any one of the agents in Tables 3, 4, 5, 6, 7, 8A, or 8B and the antisense strand comprises a nucleotide

sequence of any one of the agents in Tables 3, 4, 5, 6, 7, 8A, or 8B. Substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand are modified nucleotides, and the dsRNA agent is conjugated to a ligand.

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

In another aspect, the present invention provides a dsRNA agent that targets a hotspot region of a plasminogen (PLG) mRNA.

The present invention also provides cells, vectors, and pharmaceutical compositions which include any of the dsRNA agents of the invention. The dsRNA agents may be formulated in an unbuffered solution, *e.g.*, saline or water, or in a buffered solution, *e.g.*, a solution 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 plasminogen (PLG) 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 PLG in the cell.

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

In one embodiment, the PLG expression is inhibited by at least 20%, 25%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or to below the level of detection of PLG expression. In another embodiment the PLG expression is inhibited by about 50% or less. In a specific embodiment, the PLG expression is inhibited by about 50%.

In one embodiment, the human subject suffers from a PLG-associated disease, disorder, or condition. In one embodiment, the PLG-associated disease, disorder, or condition is a bleeding disorder, such as hereditary hemorrhagic telangiectasia (HHT). In one embodiment, a symptom of the bleeding disorder is heavy menstrual bleeding (HMB). In one embodiment, the bleeding disorder is selected from the group consisting of PAI-1 deficiency, hereditary hemorrhagic telangiectasia (HHT), heavy menstrual bleeding (HMB), von Willebrand disease, low factor XI levels, platelet defects, hemophilia A, hemophilia B, afibrinogenemia, parahemophilia, low factor VIII levels, low factor IX levels, low factor VII levels, low factor XIII levels, low factor X levels, low factor V levels, low factor II levels, nose bleeds, bleeding gums, easy bruising, postpartum bleeding, and excessive bleeding following surgery. In one embodiment, the bleeding disorder is hereditary hemorrhagic telangiectasia (HHT). In one embodiment, the PLG-associated disease, disorder, or condition is a surgical procedure such as cardiac surgery, oral and maxillo-facial surgery, liver surgery, nephrolithotomy, orthopedic surgery, gynecologic surgery, trauma intervention, tooth extraction, or dermatologic procedures. In one embodiment, the subject is treated pre-surgery to prevent excessive bleeding. In another embodiment, the PLG-associated disease, disorder, or condition is melasma or hyperpigmentation of the skin.

In one aspect, the present invention provides a method of inhibiting the expression of PLG 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 PLG in the subject.

In another aspect, the present invention provides a method of treating a subject suffering from a PLG-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, thereby treating the subject suffering from a PLG-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 a PLG 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 a PLG gene.

In one embodiment, the administration of the dsRNA agent or the pharmaceutical composition to the subject causes a decrease in PLG activity, a decrease in PLG protein accumulation, and/or a decrease in excessive bleeding in a subject.

In one embodiment, the PLG-associated disease, disorder, or condition is a bleeding disorder.

In one embodiment, a symptom of the bleeding disorder is heavy menstrual bleeding (HMB).

In one embodiment, the bleeding disorder is hereditary hemorrhagic telangiectasia (HHT).

In one embodiment, the bleeding disorder is selected from the group consisting of hereditary hemorrhagic telangiectasia (HHT), heavy menstrual bleeding (HMB), PAI-1 deficiency, von Willebrand disease, low factor XI levels, platelet defects, hemophilia A, hemophilia B, afibrinogenemia, parahemophilia, low factor VIII levels, low factor IX levels, low factor VII levels, low factor XIII levels, low factor X levels, low factor V levels, low factor II levels, nose bleeds, bleeding gums, easy bruising, postpartum bleeding, and excessive bleeding following surgery.

In one embodiment, the PLG-associated disease, disorder, or condition is a surgical procedure such as cardiac surgery, oral and maxillo-facial surgery, liver surgery, nephrolithotomy, orthopedic surgery, gynecologic surgery, trauma intervention, tooth extraction, or dermatologic procedures.

In one embodiment, the PLG-associated disease, disorder, or condition is melasma or hyperpigmentation of the skin.

In one embodiment, the subject is treated pre-surgery to prevent excessive bleeding.

In one embodiment, the bleeding disorder is a mucocutaneous bleeding disorder (MCB). In one embodiment, the mucocutaneous bleeding disorder is selected from the group consisting of inherited platelet disorders (IPD), hereditary hemorrhagic telangiectasia (HHT), hypermobility spectrum disorders (HSD), Ehlers-Danlos syndromes (EDS), and von Willebrand disease (VWD).

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 PLG in the subject.

In one aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of plasminogen (PLG) 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 3, 4, 5, 6, 7, 8A, or 8B, and the antisense strand comprises a nucleotide sequence of any one of the agents in any one of Tables 3, 4, 5, 6, 7, 8A, or 8B, 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.

In one embodiment, the RNAi agent is a pharmaceutically acceptable salt thereof. "Pharmaceutically acceptable salts" of each of RNAi agents herein include, but are not limited to, a sodium salt, a calcium salt, a lithium salt, a potassium salt, an ammonium salt, a magnesium salt, and mixtures thereof. One skilled in the art will appreciate that the RNAi agent, when provided as a polycationic salt having one cation per free acid group of the optionally modified phosophodiester backbone and/or any other acidic modifications (*e.g.*, 5′-terminal phosphonate groups). For example, an oligonucleotide of "n" nucleotides in length contains n-1 optionally modified phosophodiesters, so that an oligonucleotide of 21 nt in length may be provided as a salt having up to 20 cations (*e.g*, 20 sodium cations). Similarly, an RNAi agents having a sense strand of 21 nt in length and an antisense strand of 23 nt in length may be provided as a salt having up to 42 cations (*e.g*, 42 sodium cations). In the preceding example, where the RNAi agent also includes a 5′-terminal phosphate or a 5′-terminal vinylphosphonate group, the RNAi agent may be provided as a salt having up to 44 cations (*e.g*, 44 sodium cations).

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 depicts the results of a multi-dose *in vitro* screen with 1100 PLG siRNA duplexes in transfected primary human hepatocytes (PHH). The final duplex concentration was 10 nM (diamond shape), 1 nM (square shape), or 0.1 nM (triangle shape) and the results are plotted relative to the position of the duplex on the human NM_000301 transcript.

FIG. 2 illustrates the percent plasma PLG antigen remaining (measured by ELISA) in an *in vivo* single dose study in PXB mice. Exemplary PLG siRNA duplexes were administered at 0.5 mg/kg and PLG levels were measured in plasma at the indicated timepoints.

FIG. 3 illustrates the percent plasma human PLG antigen remaining (measured by ELISA) in an *in vivo* single dose study in PXB mice. An exemplary PLG siRNA duplex was administered at 1 mg/kg and 3 mg/kg and PLG levels were measured in plasma at the indicated timepoints.

FIG. 4 illustrates the percent plasma human PLG antigen remaining (measured by ELISA) in an *in vivo* single dose study in PXB mice. An exemplary PLG siRNA duplex was administered at 0.3mg/kg, 1 mg/kg and 3 mg/kg and PLG levels were measured in plasma at the indicated timepoints.

FIG. 5 illustrates the percent plasma human PLG antigen remaining (measured by ELISA) in an *in vivo* single dose study in PXB mice. An exemplary PLG siRNA duplex was administered at 0.3mg/kg, 1 mg/kg and 3 mg/kg and PLG levels were measured in plasma at the indicated timepoints.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides iRNA compositions, which effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of a PLG gene. The PLG 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 PLG gene, and for treating a subject who would benefit from inhibiting or reducing the expression of a PLG gene, *e.g.*, a subject that would benefit from a reduction in bleeding, *e.g.*, a subject suffering or prone to suffering from a PLG-associated disease disorder, or condition, such as a subject suffering or prone to suffering from bleeding disorders (i.e., heavy menstrual bleeding), *e.g.*, a subject suffering from hereditary hemorrhagic telangiectasia (HHT), heavy menstrual bleeding (HMB), PAI-1 deficiency, von Willebrand disease, low factor XI levels, platelet defects, hemophilia A, hemophilia B, afibrinogenemia, parahemophilia, low factor VIII levels, low factor IX levels, low factor VII levels, low factor XIII levels, low factor X levels, low factor V levels, low factor II levels, nose bleeds, bleeding gums, easy bruising, postpartum bleeding, or excessive bleeding following surgery.

The iRNAs of the invention targeting PLG 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 a PLG 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 a PLG 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 a PLG 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 a PLG gene. Thus, methods and compositions including these iRNAs are useful for treating a subject who would benefit from inhibiting or reducing the expression of a PLG gene, *e.g.*. a subject that would benefit from a reduction of bleeding, *e.g.*, a subject suffering or prone to suffering from a PLG-associated disease disorder, or condition, such as a subject suffering or prone to suffering from bleeding disorder, *e.g.*, a subject suffering from hereditary hemorrhagic telangiectasia (HHT), heavy menstrual bleeding (HMB), PAI-1 deficiency, von Willebrand disease, low factor XI levels, platelet defects, hemophilia A, hemophilia B, afibrinogenemia, parahemophilia, low factor VIII levels, low factor IX levels, low factor VII levels, low factor XIII levels, low factor X levels, low factor V levels, low factor II levels, nose bleeds, bleeding gums, easy bruising, postpartum bleeding, or excessive bleeding following surgery.

The following detailed description discloses how to make and use compositions containing iRNAs to inhibit the expression of a PLG 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 ±10%. In certain embodiments, about means ±5%. When about is present before a series of numbers or a range, it is understood that "about" can modify each of the numbers in the series or range.

The term "PLG," also known as "Plasminogen," "Plasmin," "HAE4," "EC 3.4.21.7," and "EC 3.4.21," refers to the well-known gene encoding a PLG 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 PLG that maintain at least one *in vivo* or *in vitro* activity of a native PLG.

Plasminogen (PLG) is a serine protease and mediates fibrinolysis or dissolving of fibrin blood clots. PLG is highly expressed by the liver and to a lesser extent by the kidney. Plasminogen is released from the liver into systemic circulation. Since plasminogen is the main driver of fibrinolysis, reducing plasminogen levels or activity could be beneficial in patients with bleeding disorders. Non-limiting examples of bleeding disorders include hereditary hemorrhagic telangiectasia (HHT), heavy menstrual bleeding (HMB), PAI-1 deficiency, von Willebrand disease, low factor XI levels, platelet defects, hemophilia A, hemophilia B, afibrinogenemia, parahemophilia, low factor VIII levels, low factor IX levels, low factor VII levels, low factor XIII levels, low factor X levels, low factor V levels, low factor II levels, nose bleeds, bleeding gums, easy bruising, postpartum bleeding, or excessive bleeding following surgery.

In one embodiment, the bleeding disorder is a mucocutaneous bleeding disorder (MCB). The biology of MCB is not as well understood as other bleeding disorders, such as hemophilia, and can take a long time to diagnose. MCB symptoms include epistaxis (nosebleeds), heavy menstrual bleeding, post-partum hemorrhage, digestive tract bleeding, easy bruising, prolonged bleeding, and bleeding gums. TXA is used as a treatment to reduce bleeding in MCB patients. Non-limiting examples of mucocutaneous bleeding disorders include inherited platelet disorders (IPD), hereditary hemorrhagic telangiectasia (HHT), hypermobility spectrum disorders (HSD), Ehlers-Danlos syndromes (EDS), and von Willebrand disease (VWD).

Exemplary nucleotide and amino acid sequences of PLG can be found, for example, at GenBank Accession No. NM_000301.5 (SEQ ID NO: 1; reverse complement SEQ ID NO: 2) and GenBank Accession No. NM_001168338.1 (SEQ ID NO: 3; reverse complement SEQ ID NO: 4) for Homo sapiens PLG; GenBank Accession No. XM_005551498.2 (SEQ ID NO: 685; reverse complement SEQ ID NO: 686) for Macaca fascicularis PLG; GenBank Accession No. NM_008877.3 (SEQ ID NO: 687; reverse complement SEQ ID NO: 688) for Mus musculus PLG; and GenBank Accession No. NM_053491.2 (SEQ ID NO: 689; reverse complement SEQ ID NO: 690) for Rattus norvegicus PLG.

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

Further information on PLG is provided, for example in the NCBI Gene database at http://www.ncbi.nlm.nih.gov/gene/5340.

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

In some aspects, the iRNA that is substantially complementary to a region of a human PLG mRNA cross reacts with mouse PLG mRNA. In some aspects, the iRNA that is substantially complementary to a region of a mouse PLG mRNA cross reacts with human PLG mRNA and represent potential candidates for human targeting. In some embodiments, the iRNA that is substantially complementary to a region of a mouse or human PLG mRNA cross reacts with rat, monkey, and/or rabbit PLG mRNA.

As used herein, "target sequence" refers to a contiguous portion of the nucleotide sequence of an mRNA molecule formed during the transcription of a PLG gene, including mRNA that is a product of RNA processing of a primary transcription product. In one embodiment, 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 PLG gene.

The target sequence of a PLG 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 2). 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 PLG 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.*, a PLG 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 (ssRNA) generated within a cell and which promotes the formation of a RISC complex to effect silencing of the target gene, *i.e.*, a PLG 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.*, a PLG 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.*, a PLG 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.*, a PLG 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 antisense 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.*, a PLG 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.*. a PLG 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 PLG). For example, a polynucleotide is complementary to at least a part of a PLG mRNA if the sequence is substantially complementary to a non-interrupted portion of an mRNA encoding PLG.

Accordingly, in some embodiments, the antisense strand polynucleotides disclosed herein are fully complementary to the target PLG sequence. In other embodiments, the antisense strand polynucleotides disclosed herein are substantially complementary to the target PLG 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 3, or a fragment of SEQ ID NO:1 or 3, 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 PLG 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: 2 or 4, or a fragment of any one of SEQ ID NO: 2 or 4, 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 PLG 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 3, 4, 5, 6, 7, 8A, or 8B, or a fragment of any one of the sense strands in any one of Tables 3, 4, 5, 6, 7, 8A, or 8B, such as 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 a PLG gene," as used herein, includes inhibition of expression of any PLG gene (such as, *e.g.*, a mouse PLG gene, a rat PLG gene, a monkey PLG gene, or a human PLG gene) as well as variants or mutants of a PLG gene that encode a PLG protein.

"Inhibiting expression of a PLG gene" includes any level of inhibition of a PLG gene, *e.g.*, at least partial suppression of the expression of a PLG 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%. In some embodiments, inhibition is by at least about 50%.

The expression of a PLG gene may be assessed based on the level of any variable associated with PLG gene expression, *e.g.*, PLG mRNA level or PLG protein level. The expression of a PLG gene may also be assessed indirectly based on, for example, the levels of PLG activity 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 a PLG gene, is assessed by a reduction of the amount of PLG mRNA which can be isolated from, or detected, in a first cell or group of cells in which a PLG gene is transcribed and which has or have been treated such that the expression of a PLG 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 PLG expression; a human at risk for a disease, disorder or condition that would benefit from reduction in PLG expression; a human having a disease, disorder or condition that would benefit from reduction in PLG expression; and/or human being treated for a disease, disorder or condition that would benefit from reduction in PLG expression as described herein.

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 PLG gene expression and/or PLG protein production, *e.g.*, a PLG-associated disease, such as a bleeding disorder (i.e., heavy

menstrual bleeding) and melasma. In one embodiment, the bleeding disorder is hereditary hemorrhagic telangiectasia (HHT). In one embodiment, the bleeding disorder is heavy menstrual bleeding (HMB). In another embodiment, the bleeding disorder is selected from the group consisting of PAI-1 deficiency, hereditary hemorrhagic telangiectasia (HHT), von Willebrand disease, low factor XI levels, platelet defects, hemophilia A, hemophilia B, afibrinogenemia, parahemophilia, low factor VIII levels, low factor IX levels, low factor VII levels, low factor XIII levels, low factor X levels, low factor V levels, low factor II levels, nose bleeds, bleeding gums, easy bruising, postpartum bleeding, and excessive bleeding following surgery. "Treatment" can also mean prolonging survival as compared to expected survival in the absence of treatment.

The term "lower" in the context of a PLG-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 PLG 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 a PLG 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 PLG gene expression, such as excessive bleeding. 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 bleeding) delayed (*e.g.*, by days, weeks, months or years) is considered effective prevention.

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

In one embodiment, an "PLG-associated disease" is a bleeding disorder. A "bleeding disorder" is any disease, disorder, or condition associated with heavy or excessive bleeding. Non-limiting examples of a bleeding disorder include hereditary hemorrhagic telangiectasia (HHT), heavy menstrual bleeding (HMB), PAI-1 deficiency, von Willebrand disease, low factor XI levels, platelet defects, hemophilia A, hemophilia B, afibrinogenemia, parahemophilia, low factor VIII levels, low factor IX levels, low factor VII levels, low factor XIII levels, low factor X levels, low factor V levels, low factor II levels, nose bleeds, bleeding gums, easy bruising, postpartum bleeding, and excessive bleeding following surgery.

In one embodiment, the bleeding disorder is hereditary hemorrhagic telangiectasia (HHT). HHT is a genetic blood vessel disorder which leads to excessive bleeding, affecting males and females of all ages and all ethnic backgrounds. There are about 70,000 HHT patients in the United States and 1.4 million with HHT

worldwide. There are three known genetic mutations in the TGFβ pathway in HHT, including mutations in the Endoglin, Smad4, and ALK1 genes which are involved in endothelial migration during angiogenesis and vascular remodeling. Patients with HHT have abnormal fragile blood vessels that bleed easily and have locally increased fibrinolysis and vascular malformations, such as telangiectasia and arteriovenous malformations. About 90% of people with HHT have recurring nosebleeds varying in frequency and severity, with nosebleeds greater than 5 times a week and nosebleeds lasting greater than five hours which may require emergency room visits and transfusions. Patients with HHT also may experience gastrointestinal bleeding, heavy menstrual bleeding (HMB), anemia, and frequent iron/blood transfusions.

There are currently no FDA approved drugs for treating HHT. Tranexamic acid (TXA) is an oral antifibrinolytic drug that is used off-label in HHT patients but is not an ideal therapy as it has poor bioavailability, a high pill burden (2 large tablets, 3-4 times a day), and off target side effects. Therefore, there is a need for a long-lasting effective therapy for HHT. In one embodiment, a symptom of a bleeding disorder can be heavy menstrual bleeding (HMB).

HMB is excessive menstrual blood loss which interferes with a woman's physical, social, emotional and/or material quality of life. One in five women aged 30-55 years perceive their menstrual bleeding to be abnormal. HMB is a significant burden for more than 10 million American women each year. HMB is associated with iron deficiency anemia, fatigue, and time lost from school/ work /activities. Greater than $1 billion is spent every year for the treatment of HMB.

Causes of HMB are classified by the acronym PALM-COEIN: Polyp, Adenomyosis, Leiomyoma, Malignancy, Coagulopathy, Ovulatory dysfunction, endometrial, latrogenic (for example, copper IUD intrauterine system), and not otherwise specified (for example, a caesarean scar defect). Uterine fibroids and polyps are among the most reported drivers of HMB. Approximately 30% of women with HMB have a known bleeding disorder, such as von Willebrand disease, Low factor XI levels, or platelet defects. Approximately 50% of women with HMB have no pathology implicated as a cause.

The standard of care for HMB includes tranexamic acid (TXA), an inhibitor of plasminogen activation; intrauterine devices (IUDs), such as Mirena; and/or oral contraceptive pills (OCPs). TXA is typically used in women who do not want or cannot tolerate hormones. Treatment can include layering of OCP or TXA with an IUD.

However, these treatments have side effects which can cause discontinuation. Approximately 40% of women with HMB discontinue Mirena IUD within two years due to lack of effectiveness (60%), hormonal side effects (20%) and irregular bleeding. Fifteen percent of women with an IUD required add-on TXA. Other side effects include perforation into the wall of the uterus, expulsion or displacement of the IUD, bleeding between periods, headaches, acne, and breast tenderness. Side effects of OCPs include nausea, breast tenderness, headaches, decreased libido, and thrombosis. TXA, which inhibits PLG activity, has side effects including menstrual discomfort, headache, back pain, nausea and vomiting, and musculoskeletal pain. Off-target inhibition of spinal $GABA_A$ (γ-Aminobutyric acid type A) and glycine receptors by TXA can

dysregulate pain processing and increase risk of seizures (Ohashi et al., 2015, *Sci Rep.* 5:13458). Therefore, there is a need for alternative treatments for HMB.

The dsRNA agents provided herein for inhibiting expression of plasminogen can be used to treat bleeding disorders, such as HMB. The potential advantages of a plasminogen lowering siRNA approach versus current standard of care in HMB is that siRNA is a non-hormonal option thereby avoiding the hormonal side effects of OCP and Mirena IUD, avoid the side-effects of TXA, infrequent administration, and potentially lower thrombotic risk.

Patients with genetic disorders resulting in plasminogen deficiency (e.g., type I or type II plasminogen deficiency), do not have an increased risk of thrombosis deficiency (Schuster V. et al., 2007, *J Thromb Haemost*. 5: 2315–22). However, these patients, having little to no PLG activity, experience ligneous lesions caused by the deposition of fibrin including ligneous conjunctivitis, ligneous gingivitis, ligneous cervicitis, and ligneous endometritis. Treatment for patients with plasminogen deficiency includes i.v. infusion (administered every 2-4 days) of purified, human plasma-donor derived Glu-plasminogen. Studies with TXA indicate that a lower dose of TXA may be equally as effective in treating HMB as the standard dosing. (The minimal effective dose of tranexamic acid in women with menorrhagia XXIV Congress of the International Society on Thrombosis and Haemostasis (2013)). Therefore, less potent plasminogen suppression of approximately 50% or less may be sufficient. Accordingly, to minimize side effects of PLG deficiency, such as development of lesions, the knockdown of PLG by the dsRNA agents provided herein can be selected or designed to achieve a 50% or less knockdown of PLG. In some embodiments, the dsRNA agents provided herein reduce PLG expression by about 50%, 45%, 40%, 45%, 30%, 25%, 20%, 15%, 10%, 5%, or less.

In one embodiment, a person that would benefit from a decrease in PLG gene expression or protein activity is a woman with fibroids. In some embodiments, a person that would benefit from a decrease in PLG gene expression or protein activity is a woman with HMB that has fibroids, has a known bleeding disorder, has bleeding of unknown cause for whom IUD or OCP are not sufficient, already takes tranexamic acid (TXA), does not tolerate hormonal therapy (IUD or OCP), does not tolerate TXA, or does not want surgery or hormonal options.

"Therapeutically effective amount," as used herein, is intended to include the amount of an RNAi agent that, when administered to a subject having a PLG-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 a PLG-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 "prophylactically 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 a PLG gene. In one embodiment, the iRNA agent includes double stranded ribonucleic acid (dsRNA) molecules for inhibiting the expression of a PLG 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 bleeding disorder or condition.

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 a PLG 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 rodent 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 a PLG 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 PLG 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 3, 4, 5, 6, 7, 8A, or 8B, 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 3, 4, 5, 6, 7, 8A, or 8B. In this aspect, one of the two sequences is complementary to the other of the two sequences, with one of the sequences being substantially complementary to a sequence of an mRNA generated in the expression of a PLG 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 3, 4, 5, 6, 7, 8A, or 8B, and the second oligonucleotide is described as the corresponding antisense strand (guide strand) of the sense strand in any one of Tables 3, 4, 5, 6, 7, 8A, or 8B. 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 3, 4, 5, 6, 7, 8A, or 8B 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 3, 4, 5, 6, 7, 8A, or 8B 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 a PLG 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 3, 4, 5, 6, 7, 8A, or 8B identify a site(s) in a PLG 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 a PLG 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 a PLG gene. Consideration of the efficacy of iRNAs with mismatches in inhibiting expression of a PLG gene is important, especially if the particular region of complementarity in a PLG gene is known to have polymorphic sequence variation within the population.

An RNA target may have regions, or spans of the target RNA's nucleotide sequence, which are relatively more susceptible or amenable than other regions of the RNA target to mediating cleavage of the RNA target via RNA interference induced by the binding of an RNAi agent to that region. The increased susceptibility to RNA interference within such "hotspot regions" (or simply "hotspots") means that iRNA agents targeting the region will likely have higher efficacy in inducing iRNA interference than iRNA agents which target other regions of the target RNA. For example, without being bound by theory, the accessibility of a target region of a target RNA may influence the efficacy of iRNA agents which target that region, with some hotspot regions having increased accessibility. Secondary structures, for instance, that form in the RNA target (e.g., within or proximate to hotspot regions) may affect the ability of the iRNA agent to bind the target region and induce RNA interference.

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

Compared regions of the target RNA may be empirically evaluated for identification of hotspots using efficacy data obtained from in vitro or in vivo screening assays. For example, RNAi agents targeting various regions that span a target RNA may be compared for frequency of efficacious iRNA agents (e.g., the amount by which target gene expression is inhibited, such as measured by mRNA expression or protein expression) that bind each region. In general, a hotspot can be recognized by observing clustering of multiple efficacious RNAi agents that bind to a limited region of the RNA target. A hotspot may be sufficiently characterized as such by observing efficacy of iRNA agents which cumulatively span at least about 60% of the target region identified as a hotspot, such as about 70%, about 80%, about 90%, or about 95% or more of the length of the region, including both ends of the region (i.e. at least about 60%, 70%, 80%, 90%, or 95% or more of the nucleotides within the region, including the nucleotides at each end of the region, were targeted by an iRNA agent). According to some aspects of the invention, an iRNA agent which demonstrates at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% inhibition over the region (e.g., no more than about 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, 10%, or 5% mRNA remaining) may be identified as efficacious.

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

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

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

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 phosphonate (5'-VP). In one embodiment, the phosphate mimic is a 5'-cyclopropyl phosphonate. In some embodiments, the 5'-end of the antisense strand of the double-stranded iRNA agent does not contain a 5'-vinyl phosphonate (VP).

In one embodiment, at least one of the modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a glycol modified nucleotide (GNA), e.g., Ggn, Cgn, Tgn, or Agn, a nucleotide with a 2' phosphate, e.g., G2p, C2p, A2p or U2p, and, a vinyl-phosphonate nucleotide; and combinations thereof. In other embodiments, each of the duplexes of Tables 3, 4, 5, 6, 7, 8A, or 8B may be particularly modified to provide another double-stranded iRNA agent of the present disclosure. In one example, the 3'-terminus of each sense duplex may be modified by removing the 3'-terminal L96 ligand and exchanging the two phosphodiester internucleotide linkages between the three 3'-terminal nucleotides with phosphorothioate internucleotide linkages. That is, the three 3'-terminal nucleotides (N) of a sense sequence of the formula:

$$5'\text{-}\ N_1\text{-}\ldots\ \text{-}N_{n-2}N_{n-1}N_nL96\ 3'$$

may be replaced with

$$5'\text{-}\ N_1\text{-}\ldots\ \text{-}N_{n-2}\underline{s}N_{n-1}\underline{s}N_n\ 3'.$$

That is, for example, AD-2042815, the sense sequence:

gsuscaacAfaCfAfUfccugggaa**uuuL96** (SEQ ID NO: 279)

may be replaced with

gsuscaacAfaCfAfUfccugggaa**ususu** (SEQ ID NO: 684)

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

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 a PLG gene which is selected from the group of agents listed in any one of Tables 3, 4, 5, 6, 7, 8A, or 8B. 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.*, a PLG 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 nucleotides 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 which is at least 25 nucleotides in length, and the second strand is sufficiently complementary 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 1st nucleotide from the 5'-end of the antisense strand, or, the count starting from the 1st 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 adjacent 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 antisense 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 activity 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. Alternatively, 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-stranded 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 mismatch 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):

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

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-N_a-YYY-N_b-ZZZ-N_a-n_q 3' (Ib);

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

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

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

When the sense strand is represented as formula (Ic), N_b represents an oligonucleotide sequence comprising 0-10, 0-7, 0-10, 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 an 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 0 modified 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 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.

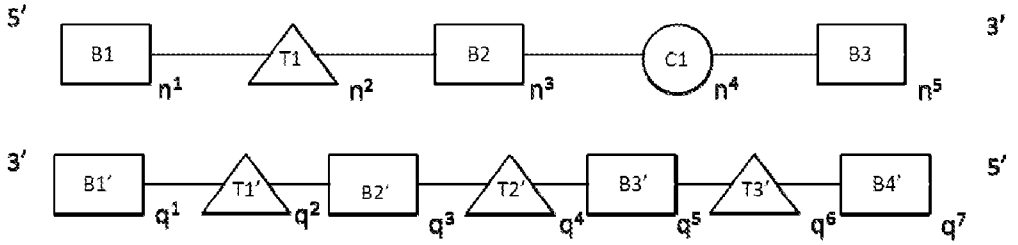
As described in more detail below, the RNAi agent that contains conjugations of one or more carbohydrate moieties to a RNAi agent can optimize one or more properties of the RNAi agent. In many cases, the carbohydrate moiety will be attached to a modified subunit of the RNAi agent. For example, the ribose 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 decalin; preferably, the acyclic group is selected from serinol backbone or diethanolamine backbone.

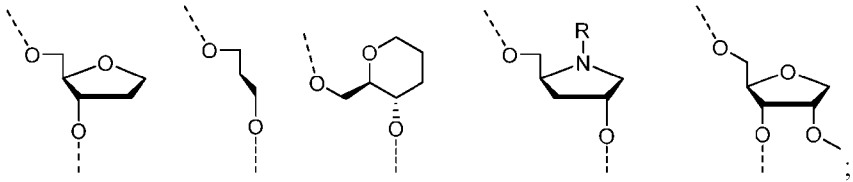
In another embodiment of the invention, an iRNA agent comprises a sense strand and an antisense strand, each strand having 14 to 40 nucleotides. The RNAi agent may be represented by formula (L):

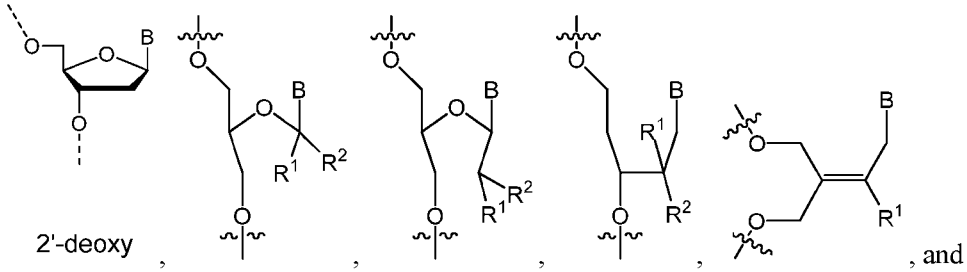


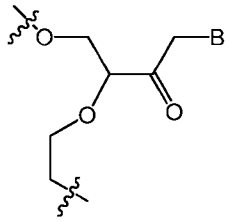
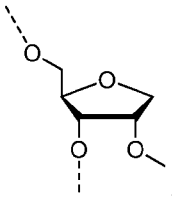
(L),

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:


2'-deoxy , , , , , 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).

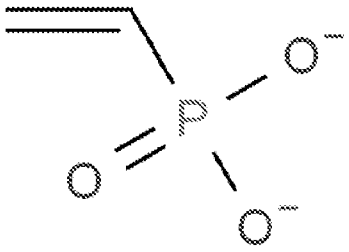
In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1,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

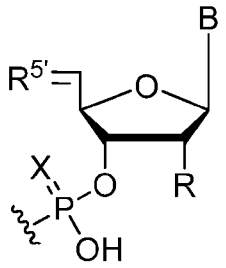
In certain embodiments, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-F,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

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



In exemplary embodiments, a 5' vinyl phosphonate modified nucleotide of the disclosure has the structure:



wherein X is O or S;

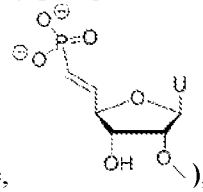
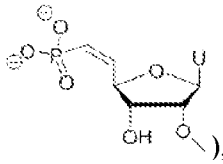
R is hydrogen, hydroxy, fluoro, or C_{1-20}alkoxy (*e.g.*, methoxy or n-hexadecyloxy);

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

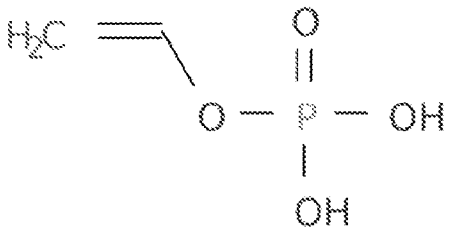
B is a nucleobase or a modified nucleobase, optionally where B is adenine, guanine, cytosine, thymine, or uracil.

In one embodiment, $R^{5'}$ is $=C(H)-P(O)(OH)_2$ and the double bond between the C5' carbon and R5' is in the E orientation. In another embodiment, R is methoxy and $R^{5'}$ is $=C(H)-P(O)(OH)_2$ and the double bond between the C5' carbon and R5' is in the E orientation. In another embodiment, X is S, R is methoxy, and $R^{5'}$ is $=C(H)-P(O)(OH)_2$ and the double bond between the C5' carbon and R5' is in the E orientation.

A vinyl phosphonate of the instant disclosure may be attached to either the antisense or the sense strand of a dsRNA of the disclosure. In certain preferred embodiments, a vinyl phosphonate of the instant disclosure is attached to the antisense strand of a dsRNA, optionally at the 5' end of the antisense strand of the dsRNA. The dsRNA agent can comprise a phosphorus-containing group at the 5'-end of the sense strand or antisense strand. The 5'-end phosphorus-containing group can be 5'-end phosphate (5'-P), 5'-end phosphorothioate (5'-PS), 5'-end phosphorodithioate (5'-PS2), 5'-end vinylphosphonate (5'-VP), 5'-end methylphosphonate (MePhos), or 5'-deoxy-5'-C-malonyl. When the 5'-end phosphorus-containing

group is 5'-end vinylphosphonate (5'-VP), the 5'-VP can be either 5'-E-VP isomer (i.e., trans-vinylphosphonate, ), 5'-Z-VP isomer (i.e., cis-vinylphosphonate, ), or mixtures thereof.

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



Another exemplary vinyl phosphate structure includes the preceding structure, where $R^{5'}$ is =C(H)-$OP(O)(OH)_2$ and the double bond between the C5' carbon and $R^{5'}$ is in the E or Z orientation (*e.g.*, E orientation). For example, when the phosphate mimic is a 5'-vinyl phosphate, the 5'-terminal nucleotide can have the immediately structure, where the phosphonate group is replaced by a phosphate.

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 3, 4, 5, 6, 7, 8A, or 8B. 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 Conjugates

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 cross-linked 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: 5). An RFGF analogue (*e.g.*, amino acid sequence AALLPVLLAAP (SEQ ID NO: 6) 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: 7) and the Drosophila Antennapedia protein (RQIKIWFQNRRMKWKK (SEQ ID NO: 8) 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.

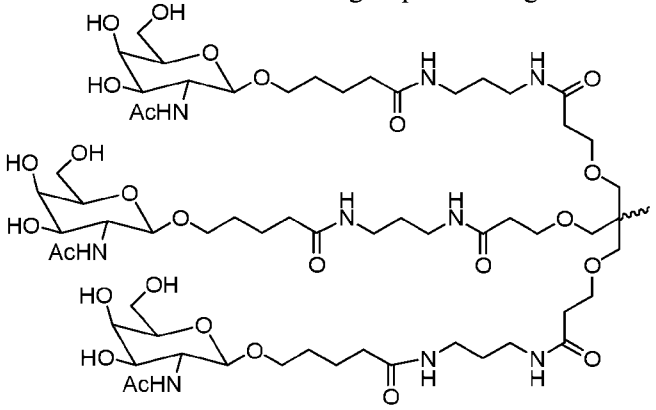
An RGD peptide for use in the compositions and methods of the invention may be linear or cyclic, and may be modified, *e.g.*, glyciosylated or methylated, to facilitate targeting to a specific tissue(s). RGD-containing peptides and peptidiomimemtics may include D-amino acids, as well as synthetic RGD 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).

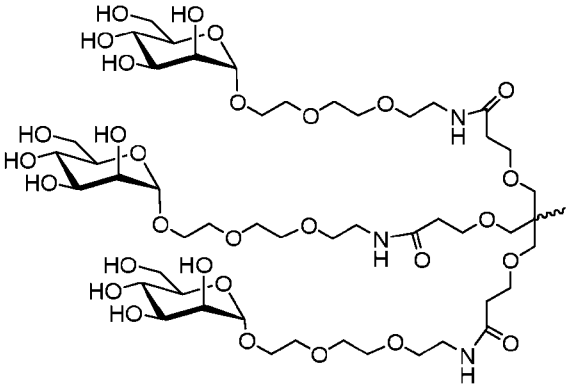
C. Carbohydrate Conjugates

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).

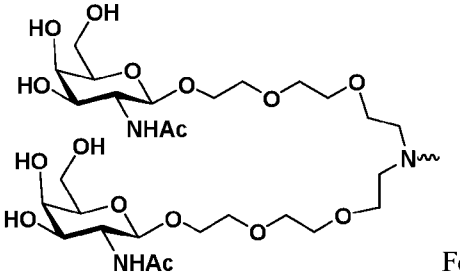
In one embodiment, a carbohydrate conjugate for use in the compositions and methods of the invention is selected from the group consisting of:



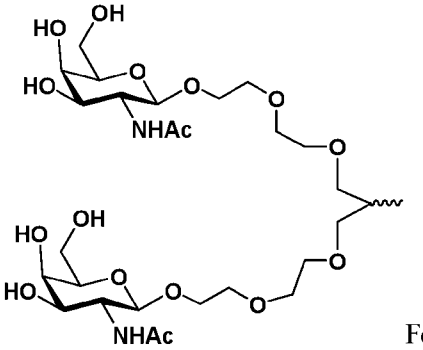
Formula II,



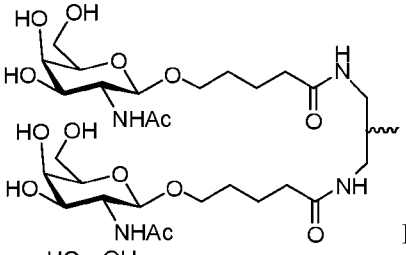
Formula III,



Formula IV,



Formula V,



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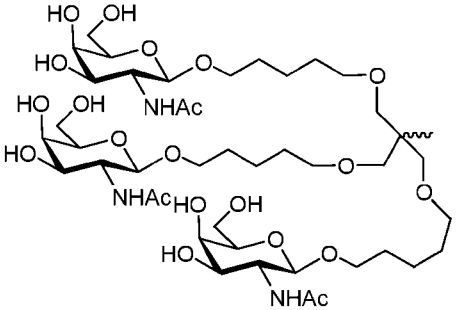

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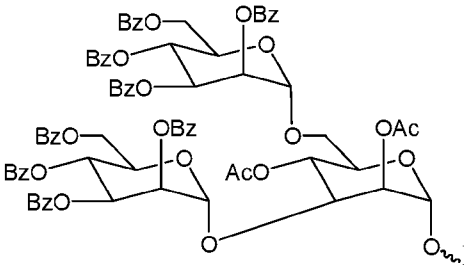

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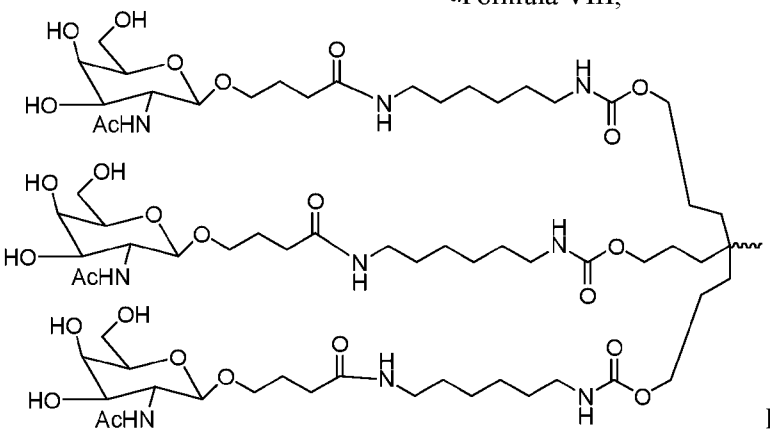

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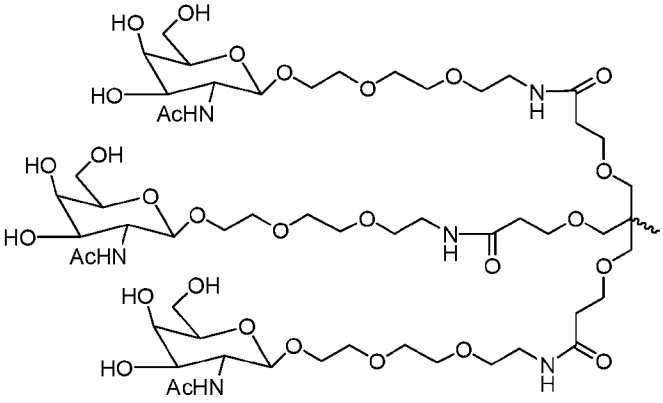

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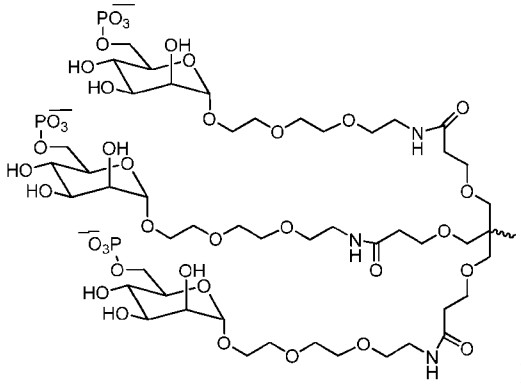

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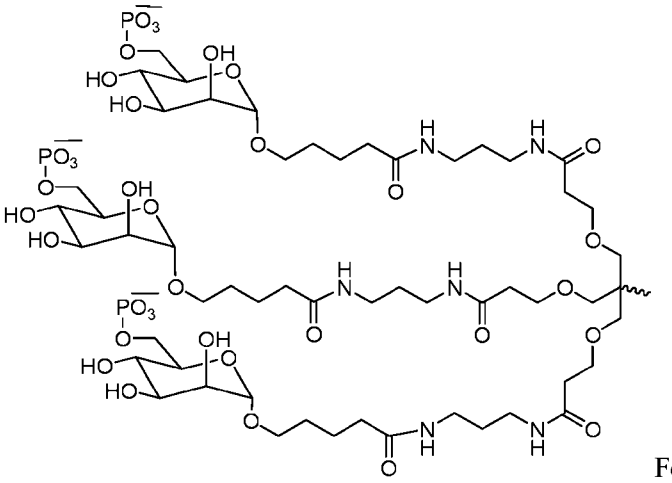

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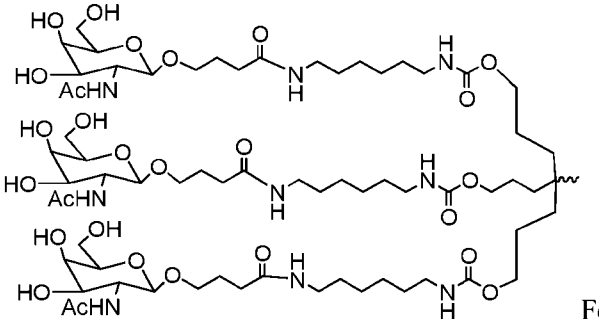

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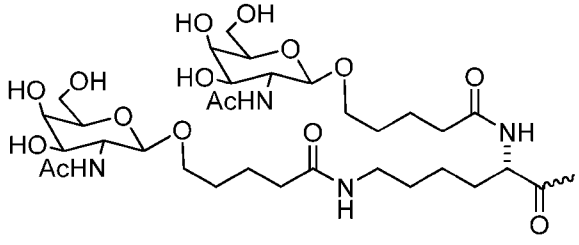

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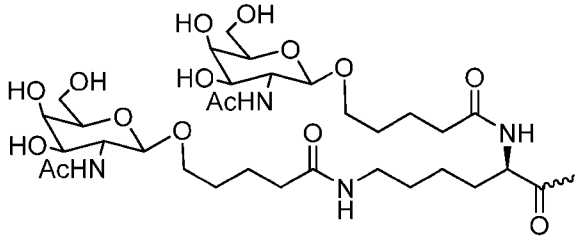

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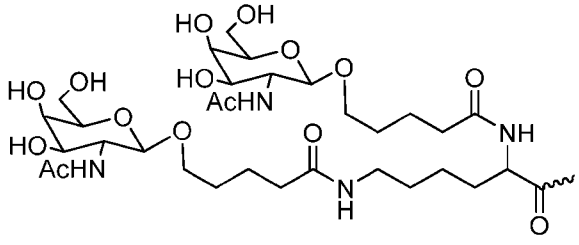

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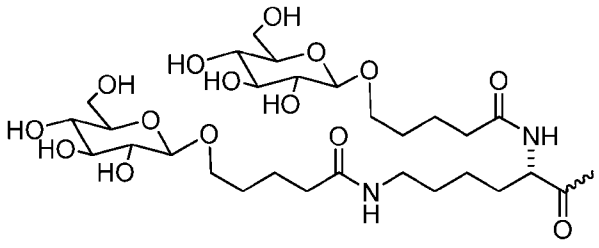
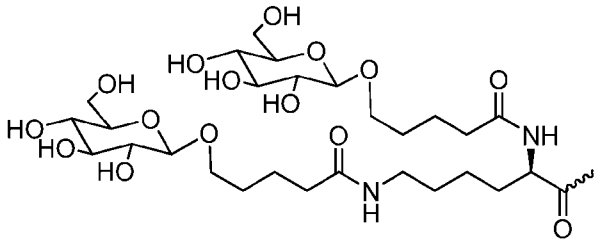
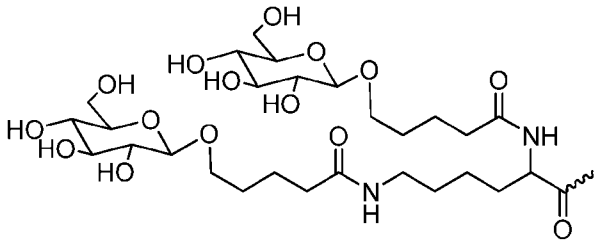


Formula XVII,



Formula XVIII,



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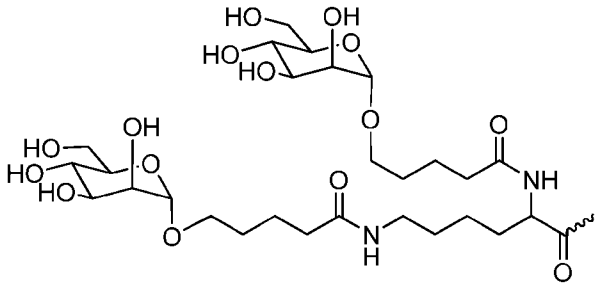
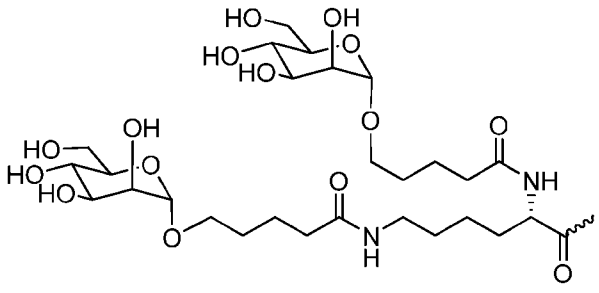
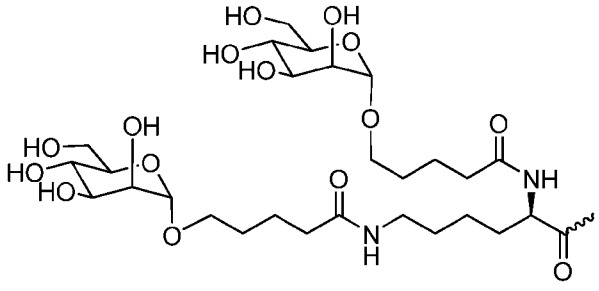


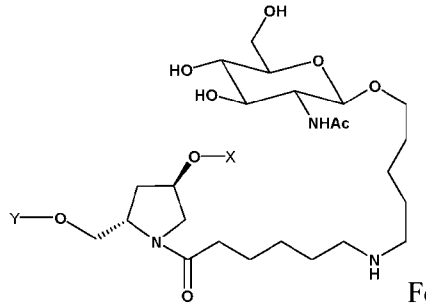
Formula XX,



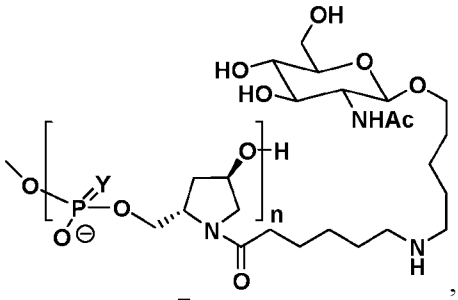
Formula XXI,



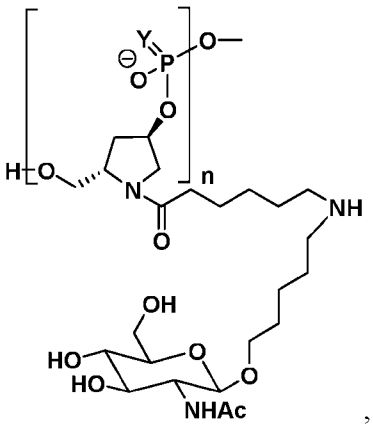
Formula XXII,



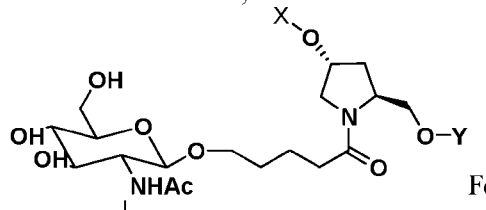
Formula XXIII;



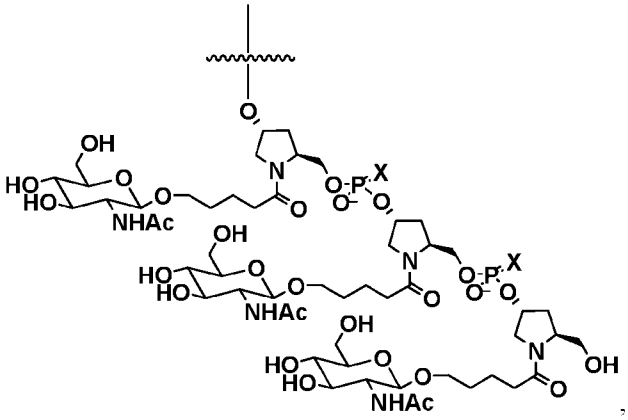
, wherein Y is O or S and n is 3 -6 (Formula XXIV);



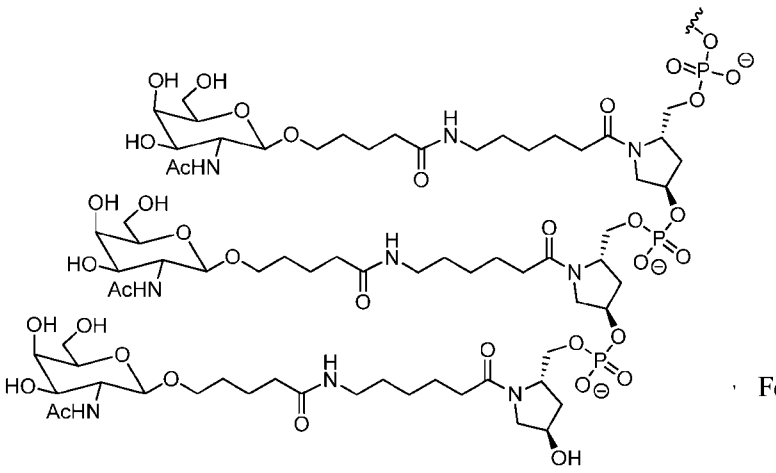
, wherein Y is O or S and n is 3-6 (Formula XXV);



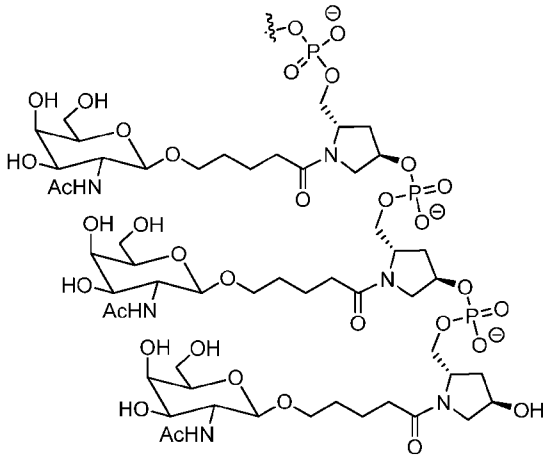
Formula XXVI;



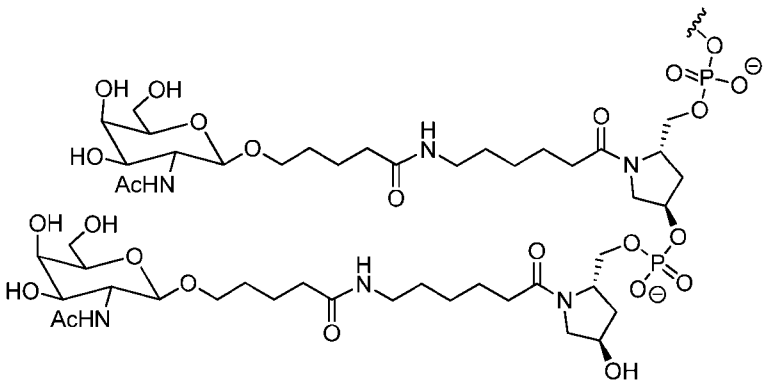
, wherein X is O or S (Formula XXVII);



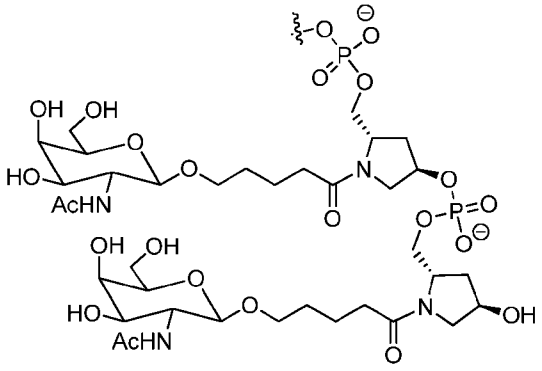
Formula XXVIII;



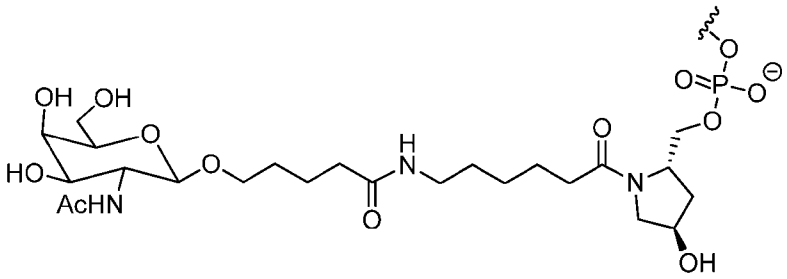
Formula XXIX;



Formula XXX;

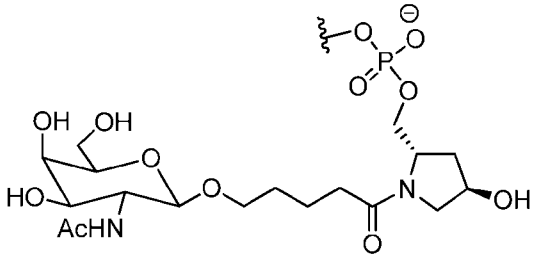


Formula XXXI;

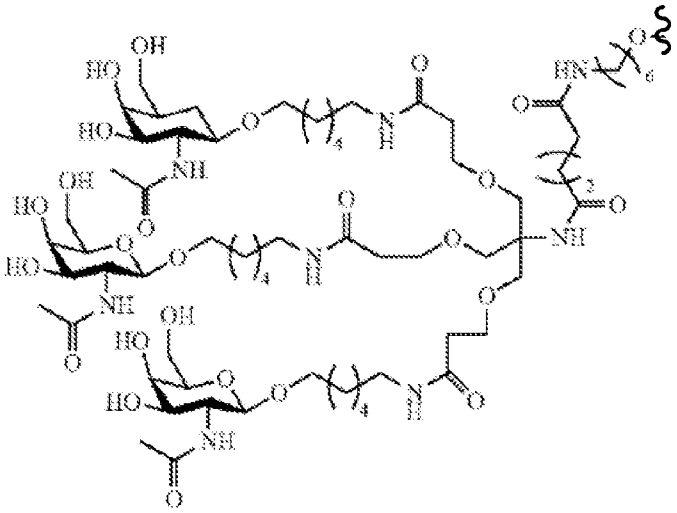


Formula XXXII;

, and

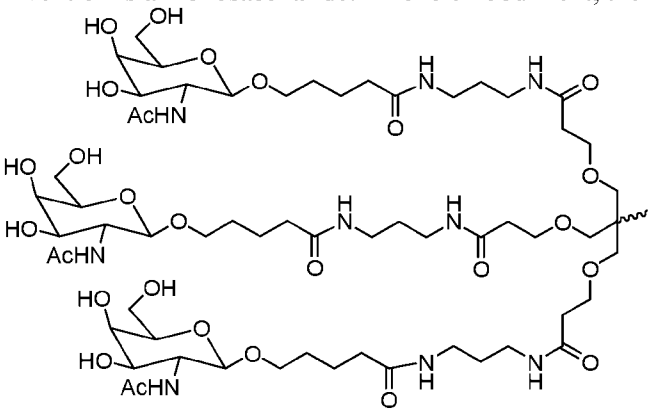


Formula XXXIII.



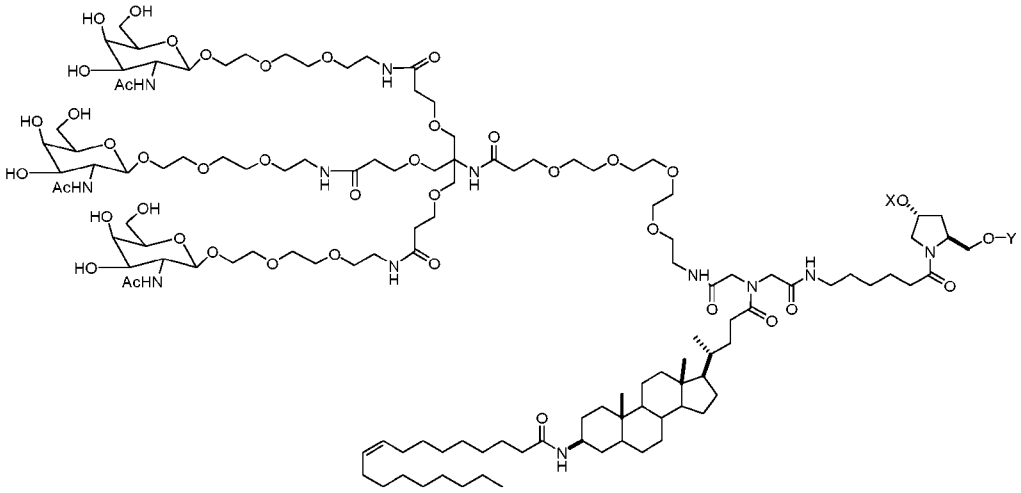
Formula XXXIV.

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 XXXV),

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 embodiment, 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 acid 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

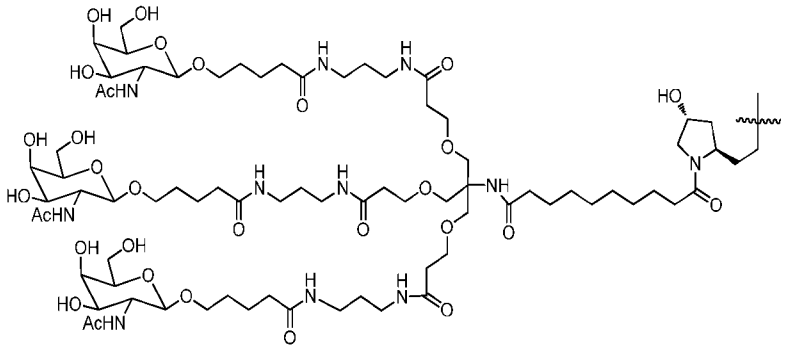
In another embodiment, a cleavable linker comprises an ester-based cleavable linking group. An ester-based cleavable linking group is cleaved by enzymes such as esterases and amidases in cells. Examples of ester-based cleavable linking groups include but are not limited to esters of alkylene, alkenylene 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

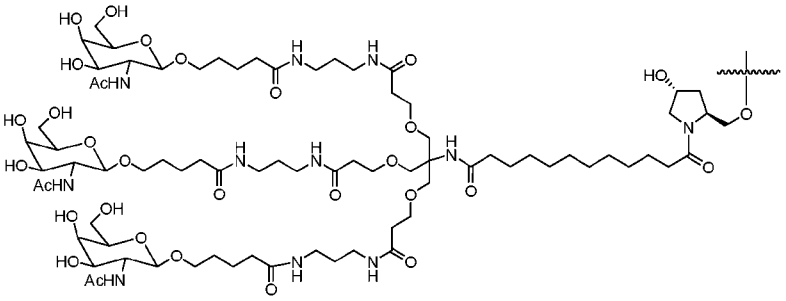
In yet another embodiment, a cleavable linker comprises a peptide-based cleavable linking group. A peptide-based cleavable linking group is cleaved by enzymes such as peptidases and proteases in cells. Peptide-based cleavable linking groups are peptide bonds formed between amino acids to yield oligopeptides (*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.

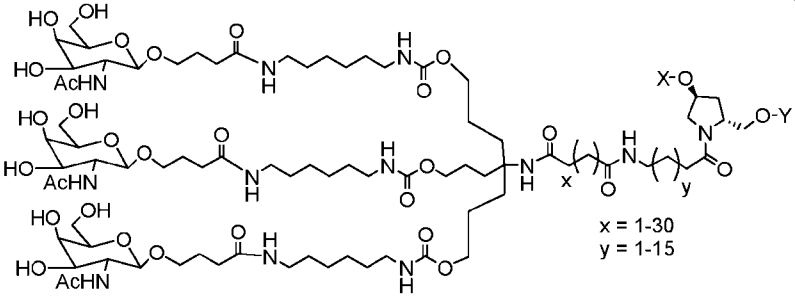
In one embodiment, an iRNA of the invention is conjugated to a carbohydrate through a linker. Non-limiting examples of iRNA carbohydrate conjugates with linkers of the compositions and methods of the invention include, but are not limited to,



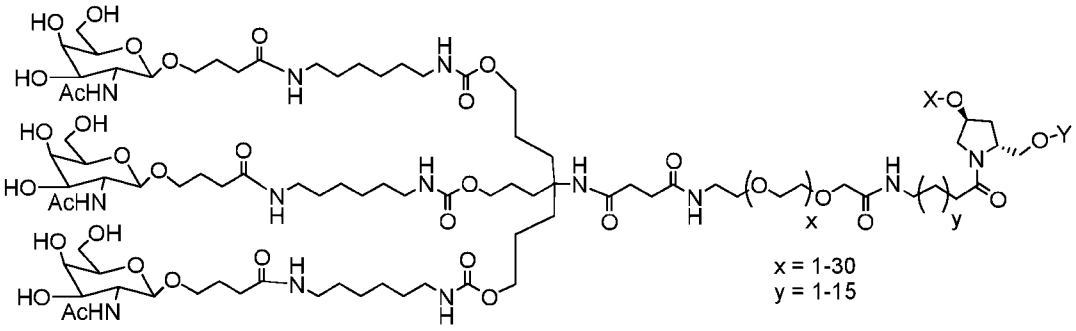
(Formula XXXVI),



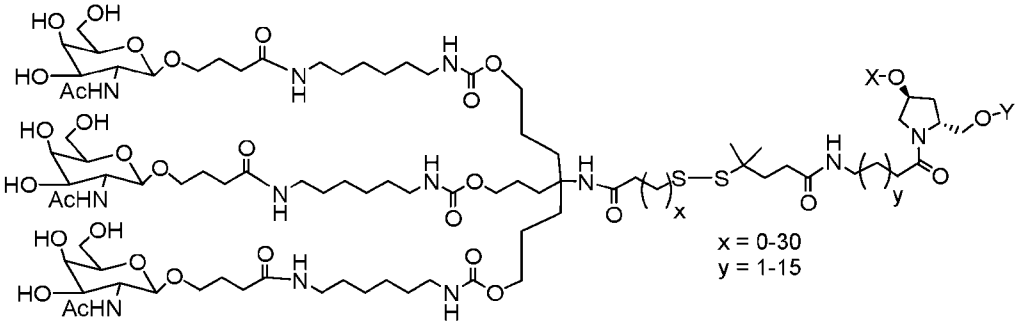
(Formula XXXVII),



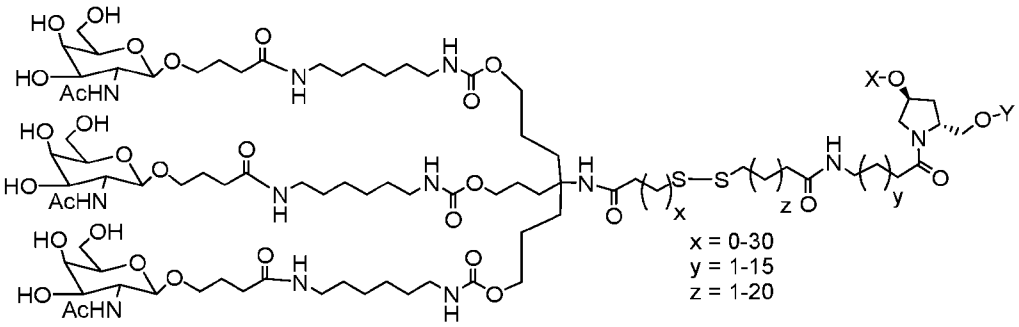
(Formula XXXIII),



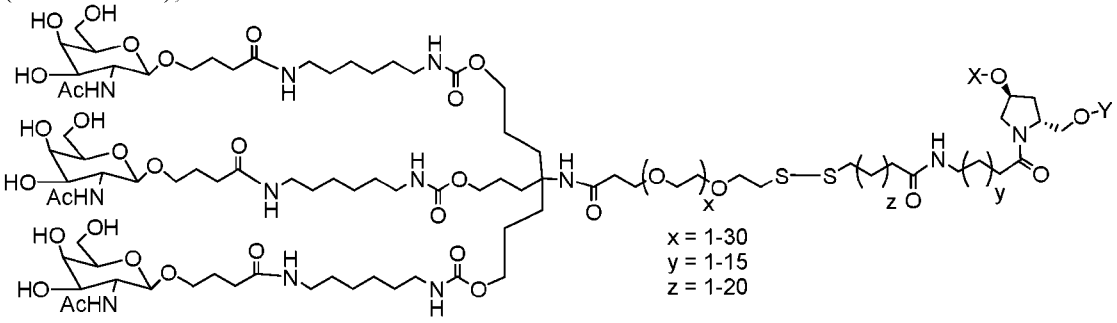
(Formula XXXIX),



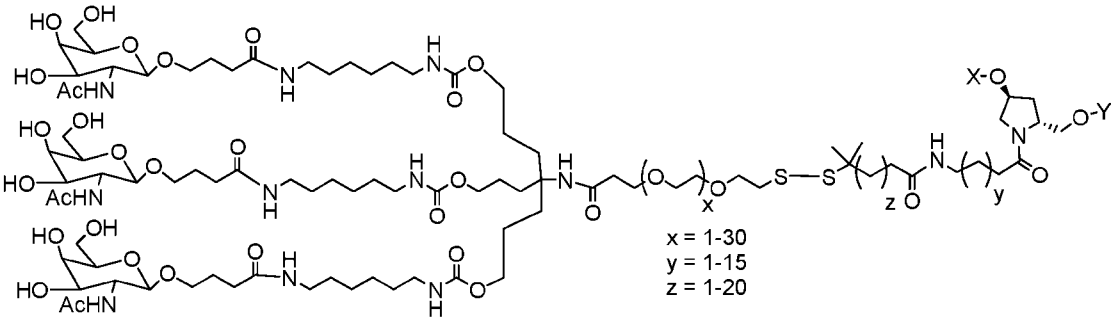
(Formula XL),



(Formula XLI),



(Formula XLII), and

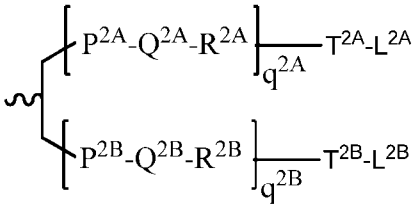


(Formula XLIII), when one of X or Y is an oligonucleotide, the other is a hydrogen.

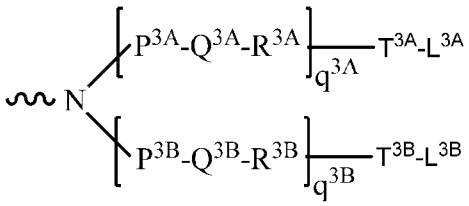
In certain embodiments of the compositions and methods of the invention, a ligand is one or more GalNAc (N-acetylgalactosamine) derivatives attached through a bivalent or trivalent branched linker.

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 XLIV – XLVII:

Formula XLIV



Formula XLV



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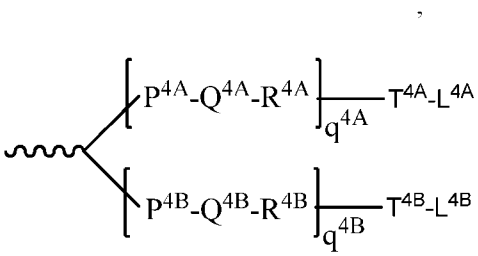

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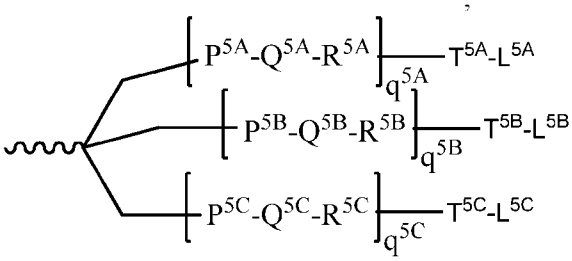


;

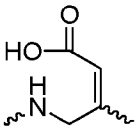
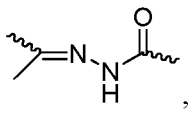
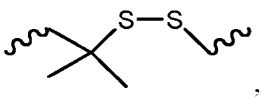
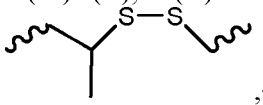
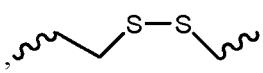
Formula XLVI Formula XLVII

wherein:

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

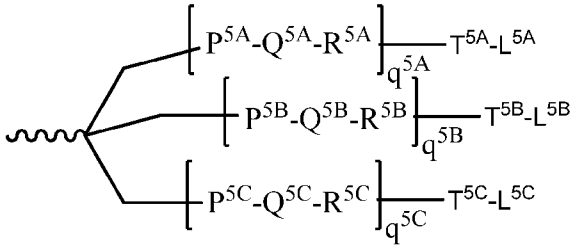
P^{2A}, P^{2B}, P^{3A}, P^{3B}, P^{4A}, P^{4B}, P^{5A}, P^{5B}, P^{5C}, T^{2A}, T^{2B}, T^{3A}, T^{3B}, T^{4A}, T^{4B}, T^{4A}, T^{5B}, T^{5C} are each independently for each occurrence absent, CO, NH, O, S, OC(O), NHC(O), CH_2, CH_2NH or CH_2O;

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

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

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

Formula XLIII



,

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.

V. 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 bleeding disorder) 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 al.* (2002) *BMC Neurosci.* 3:18; Shishkina, GT., *et al.* (2004) *Neuroscience* 129:521-528; Thakker, ER., *et al.* (2004) *Proc. Natl. Acad. Sci. U.S.A.* 101:17270-17275; Akaneya,Y., *et al.* (2005) *J. Neurophysiol.* 93:594-602) and to the lungs by intranasal administration (Howard, KA. *et al.*, (2006) *Mol. Ther.* 14:476-484; Zhang, X. *et al.*, (2004) *J. Biol. Chem.* 279:10677-10684; Bitko, V. *et al.*, (2005) *Nat. Med.* 11:50-55). For administering an iRNA systemically for the treatment of a disease, the RNA can be modified or alternatively delivered using a drug delivery system; both methods act to prevent the rapid degradation of the dsRNA by endo- and exo-nucleases *in vivo*. Modification of the RNA or the pharmaceutical carrier can also permit targeting of the iRNA composition to the target tissue and avoid undesirable off-target effects. iRNA molecules can be modified by chemical conjugation to 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 PLG 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.

VI. 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 plasminogen (PLG) 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 or 3, 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: 2 or 4; 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 or 3, and said antisense strand comprises at least 15 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 2 or 4.

In another embodiment, provided herein are pharmaceutical compositions comprising a dsRNA agent that inhibits expression of PLG 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 3, 4, 5, 6, 7, 8A, or 8B; 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 3, 4, 5, 6, 7, 8A, or 8B.

The pharmaceutical compositions containing the iRNA of the invention are useful for treating a disease or disorder associated with the expression or activity of a PLG gene, *e.g.*, a bleeding disorder.

Such pharmaceutical compositions are formulated based on the mode of delivery. One example is compositions that are formulated for systemic administration via parenteral delivery, *e.g.*, by intravenous (IV), intramuscular (IM) or for subcutaneous 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 a PLG 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 a PLG-associated disease, disorder, or condition that would benefit from reduction in the expression of PLG. 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, mouse thrombosis models, mouse stroke models, hemophilia A mouse models (FVIII deficient mice). Non-limiting examples of such models for in vivo testing of iRNA include Strilchuk et al., *Int. Society on Throm. and Haemost.* abstract 2021; Batty, et al., *Int. Society on Throm. and Haemost.* abstract 2021; and Singh et al., 2016. *J. Thromb. Haemost.* 14(9): 1822-32.

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 invention dissolved 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 pharmaceutical 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 dipalmitoylphosphatidylethanolamine 5-carboxyspermyl-amide ("DPPES") (see, e.g., US Patent 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), 1,2-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), 1,2-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.

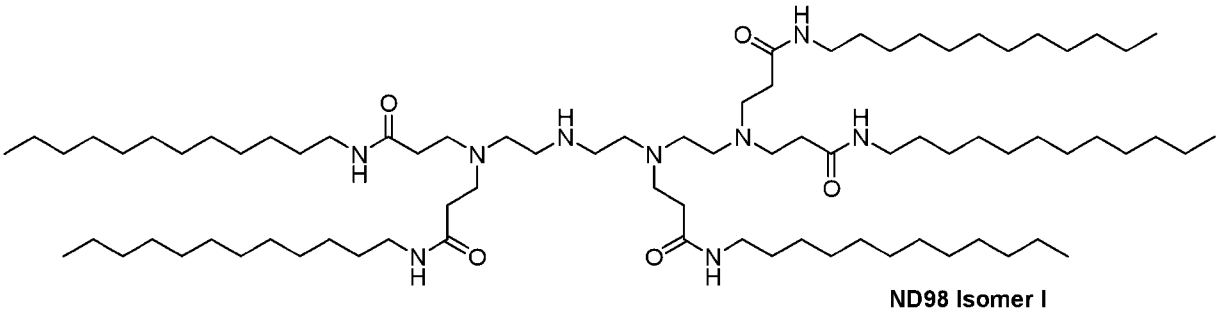
The conjugated lipid that inhibits aggregation of particles may be, for example, a polyethyleneglycol (PEG)-lipid including, without limitation, a PEG-diacylglycerol (DAG), a PEG-dialkyloxypropyl (DAA), a PEG-phospholipid, a PEG-ceramide (Cer), or a mixture thereof. The PEG-DAA conjugate may be, for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

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

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 I

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

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

Table 1: Exemplary lipid formulations

	Cationic Lipid	**cationic lipid/non-cationic lipid/cholesterol/PEG-lipid conjugate Lipid:siRNA ratio**
SNALP	1,2-Dilinolenyloxy-N,N-dimethylaminopropane (DLinDMA)	DLinDMA/DPPC/Cholesterol/PEG-cDMA (57.1/7.1/34.4/1.4) lipid:siRNA ~ 7:1
S-XTC	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DPPC/Cholesterol/PEG-cDMA 57.1/7.1/34.4/1.4 lipid:siRNA ~ 7:1
LNP05	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DSPC/Cholesterol/PEG-DMG 57.5/7.5/31.5/3.5 lipid:siRNA ~ 6:1
LNP06	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DSPC/Cholesterol/PEG-DMG 57.5/7.5/31.5/3.5 lipid:siRNA ~ 11:1
LNP07	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DSPC/Cholesterol/PEG-DMG 60/7.5/31/1.5, lipid:siRNA ~ 6:1

LNP08	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DSPC/Cholesterol/PEG-DMG 60/7.5/31/1.5, lipid:siRNA ~ 11:1
LNP09	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DSPC/Cholesterol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA 10:1
LNP10	(3aR,5s,6aS)-N,N-dimethyl-2,2-di((9Z,12Z)-octadeca-9,12-dienyl)tetrahydro-3aH-cyclopenta[d][1,3]dioxol-5-amine (ALN100)	ALN100/DSPC/Cholesterol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA 10:1
LNP11	(6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate (MC3)	MC-3/DSPC/Cholesterol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA 10:1
LNP12	1,1'-(2-(4-(2-((2-(bis(2-hydroxydodecyl)amino)ethyl)(2-hydroxydodecyl)amino)ethyl)piperazin-1-yl)ethylazanediyl)didodecan-2-ol (C12-200)	C12-200/DSPC/Cholesterol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA 10:1
LNP13	XTC	XTC/DSPC/Chol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA: 33:1
LNP14	MC3	MC3/DSPC/Chol/PEG-DMG 40/15/40/5 Lipid:siRNA: 11:1
LNP15	MC3	MC3/DSPC/Chol/PEG-DSG/GalNAc-PEG-DSG 50/10/35/4.5/0.5 Lipid:siRNA: 11:1
LNP16	MC3	MC3/DSPC/Chol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA: 7:1
LNP17	MC3	MC3/DSPC/Chol/PEG-DSG 50/10/38.5/1.5 Lipid:siRNA: 10:1
LNP18	MC3	MC3/DSPC/Chol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA: 12:1
LNP19	MC3	MC3/DSPC/Chol/PEG-DMG 50/10/35/5 Lipid:siRNA: 8:1
LNP20	MC3	MC3/DSPC/Chol/PEG-DPG 50/10/38.5/1.5 Lipid:siRNA: 10:1
LNP21	C12-200	C12-200/DSPC/Chol/PEG-DSG 50/10/38.5/1.5 Lipid:siRNA: 7:1
LNP22	XTC	XTC/DSPC/Chol/PEG-DSG 50/10/38.5/1.5 Lipid:siRNA: 10:1

DSPC: distearoylphosphatidylcholine

DPPC: dipalmitoylphosphatidylcholine

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

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

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

SNALP (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 chenodeoxycholic acid (CDCA) and ursodeoxychenodeoxycholic acid (UDCA), cholic acid, dehydrocholic acid, deoxycholic acid, glucholic acid, glycholic acid, glycodeoxycholic acid, taurocholic acid, taurodeoxycholic acid, sodium tauro-24,25-dihydro-fusidate and sodium glycodihydrofusidate. Suitable fatty acids include arachidonic acid, undecanoic acid, oleic acid, lauric acid, caprylic acid, capric acid, myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, dicaprate, tricaprate, monoolein, dilaurin, glyceryl 1-monocaprate, 1-dodecylazacycloheptan-2-one, an acylcarnitine, an acylcholine, or a monoglyceride, a diglyceride or a pharmaceutically acceptable salt thereof (*e.g.*, sodium). In some embodiments, combinations of penetration enhancers are used, for example, fatty acids/salts in combination

with bile acids/salts. One exemplary combination is the sodium salt of lauric acid, capric acid and UDCA. Further penetration enhancers include polyoxyethylene-9-lauryl ether, polyoxyethylene-20-cetyl ether. DsRNAs featured in the 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 a PLG-associated disease, disorder, or condition. Examples of such agents include, but are not limited to, tranexamic acid (TXA), oral contraceptive pills (OCP), intrauterine devices (IUDs), such as Mirena IUD and Kyleena IUD, other progestin approaches, endometrial ablation, total or subtotal hysterectomy, myomectomy, uterine artery embolization, human plasma-donor derived Glu-plasminogen, inhibitors of the plasminogen pathway, 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 PLG 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.

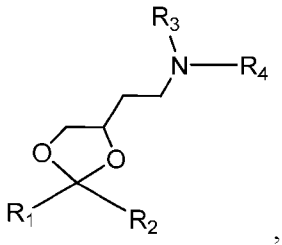
The terms "optionally substituted alkyl", "optionally substituted alkenyl", "optionally substituted alkynyl", "optionally substituted acyl", and "optionally substituted heterocycle" means that, when substituted, at least one hydrogen atom is replaced with a substituent. In the case of an oxo substituent (=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:

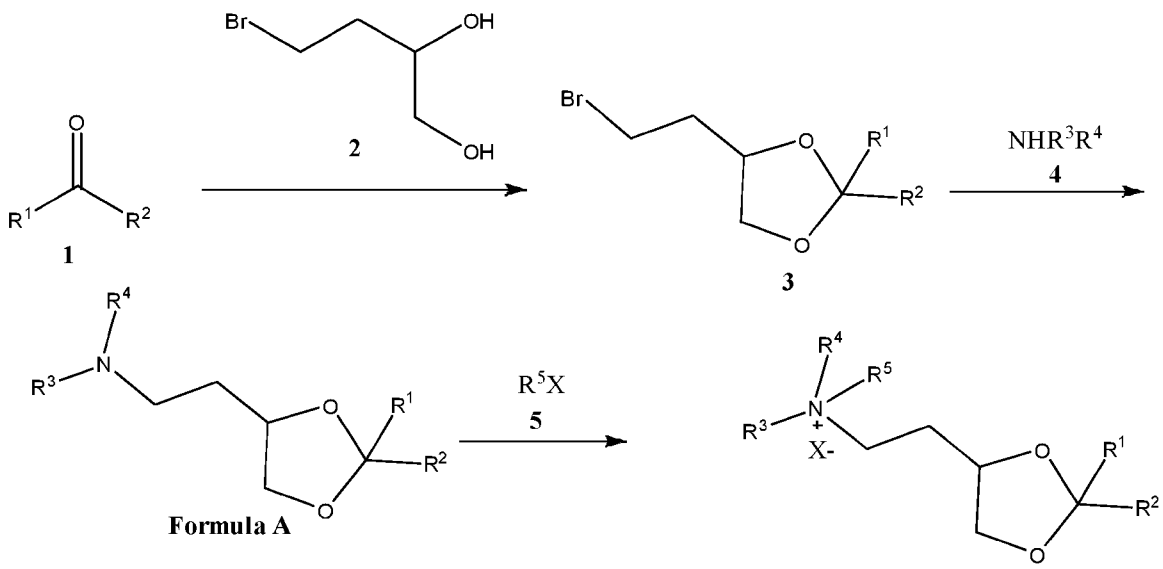


,

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

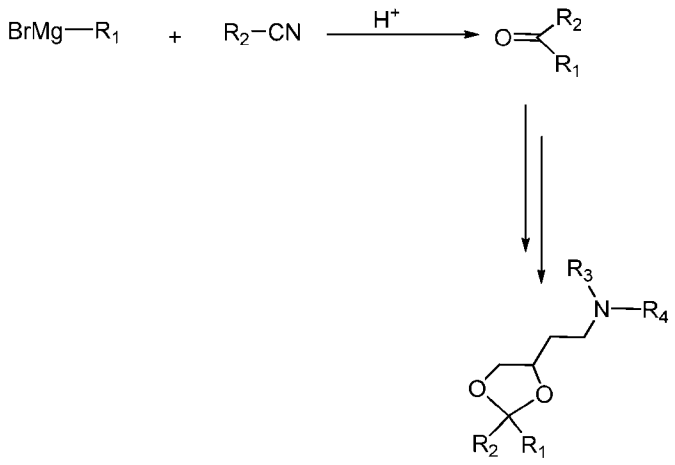
following Reaction Schemes 1 or 2, wherein all substituents are as defined above unless indicated otherwise.

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



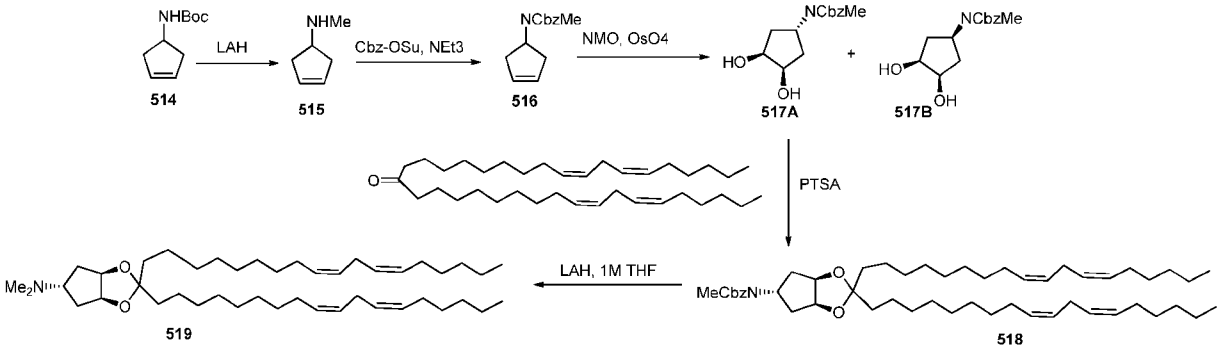
Alternatively, the ketone 1 starting material can be prepared according to Scheme 2. Grignard reagent 6 and cyanide 7 can be purchased or prepared according to methods known to those of ordinary skill in the art. Reaction of 6 and 7 yields ketone 1. Conversion of ketone 1 to the corresponding lipids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

VII. 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 PLG 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 a PLG gene.

Reduction in gene expression can be assessed by any methods known in the art. For example, a reduction in the expression of PLG may be determined by determining the mRNA expression level of PLG using methods routine to one of ordinary skill in the art, *e.g.*, Northern blotting, qRT-PCR; by determining the protein level of PLG using methods routine to one of ordinary skill in the art, such as Western blotting, ELISA, or immunological techniques. A reduction in the expression of PLG may also be assessed indirectly by measuring a decrease in biological activity of PLG, *e.g.*, a decrease in the serine protease activity of PLG.

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 a PLG 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.

PLG 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 a preferred embodiment, PLG expression is inhibited by at least 20%. In another preferred embodiment, PLG expression is inhibited by about 50%.

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 PLG 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 PLG gene of the mammal to be treated and the second iRNA includes a nucleotide sequence that is complementary to at least a part of an RNA transcript of a second 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 PLG, 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 a PLG gene in a mammal. The methods include administering to the mammal a composition comprising a dsRNA that targets a PLG gene in a cell of the mammal, thereby inhibiting expression of the PLG gene in the cell.

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

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

The present invention also provides therapeutic and prophylactic methods which include administering to a subject having, or prone to developing a bleeding disorder, 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 PLG expression, *e.g.*, a PLG-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 PLG or a pharmaceutical composition comprising a dsRNA that inhibits expression of PLG, 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 PLG expression, *e.g.*, a bleeding disorder. 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, a PLG-associated disease, disorder, or condition is a bleeding disorder. Non-limiting examples of bleeding disorders include hereditary hemorrhagic telangiectasia (HHT), heavy menstrual bleeding (HMB), PAI-1 deficiency, von Willebrand disease, low factor XI levels, platelet defects, hemophilia A, hemophilia B, afibrinogenemia, parahemophilia, low factor VIII levels, low factor IX levels, low factor VII levels, low factor XIII levels, low factor X levels, low factor V levels, low factor II levels, nose bleeds, bleeding gums, easy bruising, postpartum bleeding, or excessive bleeding following surgery.

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 PLG for treating a subject, *e.g.*, a subject that would benefit from a reduction and/or inhibition of PLG expression, *e.g.*, a PLG-associated disease, *e.g.*, a bleeding disorder.

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

In another aspect, the present invention provides use of an iRNA agent, *e.g.*, a dsRNA, of the invention targeting a PLG gene or a pharmaceutical composition comprising an iRNA agent targeting a PLG 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 PLG expression, *e.g.*, a bleeding disorder.

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

bleeding disorder (*e.g.*, heavy menstrual bleeding). In one embodiment, the bleeding disorder is hereditary hemorrhagic telangiectasia (HHT), heavy menstrual bleeding (HMB), PAI-1 deficiency, von Willebrand disease, low factor XI levels, platelet defects, hemophilia A, hemophilia B, afibrinogenemia, parahemophilia, low factor VIII levels, low factor IX levels, low factor VII levels, low factor XIII levels, low factor X levels, low factor V levels, low factor II levels, nose bleeds, bleeding gums, easy bruising, postpartum bleeding, or excessive bleeding following surgery.

In the methods (and uses) of the invention which comprise administering to a subject a first dsRNA agent targeting PLG and a second dsRNA agent, the first and second dsRNA agents may be formulated in the same composition or different compositions and may be 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.*, a PLG 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. 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 PLG 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 PLG levels, *e.g.*, in a cell, tissue, blood, urine or other compartment of the patient by at least 20%. In another preferred embodiment, administration of the iRNA can reduce PLG levels, *e.g.*, in a cell, tissue, blood, urine or other compartment of the patient by about 50%.

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 PLG gene is decreased, such as for about 1, 2, 3, 4, 5, 6, 7, 8, 12, 16, 18, 24 hours, 28, 32, or about 36 hours. In one embodiment, expression of the target PLG 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 PLG 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 PLG-associated disease, disorder, or condition (*e.g.*, a bleeding disorder). 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 bleeding disorder may be assessed, for example, by periodic monitoring of the amount and/or duration of bleeding. 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 bleeding disorder indicates that administration in a clinically appropriate manner results in a beneficial effect for at least a statistically significant fraction of patients, such as an 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 bleeding disorders 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 PLG expression or PLG, *e.g.,* a subject having a PLG-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 a second target, *e.g.*, for treating a subject that would benefit from reduction and/or inhibition of PLG expression and expression of a second target, *e.g.,* a subject having a PLG-associated disease disorder, or condition (*e.g.*., bleeding disorder), in combination with other pharmaceuticals and/or other therapeutic methods, *e.g.*, with known pharmaceuticals and/or known therapeutic methods, such as, for example, those which are currently employed for treating these disorders. For example, in certain embodiments, an iRNA agent or pharmaceutical composition of the invention is administered in combination with, *e.g.*, tranexamic acid (TXA), anti-angiogenic drugs, such as drugs that target the VEGF pathway, oral contraceptive pills (OCP), intrauterine devices (IUDs), such as Mirena IUD and Kyleena IUD, other progestin approaches, endometrial ablation, total or subtotal hysterectomy, myomectomy, uterine artery embolization, human plasma-donor derived Glu-plasminogen, inhibitors of the plasminogen pathway, or a combination of any of the foregoing.

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.

VIII. 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 PLG 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 PLG. 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 PLG (*e.g.*, means for measuring the inhibition of PLG mRNA and/or PLG protein). Such means for measuring the inhibition of PLG may comprise a means for obtaining a sample from a subject, such as, e.g., a blood 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.

PLG iRNA Design, Synthesis, and Selection

Nucleic acid sequences provided herein are represented using standard nomenclature. *See* the abbreviations of Table 2. It will be understood that these monomers, when present in an oligonucleotide, are mutually linked by 5'-3'-phosphodiester bonds. The abbreviations are understood to omit the 3'-phosphate (i.e., they are 3'-OH) when placed at the 3'-terminal position of an oligonucleotide.

TABLE 2: Abbreviations of nucleotide monomers used in nucleic acid sequence representation.

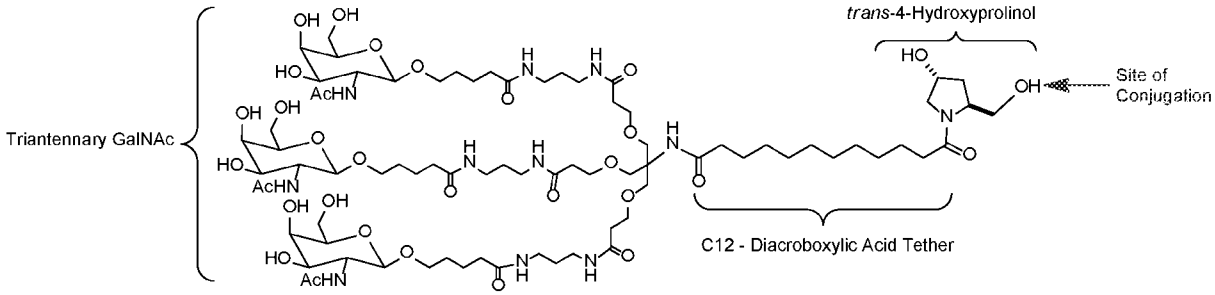
Abbreviation	Nucleotide(s)
A	Adenosine-3'-phosphate
Ab	beta-L-adenosine-3`-phosphate
Abs	beta-L-adenosine-3`-phosphorothioate
Af	2'-fluoroadenosine-3'-phosphate
Afs	2'-fluoroadenosine-3'-phosphorothioate

Abbreviation	Nucleotide(s)
As	adenosine-3'-phosphorothioate
(A2p)	adenosine-2`-phosphate
(A2ps)	adenosine-2`-phosphorothioate
C	cytidine-3'-phosphate
Cb	beta-L-cytidine-3`-phosphate
Cbs	beta-L-cytidine-3'-phosphorothioate
Cf	2'-fluorocytidine-3'-phosphate
Cfs	2'-fluorocytidine-3'-phosphorothioate
Cs	cytidine-3`-phosphorothioate
(C2p)	cytidine-2`-phosphate
(C2ps)	cytidine-2`-phosphorothioate
G	guanosine-3'-phosphate
Gb	beta-L-guanosine-3`-phosphate
Gbs	beta-L-guanosine-3`-phosphorothioate
Gf	2'-fluoroguanosine-3'-phosphate
Gfs	2'-fluoroguanosine-3'-phosphorothioate
Gs	guanosine-3`-phosphorothioate
(G2p)	guanosine-2`-phosphate
(G2ps)	guanosine-2`-phosphorothioate
T	5'-methyluridine-3`-phosphate
Tf	2'-fluoro-5-methyluridine-3'-phosphate
Tfs	2'-fluoro-5-methyluridine-3'-phosphorothioate
Ts	5-methyluridine-3'-phosphorothioate
U	Uridine-3'-phosphate
Uf	2'-fluorouridine-3'-phosphate
Ufs	2'-fluorouridine -3'-phosphorothioate
Us	uridine -3'-phosphorothioate
(U2p)	uridine-2`-phosphate
(U2ps)	uridine-2`-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

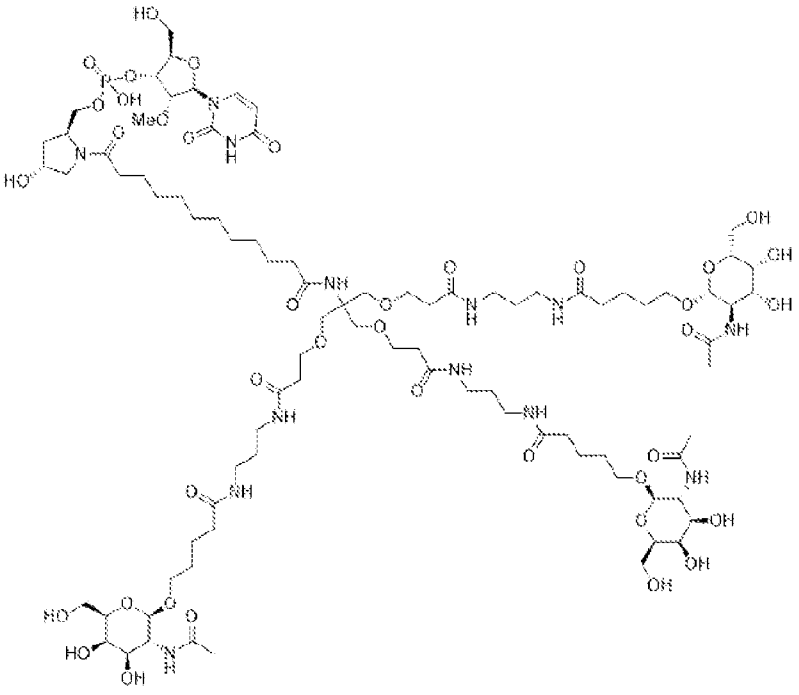
Abbreviation	Nucleotide(s)
g	2'-O-methylguanosine-3'-phosphate
gs	2'-O-methylguanosine-3'- phosphorothioate
t	2'-O-methyl-5-methyluridine-3'-phosphate
ts	2'-O-methyl-5-methyluridine-3'-phosphorothioate
u	2'-O-methyluridine-3'-phosphate
us	2'-O-methyluridine-3'-phosphorothioate
s	phosphorothioate linkage
L96[1]	N-[tris(GalNAc-alkyl)-amidodecanoyl)]-4-hydroxyprolinol; or (2S,4R)-1-[29-[[2-(acetylamino)-2-deoxy-β-D-galactopyranosyl]oxy]-14,14-bis[[3-[[3-[[5-[[2-(acetylamino)-2-deoxy-β-D-galactopyranosyl]oxy]-1-oxopentyl] amino]propyl]amino oxopropoxy]methyl]-1,12,19,25-tetraoxo-16-oxa-13,20,24-triazanonacos-1-yl]-4-hydroxy-2-hydroxymethylpyrrolidine
uL96[2]	2'-O-methyluridine-3'-phosphate ((2S,4R)-1-[29-[[2-(acetylamino)-2-deoxy-β-D-galactopyranosyl]oxy]-14,14-bis[[3-[[3-[[5-[[2-(acetylamino)-2-deoxy-β-D-galactopyranosyl]oxy]-1-oxopentyl]amino]propyl]amino]-3-oxopropoxy]methyl]-1,12,19,25-tetraoxo-16-oxa-13,20,24-triazanonacos-1-yl]-4-hydroxy-2-pyrrolidinyl)methyl ester
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)

Abbreviation	Nucleotide(s)
(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
(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:



[2]The chemical structure of uL96 is as follows:



Experimental Methods

This Example describes methods for the design, synthesis, and selection of PLG iRNA agents.

Bioinformatics

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.

Transcripts

A set of siRNAs targeting the human plasminogen gene (PLG; human NCBI refseqID NM_000301.5; NCBI GeneID: 5340; and human NCBI refseqID NM_001168338.1) were designed using custom R and

Python scripts. The human NM_000301.5 REFSEQ mRNA has a length of 3530 bases and the human NM_001168338.1 refseq mRNA has a length of 1200 bases.

siRNA Synthesis

siRNAs were synthesized and annealed using routine methods known in the art.

Briefly, siRNA sequences were synthesized at 1 μmol scale on a Mermade 192 synthesizer (BioAutomation) using the solid support mediated phosphoramidite chemistry. The solid support was controlled pore glass (500 A) loaded with custom GalNAc ligand or universal solid support (AM biochemical). Ancillary synthesis reagents, 2'-F and 2'-O-Methyl RNA and deoxy phosphoramidites were obtained from Thermo-Fisher (Milwaukee, WI) and Hongene (China). 2'F 2'-O-Methyl, GNA (glycol nucleic acids), 5'phosphate and other modifications were introduced using the corresponding phosphoramidites. Synthesis of 3' GalNAc conjugated single strands was performed on a GalNAc modified CPG support. Custom CPG universal solid support was used for the synthesis of antisense single strands. Coupling time for all phosphoramidites (100 mM in acetonitrile) was 5 min employing 5-Ethylthio-1H-tetrazole (ETT) as activator (0.6 M in acetonitrile). Phosphorothioate linkages were generated using a 50 mM solution of 3-((Dimethylamino-methylidene) amino)-3H-1,2,4-dithiazole-3-thione (DDTT, obtained from Chemgenes (Wilmington, MA, USA)) in anhydrous acetonitrile/pyridine (1:1 v/v). Oxidation time was 3 minutes. All sequences were synthesized with final removal of the DMT group ("DMT off").

Upon completion of the solid phase synthesis, oligoribonucleotides were cleaved from the solid support and deprotected in sealed 96 deep well plates using 200 μL Aqueous Methylamine reagents at 60°C for 20 minutes. For sequences containing 2' ribo residues (2'-OH) that are protected with a tert-butyl dimethyl silyl (TBDMS) group, a second step deprotection was performed using TEA.3HF (triethylamine trihydro fluoride) reagent. To the methylamine deprotection solution, 200uL of dimethyl sulfoxide (DMSO) and 300ul TEA.3HF reagent was added and the solution was incubated for additional 20min at 60°C. At the end of cleavage and deprotection step, the synthesis plate was allowed to come to room temperature and was precipitated by addition of 1mL of acetontile: ethanol mixture (9:1). The plates were cooled at -80°C for 2 hours, supernatant decanted carefully with the aid of a multi-channel pipette. The oligonucleotide pellet was re-suspended in 20mM NaOAc buffer and were desalted using a 5 mL HiTrap size exclusion column (GE Healthcare) on an AKTA Purifier System equipped with an A905 autosampler and a Frac 950 fraction collector. Desalted samples were collected in 96-well plates. Samples from each sequence were analyzed by LC-MS to confirm the identity, UV (260 nm) for quantification and a selected set of samples by IEX chromatography to determine purity.

Annealing of single strands was performed on a Tecan liquid handling robot. Equimolar mixture of sense and antisense single strands were combined and annealed in 96 well plates. After combining the complementary single strands, the 96-well plate was sealed tightly and heated in an oven at 100°C for 10

minutes and allowed to come slowly to room temperature over a period 2-3 hours. The concentration of each duplex was normalized to 10μM in 1X PBS and then submitted for *in vitro* screening assays.

A detailed list of the unmodified nucleotide sequences of the sense strand and antisense strand sequences is shown in Tables 3, 4, 7, and 8A.

A detailed list of the modified nucleotide sequences of the sense strand and antisense strand sequences is shown in Tables 5, 6, and 8B.

TABLE 3. Unmodified Sense and Antisense Strand Sequences of Human PLG dsRNA Agents

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000301.5	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000301.5
AD-2042815	GUCAACAACAUC CUGGGAUUU	9	5-25	AAAUCCCAGGAU GUUGUUGACUU	118	3-25
AD-2042896	CUUUUAUUUCUG AAAUCAGGU	10	92-112	ACCUGAUUUCAG AAAUAAAAGAA	119	90-112
AD-2042932	GAUGACUAUGU GAAUACCCAU	11	128-148	AUGGGUAUUCAC AUAGUCAUCCA	120	126-148
AD-2042938	UCACUGUUCAGU GUCACUAAU	12	155-175	AUUAGUGACACU GAACAGUGAAG	121	153-175
AD-2042970	AGCAGGAAGUA UAGAAGAAUU	13	187-207	AAUUCUUCUAUA CUUCCUGCUCC	122	185-207
AD-2042987	AAUGUGCAGCAA AAUGUGAGU	14	204-224	ACUCACAUUUUG CUGCACAUUCU	123	202-224
AD-2043006	GGAGGACGAAG AAUUCACCUU	15	223-243	AAGGUGAAUUCU UCGUCCUCCUC	124	221-243
AD-2043032	CAUUCCAAUAUC ACAGUAAAU	16	249-269	AUUUACUGUGAU AUUGGAAUGCC	125	247-269
AD-2043052	GAGCAACAAUGU GUGAUAAUU	17	269-289	AAUUAUCACACA UUGUUGCUCUU	126	267-289
AD-2043072	GGCUGAAAACAG GAAGUCCUU	18	289-309	AAGGACUUCCUG UUUUCAGCCAU	127	287-309
AD-2043088	UCCUCCAUAAUC AUUAGGAUU	19	305-325	AAUCCUAAUGAU UAUGGAGGACU	128	303-325
AD-2043108	GAGAGAUGUAG UUUUAUUUGU	20	325-345	ACAAAUAAAACU ACAUCUCUCAU	129	323-345
AD-2043131	GUAUCUCUCAGA GUGCAAGAU	21	355-375	AUCUUGCACUCU GAGAGAUACAC	130	353-375
AD-2043150	ACUGGGAAUGG AAAGAACUAU	22	374-394	AUAGUUCUUUCC AUUCCCAGUCU	131	372-394
AD-2043174	GGGACGAUGUCC AAAACAAAU	23	398-418	AUUUGUUUUGGA CAUCGUCCCUC	132	396-418
AD-2043218	GACCUAGAUUCU CACCUGCUU	24	462-482	AAGCAGGUGAGA AUCUAGGUCUG	133	460-482
AD-2043249	UGCAGGAAUCCA GACAACGAU	25	515-535	AUCGUUGUCUGG AUUCCUGCAGU	134	513-535
AD-2043266	GCUAUACUACUG AUCCAGAAU	26	552-572	AUUCUGGAUCAG UAGUAUAGCAC	135	550-572

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000301.5	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000301.5
AD-2043291	AUAUGACUACUG CGACAUUCU	27	577-597	AGAAUGUCGCAG UAGUCAUAUCU	136	575-597
AD-2043308	UUCUUGAGUGU GAAGAGGAAU	28	594-614	AUUCCUCUUCAC ACUCAAGAAUG	137	592-614
AD-2043323	AGGAAUGUAUG CAUUGCAGUU	29	609-629	AACUGCAAUGCA UACAUUCCUCU	138	607-629
AD-2043339	CAGUGGAGAAA ACUAUGACGU	30	625-645	ACGUCAUAGUUU UCUCCACUGCA	139	623-645
AD-2043358	GGCAAAAUUUCC AAGACCAUU	31	644-664	AAUGGUCUUGGA AAUUUUGCCGU	140	642-664
AD-2043419	ACGCUCAUGGAU ACAUUCCUU	32	705-725	AAGGAAUGUAUC CAUGAGCGUGU	141	703-725
AD-2043434	UUCCUUCCAAAU UUCCAAACU	33	720-740	AGUUUGGAAAUU UGGAAGGAAUG	142	718-740
AD-2043456	GAACCUGAAGAA GAAUUACUU	34	742-762	AAGUAAUUCUUC UUCAGGUUCUU	143	740-762
AD-2043483	CUUGGUGUUUCA CCACCGACU	35	789-809	AGUCGGUGGUGA AACACCAAGGC	144	787-809
AD-2043494	CUGGGAACUUUG UGACAUCCU	36	820-840	AGGAUGUCACAA AGUUCCCAGCG	145	818-840
AD-2043505	CACCUCCACCAU CUUCUGGUU	37	852-872	AACCAGAAGAUG GUGGAGGUGUU	146	850-872
AD-2043525	CCCACCUACCAG UGUCUGAAU	38	872-892	AUUCAGACACUG GUAGGUGGGAC	147	870-892
AD-2043540	CUGAAGGGAACA GGUGAAAAU	39	887-907	AUUUUCACCUGU UCCCUUCAGAC	148	885-907
AD-2043565	GCGGGAAUGUG GCUGUUACCU	40	912-932	AGGUAACAGCCA CAUUCCCGCGA	149	910-932
AD-2043617	ACAGGACACCAG AAAACUUCU	41	984-1004	AGAAGUUUUCUG GUGUCCUGUUA	150	982-1004
AD-2043627	AUUUGGAUGAA AACUACUGCU	42	1014-1034	AGCAGUAGUUUU CAUCCAAAUUU	151	1012-1034
AD-2043644	UGCCGCAAUCCU GACGGAAAU	43	1031-1051	AUUUCCGUCAGG AUUGCGGCAGU	152	1029-1051
AD-2043656	GUGCCAUACAAC CAACAGCCU	44	1063-1083	AGGCUGUUGGUU GUAUGGCACCA	153	1061-1083
AD-2043689	GUACUGUAAGA UACCGUCCUU	45	1096-1116	AAGGACGGUAUC UUACAGUACUC	154	1094-1116
AD-2043789	ACAGGAAAGAA GUGUCAGUCU	46	1241-1261	AGACUGACACUU CUUUCCUGUGG	155	1239-1261
AD-2043804	CAGUCUUGGUCA UCUAUGACU	47	1256-1276	AGUCAUAGAUGA CCAAGACUGAC	156	1254-1276
AD-2043843	UGCUGGCCUGAC AAUGAACUU	48	1315-1335	AAGUUCAUUGUC AGGCCAGCAUU	157	1313-1335
AD-2043869	GGAAUCCAGAUG CCGAUAAAU	49	1341-1361	AUUUAUCGGCAU CUGGAUUCCUG	158	1339-1361
AD-2043874	CUGGUGUUUUAC CACAGACCU	50	1366-1386	AGGUCUGUGGUA AAACACCAGGG	159	1364-1386

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000301.5	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000301.5
AD-2043886	GGGAGUACUGCAACCUGAAAU	51	1398-1418	AUUUCAGGUUGCAGUACUCCCAC	160	1396-1418
AD-2043916	GAACAGAAGCGAGUGUUGUAU	52	1428-1448	AUACAACACUCGCUUCUGUUCCU	161	1426-1448
AD-2043942	CCGCCUGUUGUCCUGCUUCCU	53	1454-1474	AGGAAGCAGGACAACAGGCGGAG	162	1452-1474
AD-2043959	UCCAGAUGUAGAGACUCCUUU	54	1471-1491	AAAGGAGUCUCUACAUCUGGAAG	163	1469-1491
AD-2043979	CCGAAGAAGACUGUAUGUUUU	55	1491-1511	AAAACAUACAGUCUUCUUCGGAA	164	1489-1511
AD-2044060	UAGACACAGCAUUUUCACUCU	56	1594-1614	AGAGUGAAAAUGCUGUGUCUAUG	165	1592-1614
AD-2044075	CACUCCAGAGACAAAUCCACU	57	1609-1629	AGUGGAUUUGUCUCUGGAGUGAA	166	1607-1629
AD-2044119	GCCGUAACCCUGAUGGUGAUU	58	1653-1673	AAUCACCAUCAGGGUUACGGCAG	167	1651-1673
AD-2044153	GUGCUACACGACAAAUCCAAU	59	1687-1707	AUUGGAUUUGUCGUGUAGCACCA	168	1685-1707
AD-2044168	UCCAAGAAAACUUUACGACUU	60	1702-1722	AAGUCGUAAAGUUUUCUUGGAUU	169	1700-1722
AD-2044184	GACUACUGUGAUGUCCCUCAU	61	1718-1738	AUGAGGGACAUCACAGUAGUCGU	170	1716-1738
AD-2044267	GCAAGUCAGUCUUAGAACAAU	62	1843-1863	AUUGUUCUAAGACUGACUUGCCA	171	1841-1863
AD-2044282	AACAAGGUUUGGAAUGCACUU	63	1858-1878	AAGUGCAUUCCAAACCUUGUUCU	172	1856-1878
AD-2044325	UGCCCACUGCUUGGAGAAGUU	64	1921-1941	AACUUCUCCAAGCAGUGGGCAGC	173	1919-1941
AD-2044364	ACCAAGAAGUGAAUCUCGAAU	65	1980-2000	AUUCGAGAUUCACUUCUUGGUGU	174	1978-2000
AD-2044384	CCGCAUGUUCAGGAAAUAGAU	66	2000-2020	AUCUAUUUCCUGAACAUGCGGUU	175	1998-2020
AD-2044433	GAAAAGAUAUUGCCUUGCUAU	67	2049-2069	AUAGCAAGGCAAUAUCUUUUCGU	176	2047-2069
AD-2044448	UGCUAAAGCUAAGCAGUCCUU	68	2064-2084	AAGGACUGCUUAGCUUUAGCAAG	177	2062-2084
AD-2044472	UCAUCACUGACAAAGUAAUCU	69	2088-2108	AGAUUACUUUGUCAGUGAUGACG	178	2086-2108
AD-2044516	CGAAUGUUUCAUCACUGGCUU	70	2152-2172	AAGCCAGUGAUGAAACAUUCGGU	179	2150-2172
AD-2044519	GAGAAACCCAAGGUACUUUUU	71	2175-2195	AAAAAGUACCUUGGGUUUCUCCC	180	2173-2195
AD-2044569	CCUGUGAUUGAGAAUAAAGUU	72	2225-2245	AACUUUAUUCUCAAUCACAGGGA	181	2223-2245
AD-2044594	AUCGCUAUGAGUUUCUGAAUU	73	2250-2270	AAUUCAGAAACUCAUAGCGAUUG	182	2248-2270
AD-2044609	UGAAUGGAAGAGUCCAAUCCU	74	2265-2285	AGGAUUGGACUCUUCCAUUCAGA	183	2263-2285

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000301.5	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000301.5
AD-2044689	GGUCCUCUGGUU UGCUUCGAU	75	2345-2365	AUCGAAGCAAAC CAGAGGACCUC	184	2343-2365
AD-2044740	GUCUAUGUUCGU GUUUCAAGU	76	2435-2455	ACUUGAAACACG AACAUAGACAC	185	2433-2455
AD-2044780	GAGUGAUGAGA AAUAAUUAAU	77	2475-2495	AUUAAUUAUUUC UCAUCACUCCC	186	2473-2495
AD-2044815	GACGCACUGACU CACCUAGAU	78	2513-2533	AUCUAGGUGAGU CAGUGCGUCAC	187	2511-2533
AD-2044857	UAGCAUGCUGGA AAUAACUGU	79	2555-2575	ACAGUUAUUUCC AGCAUGCUAAA	188	2553-2575
AD-2044882	AAUCAAACGAAG ACACUGUCU	80	2580-2600	AGACAGUGUCUU CGUUUGAUUAC	189	2578-2600
AD-2044889	ACCAGCUACGCC AAACCUCGU	81	2607-2627	ACGAGGUUUGGC GUAGCUGGUAG	190	2605-2627
AD-2044905	CUCGGCAUUUUU UGUGUUAUU	82	2623-2643	AAUAACACAAAA AAUGCCGAGGU	191	2621-2643
AD-2044926	GACUGCUGGAUU CUGUAGUAU	83	2648-2668	AUACUACAGAAU CCAGCAGUCAG	192	2646-2668
AD-2044941	UAGUAAGGUGA CAUAGCUAUU	84	2663-2683	AAUAGCUAUGUC ACCUUACUACA	193	2661-2683
AD-2044971	UCUGUACUUAAC UUUGAUUUU	85	2703-2723	AAAAUCAAAGUU AAGUACAGAGU	194	2701-2723
AD-2044995	AUUUUGGUUUU GGUCUUCAAU	86	2729-2749	AUUGAAGACCAA AACCAAAAUUU	195	2727-2749
AD-2045010	UUCAACAUUUUC AUGCUCUUU	87	2744-2764	AAAGAGCAUGAA AAUGUUGAAGA	196	2742-2764
AD-2045019	CACCAAUUUUUA AAUGGGCAU	88	2773-2793	AUGCCCAUUUAA AAAUUGGUGGG	197	2771-2793
AD-2045030	AGCUGCUUUUGA UAAGGAACU	89	2806-2826	AGUUCCUUAUCA AAAGCAGCUAA	198	2804-2826
AD-2045052	CUGCACAAAGGA CUGAGCAGU	90	2828-2848	ACUGCUCAGUCC UUUGUGCAGCU	199	2826-2848
AD-2045080	GAAGUUGUCCAC GCAUUUACU	91	2876-2896	AGUAAAUGCGUG GACAACUUCUU	200	2874-2896
AD-2045096	UUACCUCAUCAG CUAACGAGU	92	2892-2912	ACUCGUUAGCUG AUGAGGUAAAU	201	2890-2912
AD-2045120	UGACAUGCAUUU UUACUGUCU	93	2916-2936	AGACAGUAAAAA UGCAUGUCAAG	202	2914-2936
AD-2045134	CUGUCUUUAUUC CUGACACUU	94	2931-2951	AAGUGUCAGGAA UAAAGACAGUA	203	2929-2951
AD-2045152	CUGAGAUGAAU GUUUUCAAAU	95	2949-2969	AUUUGAAAACAU UCAUCUCAGUG	204	2947-2969
AD-2045167	UCAAAGCUGCAA CAUGUAUGU	96	2964-2984	ACAUACAUGUUG CAGCUUUGAAA	205	2962-2984
AD-2045172	UCAUGCAAACCG AUUCUGUUU	97	2989-3009	AAACAGAAUCGG UUUGCAUGACU	206	2987-3009
AD-2045191	UAUUGGGAAUG AAAUCUGUCU	98	3008-3028	AGACAGAUUUCA UUCCCAAUAAC	207	3006-3028

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000301.5	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000301.5
AD-2045210	CACCGACUGCUU GACUUGAGU	99	3027-3047	ACUCAAGUCAAG CAGUCGGUGAC	208	3025-3047
AD-2045233	CUGUAUAUGAU GGAGUGAACU	100	3070-3090	AGUUCACUCCAU CAUAUACAGCU	209	3068-3090
AD-2045262	GAUGUGUAACAC AAGACCAAU	101	3099-3119	AUUGGUCUUGUG UUACACAUCCA	210	3097-3119
AD-2045281	ACUGAGAGUCUG AAUGUUAUU	102	3118-3138	AAUAACAUUCAG ACUCUCAGUUG	211	3116-3138
AD-2045288	CACACGUGAGUC UAGGAUUGU	103	3145-3165	ACAAUCCUAGAC UCACGUGUGCC	212	3143-3165
AD-2045313	AAGAGCAUGUA AAUGAACAAU	104	3170-3190	AUUGUUCAUUUA CAUGCUCUUGG	213	3168-3190
AD-2045328	AACAACAAGCAA AUAUUGAAU	105	3185-3205	AUUCAAUAUUUG CUUGUUGUUCA	214	3183-3205
AD-2045354	CCACUUAUUUCC CAUUGCUAU	106	3211-3231	AUAGCAAUGGGA AAUAAGUGGUC	215	3209-3231
AD-2045381	GCCCGGUUUUGA AACAGUCUU	107	3238-3258	AAGACUGUUUCA AAACCGGGCAG	216	3236-3258
AD-2045414	UCACAGGAGAAU GACCUGUGU	108	3271-3291	ACACAGGUCAUU CUCCUGUGACC	217	3269-3291
AD-2045434	GGAGAGAUACA UGUUUAGAAU	109	3291-3311	AUUCUAAACAUG UAUCUCUCCCA	218	3289-3311
AD-2045448	GAAGAGAAAGG ACAAAGGCAU	110	3312-3332	AUGCCUUUGUCC UUUCUCUUCCU	219	3310-3332
AD-2045468	CACGUUUUACCA UUUAAAAUU	111	3332-3352	AAUUUUAAAUGG UAAAACGUGUG	220	3330-3352
AD-2045506	CAAUGCAACAGU CAUCUUACU	112	3393-3413	AGUAAGAUGACU GUUGCAUUGUU	221	3391-3413
AD-2045522	UUACAGCAGAGA AAUGCAGAU	113	3409-3429	AUCUGCAUUUCU CUGCUGUAAGA	222	3407-3429
AD-2045537	GCAGAGAAAAGC AAAACUGCU	114	3424-3444	AGCAGUUUUGCU UUUCUCUGCAU	223	3422-3444
AD-2045562	ACUGUGAAUAA AGGGUGAAUU	115	3449-3469	AAUUCACCCUUU AUUCACAGUCA	224	3447-3469
AD-2045583	UAGUCUCAAAUC CUCAAAGAU	116	3470-3490	AUCUUUGAGGAU UUGAGACUACA	225	3468-3490
AD-2045600	AGAGCUGUGUU UAUUUCAUUU	117	3487-3507	AAAUGAAAUAAA CACAGCUCUUU	226	3485-3507

Table 4. Unmodified Sense and Antisense Strand Sequences of Human PLG dsRNA Agents

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_001168338.1	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_001168338.1
AD-2055723	ACUUAAUUUGAC UAUCUGGUU	227	10-30	AACCAGAUAGUC AAAUUAAGUUA	253	8-30
AD-2055760	CUCAUGUAAGUC AACAACAUU	228	47-67	AAUGUUGUUGAC UUACAUGAGAG	254	45-67

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_001168338.1	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_001168338.1
AD-2055779	UAAGACAUUCCCUUUCAUCUU	229	521-541	AAGAUGAAAGGGAAUGUCUUACC	255	519-541
AD-2055794	CAUCUUUGUGUUCAUCUACUU	230	536-556	AAGUAGAUGAACACAAAGAUGAA	256	534-556
AD-2055857	AUGCUUCUCAAGUCCCUUAUU	231	619-639	AAUAAGGGACUUGAGAAGCAUGG	257	617-639
AD-2055893	UUUGCAUAUAACCUACAUACU	232	655-675	AGUAUGUAGGUUAUAUGCAAAUA	258	653-675
AD-2055909	AUACCUUCUCUUGUAUAAUCU	233	671-691	AGAUUAUACAAGAGAAGGUAUGU	259	669-691
AD-2055933	AAAUGCUAUUUAAUCGUUGUU	234	704-724	AACAACGAUUAAAUAGCAUUUAC	260	702-724
AD-2055947	GUUGUUAUACUGUAUUGUUUU	235	719-739	AAAACAAUACAGUAUAACAACGA	261	717-739
AD-2055958	CAUAUUGUUAUUUUCUGUCAU	236	762-782	AUGACAGAAAAUAACAAUAUGAC	262	760-782
AD-2055973	GUCAUCUUUUUCAAGUCUUUU	237	778-798	AAAAGACUUGAAAAAGAUGACAG	263	776-798
AD-2055995	CAUCCACAGUUGGUUGAAUUU	238	800-820	AAAUUCAACCAACUGUGGAUGGA	264	798-820
AD-2056048	ACUGUAUUUAGGAUAAUUUCU	239	853-873	AGAAAUUAUCCUAAAUACAGUUG	265	851-873
AD-2056062	CAUCACUUUUAAUUCAAACCU	240	872-892	AGGUUUGAAUUAAAAGUGAUGAA	266	870-892
AD-2056077	AAACCACAAUAUGUGAAUAAU	241	887-907	AUUAUUCACAUAUUGUGGUUUGA	267	885-907
AD-2056096	AGCAGAUAGAAAGAAUCUUUU	242	906-926	AAAAGAUUCUUUCUAUCUGCUUA	268	904-926
AD-2056121	GUCGAUGUUCAACUAUUUUUU	243	931-951	AAAAAAUAGUUGAACAUCGACAU	269	929-951
AD-2056154	AACAUGGUUGCUUUCUAUUUU	244	964-984	AAAAUAGAAAGCAACCAUGUUCU	270	962-984
AD-2056174	UCUUGGAUAUGGAGGUUUCUU	245	986-1006	AAGAAACCUCCAUAUCCAAGAAA	271	984-1006
AD-2056190	UUCUUGAAGACCUAGAACAUU	246	1002-1022	AAUGUUCUAGGUCUUCAAGAAAC	272	1000-1022
AD-2056206	ACAUAGAAGAAUGCCUAGUUU	247	1018-1038	AAACUAGGCAUUCUUCUAUGUUC	273	1016-1038
AD-2056234	UAUGAGUUUUAGGCCAAAUCU	248	1057-1077	AGAUUUGGCCUAAAACUCAUAGU	274	1055-1077
AD-2056249	AAAUCUGAGAAAAGAUCAAAU	249	1072-1092	AUUUGAUCUUUUCUCAGAUUUGG	275	1070-1092
AD-2056292	UAAGCAUAUCAGGUUAGAACU	250	1115-1135	AGUUCUAACCUGAUAUGCUUACU	276	1113-1135
AD-2056307	AGAACUCUCAUCACAUGUUCU	251	1130-1150	AGAACAUGUGAUGAGAGUUCUAA	277	1128-1150
AD-2056338	UGGAGCAAAAGAGUAAAUAAU	252	1161-1181	AUUAUUUACUCUUUUGCUCCACA	278	1159-1181

TABLE 5. Modified Sense and Antisense Strand Sequences of Human PLG dsRNA Agents

Duplex ID	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-2042815	gsuscaacAfaCfAfUfccugggauuuL96	279	asAfsaucCfcAfGfgaugUfuGfuugacsusu	414	AAGUCAACAACAUCCUGGGAUUG	549
AD-2042896	csusuuuaUfuUfCfUfgaaaucagguL96	280	asCfscugAfuUfUfcagaAfaUfaaaagsasa	415	UUCUUUUAUUUCUGAAAUCAGGU	550
AD-2042932	gsasugacUfaUfGfUfgaauacccauL96	281	asUfsgggUfaUfUfcacaUfaGfucaucscsa	416	UGGAUGACUAUGUGAAUACCCAG	551
AD-2042938	uscsacugUfuCfAfGfugucacuaauL96	282	asUfsuagUfgAfCfacugAfaCfagugasasg	417	CUUCACUGUUCAGUGUCACUAAG	552
AD-2042970	asgscaggAfaGfUfAfuagaagaauuL96	283	asAfsuucUfuCfUfauacUfuCfcugcuscsc	418	GGAGCAGGAAGUAUAGAAGAAUG	553
AD-2042987	asasugugCfaGfCfAfaaaugugaguL96	284	asCfsucaCfaUfUfuugcUfgCfacauuscsu	419	AGAAUGUGCAGCAAAAUGUGAGG	554
AD-2043006	gsgsaggaCfgAfAfGfaauucaccuuL96	285	asAfsgguGfaAfUfucuuCfgUfccuccsusc	420	GAGGAGGACGAAGAAUUCACCUG	555
AD-2043032	csasuuccAfaUfAfUfcacaguaaauL96	286	asUfsuuaCfuGfUfgauaUfuGfgaaugscsc	421	GGCAUUCCAAUAUCACAGUAAAG	556
AD-2043052	gsasgcaaCfaAfUfGfugugauaauuL96	287	asAfsuuaUfcAfCfacauUfgUfugcucsusu	422	AAGAGCAACAAUGUGUGAUAAUG	557
AD-2043072	gsgscugaAfaAfCfAfggaaguccuuL96	288	asAfsggaCfuUfCfcuguUfuUfcagccsasu	423	AUGGCUGAAAACAGGAAGUCCUC	558
AD-2043088	uscscuccAfuAfAfUfcauuaggauuL96	289	asAfsuccUfaAfUfgauuAfuGfgaggascsu	424	AGUCCUCCAUAAUCAUUAGGAUG	559
AD-2043108	gsasgagaUfgUfAfGfuuuuauuuguL96	290	asCfsaaaUfaAfAfacuaCfaUfcucucsasu	425	AUGAGAGAUGUAGUUUUAUUUGA	560
AD-2043131	gsusaucuCfuCfAfGfagugcaagauL96	291	asUfscuuGfcAfCfucugAfgAfgauacsasc	426	GUGUAUCUCUCAGAGUGCAAGAC	561
AD-2043150	ascsugggAfaUfGfGfaaagaacuauL96	292	asUfsaguUfcUfUfuccaUfuCfccaguscsu	427	AGACUGGGAAUGGAAAGAACUAC	562
AD-2043174	gsgsgacgAfuGfUfCfcaaaacaaauL96	293	asUfsuugUfuUfUfggacAfuCfgucccsusc	428	GAGGGACGAUGUCCAAAACAAAA	563
AD-2043218	gsasccuaGfaUfUfCfucaccugcuuL96	294	asAfsgcaGfgUfGfagaaUfcUfaggucsusg	429	CAGACCUAGAUUCUCACCUGCUA	564
AD-2043249	usgscaggAfaUfCfCfagacaacgauL96	295	asUfscguUfgUfCfuggaUfuCfcugcasgsu	430	ACUGCAGGAAUCCAGACAACGAU	565
AD-2043266	gscsuauaCfuAfCfUfgauccagaauL96	296	asUfsucuGfgAfUfcaguAfgUfauagcsasc	431	GUGCUAUACUACUGAUCCAGAAA	566
AD-2043291	asusaugaCfuAfCfUfugcgacauucuL96	297	asGfsaauGfuCfGfcaguAfgUfcauauscsu	432	AGAUAUGACUACUGCGACAUUCU	567
AD-2043308	ususcuugAfgUfGfUfgaagaggaauL96	298	asUfsuccUfcUfUfcacaCfuCfaagaasusg	433	CAUUCUUGAGUGUGAAGAGGAAU	568
AD-2043323	asgsgaauGfuAfUfGfcauugcaguuL96	299	asAfscugCfaAfUfgcauAfcAfuuccuscsu	434	AGAGGAAUGUAUGCAUUGCAGUG	569
AD-2043339	csasguggAfgAfAfAfacuaugacguL96	300	asCfsgucAfuAfGfuuuuCfuCfcacugscsa	435	UGCAGUGGAGAAAACUAUGACGG	570

Duplex ID	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-2043358	gsgscaaaAfuUfUfCfcaagaccauuL96	301	asAfsuggUfcUfUfggaaAfuUfuugccsgsu	436	ACGGCAAAAUUUCCAAGACCAUG	571
AD-2043419	ascsgcucAfuGfGfAfuacauuccuuL96	302	asAfsggaAfuGfUfauccAfuGfagcgusgsu	437	ACACGCUCAUGGAUACAUUCCUU	572
AD-2043434	ususccuuCfcAfAfAfuuuccaaacuL96	303	asGfsuuuGfgAfAfauuuGfgAfaggaasusg	438	CAUUCCUUCCAAAUUUCCAAACA	573
AD-2043456	gsasaccuGfaAfGfAfagaauuacuuL96	304	asAfsguaAfuUfCfuucuUfcAfgguucsusu	439	AAGAACCUGAAGAAGAAUUACUG	574
AD-2043483	csusugguGfuUfUfCfaccaccgacuL96	305	asGfsucgGfuGfGfugaaAfcAfccaagsgsc	440	GCCUUGGUGUUUCACCACCGACC	575
AD-2043494	csusgggaAfcUfUfUfgugacauccuL96	306	asGfsgauGfuCfAfcaaaGfuUfcccagscsg	441	CGCUGGGAACUUUGUGACAUCCC	576
AD-2043505	csasccucCfaCfCfAfucuucugguuL96	307	asAfsccaGfaAfGfauggUfgGfaggugsusu	442	AACACCUCCACCAUCUUCUGGUC	577
AD-2043525	cscscaccUfaCfCfAfgugucugaauL96	308	asUfsucaGfaCfAfcuggUfaGfgugggsasc	443	GUCCCACCUACCAGUGUCUGAAG	578
AD-2043540	csusgaagGfgAfAfCfaggugaaaauL96	309	asUfsuuuCfaCfCfuguuCfcCfuucagsasc	444	GUCUGAAGGGAACAGGUGAAAAC	579
AD-2043565	gscsgggaAfuGfUfGfgcuguuaccuL96	310	asGfsguaAfcAfGfccacAfuUfcccgcsgsa	445	UCGCGGGAAUGUGGCUGUUACCG	580
AD-2043617	ascsaggaCfaCfCfAfgaaaacuucuL96	311	asGfsaagUfuUfUfcuggUfgUfccugususa	446	UAACAGGACACCAGAAAACUUCC	581
AD-2043627	asusuuggAfuGfAfAfaacuacugcuL96	312	asGfscagUfaGfUfuuucAfuCfcaaaususu	447	AAAUUUGGAUGAAAACUACUGCC	582
AD-2043644	usgsccgcAfaUfCfCfugacggaaauL96	313	asUfsuucCfgUfCfaggaUfuGfcggcasgsu	448	ACUGCCGCAAUCCUGACGGAAAA	583
AD-2043656	gsusgccaUfaCfAfAfccaacagccuL96	314	asGfsgcuGfuUfGfguugUfaUfggcacscsa	449	UGGUGCCAUACAACCAACAGCCA	584
AD-2043689	gsusacugUfaAfGfAfuaccguccuuL96	315	asAfsggaCfgGfUfaucuUfaCfaguacsusc	450	GAGUACUGUAAGAUACCGUCCUG	585
AD-2043789	ascsaggaAfaGfAfAfgugucagucuL96	316	asGfsacuGfaCfAfcuucUfuUfccugusgsg	451	CCACAGGAAAGAAGUGUCAGUCU	586
AD-2043804	csasgucuUfgGfUfCfaucuaugacuL96	317	asGfsucaUfaGfAfugacCfaAfgacugsasc	452	GUCAGUCUUGGUCAUCUAUGACA	587
AD-2043843	usgscuggCfcUfGfAfcaugaacuuL96	318	asAfsguuCfaUfUfgucaGfgCfcagcasusu	453	AAUGCUGGCCUGACAAUGAACUA	588
AD-2043869	gsgsaaucCfaGfAfUfgccgauaaauL96	319	asUfsuuaUfcGfGfcaucUfgGfauuccsusg	454	CAGGAAUCCAGAUGCCGAUAAAG	589
AD-2043874	csusggugUfuUfUfAfccacagaccuL96	320	asGfsgucUfgUfGfguaaAfaCfaccagsgsg	455	CCCUGGUGUUUUACCACAGACCC	590
AD-2043886	gsgsgaguAfcUfGfCfaaccugaaauL96	321	asUfsuucAfgGfUfugcaGfuAfcucccsasc	456	GUGGGAGUACUGCAACCUGAAAA	591
AD-2043916	gsasacagAfaGfCfGfaguguguauL96	322	asUfsacaAfcAfCfucgcUfuCfuguucscsu	457	AGGAACAGAAGCGAGUGUUGUAG	592
AD-2043942	cscsgccuGfuUfGfUfccugcuuccuL96	323	asGfsgaaGfcAfGfgacaAfcAfggcggsasg	458	CUCCGCCUGUUGUCCUGCUUCCA	593
AD-2043959	uscscagaUfgUfAfGfagacuccuuuL96	324	asAfsaggAfgUfCfucuaCfaUfcuggasasg	459	CUUCCAGAUGUAGAGACUCCUUC	594

Duplex ID	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-2043979	cscsgaagAfaGfAfCfuguauguuuuL96	325	asAfsaacAfuAfCfagucUfuCfuucggsasa	460	UUCCGAAGAAGACUGUAUGUUUG	595
AD-2044060	usasgacaCfaGfCfAfuuuucacucuL96	326	asGfsaguGfaAfAfaugcUfgUfgucuasusg	461	CAUAGACACAGCAUUUUCACUCC	596
AD-2044075	csascuccAfgAfGfAfcaaauccacuL96	327	asGfsuggAfuUfUfgucuCfuGfgagugsasa	462	UUCACUCCAGAGACAAAUCCACG	597
AD-2044119	gscscguaAfcCfCfUfgauggugauuL96	328	asAfsucaCfcAfUfcaggGfuUfacggcsasg	463	CUGCCGUAACCCUGAUGGUGAUG	598
AD-2044153	gsusgcuaCfaCfGfAfcaaauccaauL96	329	asUfsuggAfuUfUfgucgUfgUfagcacscsa	464	UGGUGCUACACGACAAAUCCAAG	599
AD-2044168	uscscaagAfaAfAfCfuuuacgacuuL96	330	asAfsgucGfuAfAfaguuUfuCfuuggasusu	465	AAUCCAAGAAAACUUUACGACUA	600
AD-2044184	gsascuacUfgUfGfAfugucccucauL96	331	asUfsgagGfgAfCfaucaCfaGfuagucsgsu	466	ACGACUACUGUGAUGUCCCUCAG	601
AD-2044267	gscsaaguCfaGfUfCfuuagaacaauL96	332	asUfsuguUfcUfAfagacUfgAfcuugcscsa	467	UGGCAAGUCAGUCUUAGAACAAG	602
AD-2044282	asascaagGfuUfUfGfgaaugcacuuL96	333	asAfsgugCfaUfUfccaaAfcCfuuguuscsu	468	AGAACAAGGUUUGGAAUGCACUU	603
AD-2044325	usgscccaCfuGfCfUfuggagaaguuL96	334	asAfscuuCfuCfCfaagcAfgUfgggcasgsc	469	GCUGCCCACUGCUUGGAGAAGUC	604
AD-2044364	ascscaagAfaGfUfGfaaucucgaauL96	335	asUfsucgAfgAfUfucacUfuCfuuggusgsu	470	ACACCAAGAAGUGAAUCUCGAAC	605
AD-2044384	cscsgcauGfuUfCfAfggaaauagauL96	336	asUfscuaUfuUfCfcugaAfcAfugcggsusu	471	AACCGCAUGUUCAGGAAAUAGAA	606
AD-2044433	gsasaaagAfuAfUfUfgccuugcuauL96	337	asUfsagcAfaGfGfcaauAfuCfuuuucsgsu	472	ACGAAAAGAUAUUGCCUUGCUAA	607
AD-2044448	usgscuaaAfgCfUfAfagcaguccuuL96	338	asAfsggaCfuGfCfuuagCfuUfuagcasasg	473	CUUGCUAAAGCUAAGCAGUCCUG	608
AD-2044472	uscsaucaCfuGfAfCfaaaguaaucuL96	339	asGfsauuAfcUfUfugucAfgUfgaugascsg	474	CGUCAUCACUGACAAAGUAAUCC	609
AD-2044516	csgsaaugUfuUfCfAfucacuggcuuL96	340	asAfsgccAfgUfGfaugaAfaCfauucgsgsu	475	ACCGAAUGUUUCAUCACUGGCUG	610
AD-2044519	gsasgaaaCfcCfAfAfgguacuuuuuL96	341	asAfsaaaGfuAfCfcuugGfgUfuucucscsc	476	GGGAGAAACCCAAGGUACUUUUG	611
AD-2044569	cscsugugAfuUfGfAfgaauaaaguuL96	342	asAfscuuUfaUfUfcucaAfuCfacaggsgsa	477	UCCCUGUGAUUGAGAAUAAAGUG	612
AD-2044594	asuscgcuAfuGfAfGfuuucugaauuL96	343	asAfsuucAfgAfAfacucAfuAfgcgaususg	478	CAAUCGCUAUGAGUUUCUGAAUG	613
AD-2044609	usgsaaugGfaAfGfAfguccaauccuL96	344	asGfsgauUfgGfAfcucuUfcCfauucasgsa	479	UCUGAAUGGAAGAGUCCAAUCCA	614
AD-2044689	gsgsuccuCfuGfGfUfuugcuucgauL96	345	asUfscgaAfgCfAfaaccAfgAfggaccsusc	480	GAGGUCCUCUGGUUUGCUUCGAG	615
AD-2044740	gsuscuauGfuUfCfGfuguuucaaguL96	346	asCfsuugAfaAfCfacgaAfcAfuagacsasc	481	GUGUCUAUGUUCGUGUUUCAAGG	616
AD-2044780	gsasgugaUfgAfGfAfaauaauuaauL96	347	asUfsuaaUfuAfUfuucuCfaUfcacucscsc	482	GGGAGUGAUGAGAAAUAAUUAAU	617
AD-2044815	gsascgcaCfuGfAfCfucaccuagauL96	348	asUfscuaGfgUfGfagucAfgUfgcgucsasc	483	GUGACGCACUGACUCACCUAGAG	618

Duplex ID	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-2044857	usasgcauGfcUfGfGfaaauaacuguL96	349	asCfsaguUfaUfUfuccaGfcAfugcuasasa	484	UUUAGCAUGCUGGAAAUAACUGG	619
AD-2044882	asasucaaAfcGfAfAfgacacugucuL96	350	asGfsacaGfuGfUfcuucGfuUfugauusasc	485	GUAAUCAAACGAAGACACUGUCC	620
AD-2044889	ascscagcUfaCfGfCfcaaaccucguL96	351	asCfsgagGfuUfUfggcgUfaGfcuggusasg	486	CUACCAGCUACGCCAAACCUCGG	621
AD-2044905	csuscggcAfuUfUfUfuuguguuauuL96	352	asAfsuaaCfaCfAfaaaaAfuGfccgagsgsu	487	ACCUCGGCAUUUUUUGUGUUAUU	622
AD-2044926	gsascugcUfgGfAfUfucuguaguauL96	353	asUfsacuAfcAfGfaaucCfaGfcagucsasg	488	CUGACUGCUGGAUUCUGUAGUAA	623
AD-2044941	usasguaaGfgUfGfAfcauagcuauuL96	354	asAfsuagCfuAfUfgucaCfcUfuacuascsa	489	UGUAGUAAGGUGACAUAGCUAUG	624
AD-2044971	uscsguaCfuUfAfAfcuuugauuuuL96	355	asAfsaauCfaAfAfguuaAfgUfacagasgsu	490	ACUCUGUACUUAACUUUGAUUUG	625
AD-2044995	asusuuugGfuUfUfUfggucuucaauL96	356	asUfsugaAfgAfCfcaaaAfcCfaaaaususu	491	AAAUUUUGGUUUUGGUCUUCAAC	626
AD-2045010	ususcaacAfuUfUfUfcaugcucuuuL96	357	asAfsagaGfcAfUfgaaaAfuGfuugaasgsa	492	UCUUCAACAUUUUCAUGCUCUUU	627
AD-2045019	csasccaaUfuUfUfUfaaaugggcauL96	358	asUfsgccCfaUfUfuaaaAfaUfuggugsgsg	493	CCCACCAAUUUUUAAAUGGGCAG	628
AD-2045030	asgscugcUfuUfUfGfauaaggaacuL96	359	asGfsuucCfuUfAfucaaAfaGfcagcusasa	494	UUAGCUGCUUUUGAUAAGGAACA	629
AD-2045052	csusgcacAfaAfGfGfacugagcaguL96	360	asCfsugcUfcAfGfuccuUfuGfugcagscsu	495	AGCUGCACAAAGGACUGAGCAGG	630
AD-2045080	gsasaguuGfuCfCfAfcgcauuuacuL96	361	asGfsuaaAfuGfCfguggAfcAfacuucsusu	496	AAGAAGUUGUCCACGCAUUUACC	631
AD-2045096	ususaccuCfaUfCfAfgcuaacgaguL96	362	asCfsucgUfuAfGfcugaUfgAfgguaasasu	497	AUUUACCUCAUCAGCUAACGAGG	632
AD-2045120	usgsacauGfcAfUfUfuuuacugucuL96	363	asGfsacaGfuAfAfaaauGfcAfugucasasg	498	CUUGACAUGCAUUUUUACUGUCU	633
AD-2045134	csusgucuUfuAfUfUfccugacacuuL96	364	asAfsgugUfcAfGfgaauAfaAfgacagsusa	499	UACUGUCUUUAUUCCUGACACUG	634
AD-2045152	csusgagaUfgAfAfUfguuuucaaauL96	365	asUfsuugAfaAfAfcauuCfaUfcucagsusg	500	CACUGAGAUGAAUGUUUUCAAAG	635
AD-2045167	uscsaaagCfuGfCfAfacauguauguL96	366	asCfsauaCfaUfGfuugcAfgCfuuugasasa	501	UUUCAAAGCUGCAACAUGUAUGG	636
AD-2045172	uscsaugcAfaAfCfCfgauucuguuuL96	367	asAfsacaGfaAfUfcgguUfuGfcaugascsu	502	AGUCAUGCAAACCGAUUCUGUUA	637
AD-2045191	usasuuggGfaAfUfGfaaaucugucuL96	368	asGfsacaGfaUfUfucauUfcCfcaauasasc	503	GUUAUUGGGAAUGAAAUCUGUCA	638
AD-2045210	csasccgaCfuGfCfUfugacuugaguL96	369	asCfsucaAfgUfCfaagcAfgUfcggugsasc	504	GUCACCGACUGCUUGACUUGAGC	639
AD-2045233	csusguauAfuGfAfUfggagugaacuL96	370	asGfsuucAfcUfCfcaucAfuAfuacagscsu	505	AGCUGUAUAUGAUGGAGUGAACC	640
AD-2045262	gsasugugUfaAfCfAfcaagaccaauL96	371	asUfsuggUfcUfUfguguUfaCfacaucscsa	506	UGGAUGUGUAACACAAGACCAAC	641
AD-2045281	ascsugagAfgUfCfUfgaauguuauuL96	372	asAfsuaaCfaUfUfcagaCfuCfucagususg	507	CAACUGAGAGUCUGAAUGUUAUU	642

Duplex ID	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-2045288	csascacgUfgAfGfUfcuaggauuguL96	373	asCfsaauCfcUfAfgacuCfaCfgugugscsc	508	GGCACACGUGAGUCUAGGAUUGG	643
AD-2045313	asasgagcAfuGfUfAfaaugaacaauL96	374	asUfsuguUfcAfUfuuacAfuGfcucuusgsg	509	CCAAGAGCAUGUAAAUGAACAAC	644
AD-2045328	asascaacAfaGfCfAfaauauugaauL96	375	asUfsucaAfuAfUfuugcUfuGfuuguuscsa	510	UGAACAACAAGCAAAUAUUGAAG	645
AD-2045354	cscsacuuAfuUfUfCfccauugcuauL96	376	asUfsagcAfaUfGfggaaAfuAfaguggsusc	511	GACCACUUAUUUCCCAUUGCUAA	646
AD-2045381	gscsccggUfuUfUfGfaaacagucuuL96	377	asAfsgacUfgUfUfucaaAfaCfcgggcsasg	512	CUGCCCGGUUUUGAAACAGUCUG	647
AD-2045414	uscsacagGfaGfAfAfugaccuguguL96	378	asCfsacaGfgUfCfauucUfcCfugugascsc	513	GGUCACAGGAGAAUGACCUGUGG	648
AD-2045434	gsgsagagAfuAfCfAfuguuuagaauL96	379	asUfsucuAfaAfCfauguAfuCfucuccscsa	514	UGGGAGAGAUACAUGUUUAGAAG	649
AD-2045448	gsasagagAfaAfGfGfacaaaggcauL96	380	asUfsgccUfuUfGfuccuUfuCfucuucscsu	515	AGGAAGAGAAAGGACAAAGGCAC	650
AD-2045468	csascguuUfuAfCfCfauuuaaaauuL96	381	asAfsuuuUfaAfAfugguAfaAfacgugsusg	516	CACACGUUUUACCAUUUAAAAUA	651
AD-2045506	csasaugcAfaCfAfGfucaucuuacuL96	382	asGfsuaaGfaUfGfacugUfuGfcauugsusu	517	AACAAUGCAACAGUCAUCUUACA	652
AD-2045522	ususacagCfaGfAfGfaaaugcagauL96	383	asUfscugCfaUfUfucucUfgCfuguaasgsa	518	UCUUACAGCAGAGAAAUGCAGAG	653
AD-2045537	gscsagagAfaAfAfGfcaaaacugcuL96	384	asGfscagUfuUfUfgcuuUfuCfucugcsasu	519	AUGCAGAGAAAAGCAAAACUGCA	654
AD-2045562	ascsugugAfaUfAfAfagggugaauuL96	385	asAfsuucAfcCfCfuuuaUfuCfacaguscsa	520	UGACUGUGAAUAAAGGGUGAAUG	655
AD-2045583	usasgucuCfaAfAfUfccucaaagauL96	386	asUfscuuUfgAfGfgauuUfgAfgacuascsa	521	UGUAGUCUCAAAUCCUCAAAGAG	656
AD-2045600	asgsagcuGfuGfUfUfuauuucauuuL96	387	asAfsaugAfaAfUfaaacAfcAfgcucususu	522	AAAGAGCUGUGUUUAUUUCAUUG	657
AD-2055723	ascsuuaaUfuUfGfAfcuaucugguuL96	388	asAfsccaGfaUfAfgucaAfaUfuaagususa	523	UAACUUAAUUUGACUAUCUGGUU	658
AD-2055760	csuscaugUfaAfGfUfcaacaacauuL96	389	asAfsuguUfgUfUfgacuUfaCfaugagsasg	524	CUCUCAUGUAAGUCAACAACAUC	659
AD-2055779	usasagacAfuUfCfCfcuuucaucuuL96	390	asAfsgauGfaAfAfgggaAfuGfucuuascsc	525	GGUAAGACAUUCCCUUUCAUCUU	660
AD-2055794	csasucuuUfgUfGfUfucaucuacuuL96	391	asAfsguaGfaUfGfaacaCfaAfagaugsasa	526	UUCAUCUUUGUGUUCAUCUACUG	661
AD-2055857	asusgcuuCfuCfAfAfgucccuuauuL96	392	asAfsuaaGfgGfAfcuugAfgAfagcausgsg	527	CCAUGCUUCUCAAGUCCCUUAUA	662
AD-2055893	ususugcaUfaUfAfAfccuacauacuL96	393	asGfsuauGfuAfGfguuaUfaUfgcaaasusa	528	UAUUUGCAUAUAACCUACAUACC	663
AD-2055909	asusaccuUfcUfCfUfuguauaaucuL96	394	asGfsauuAfuAfCfaagaGfaAfgguausgsu	529	ACAUACCUUCUCUUGUAUAAUCC	664
AD-2055933	asasaugcUfaUfUfUfaaucguuguuL96	395	asAfscaaCfgAfUfuaaaUfaGfcauuusasc	530	GUAAAUGCUAUUUAAUCGUUGUU	665
AD-2055947	gsusuguuAfuAfCfUfguauuguuuuL96	396	asAfsaacAfaUfAfcaguAfuAfacaacsgsa	531	UCGUUGUUAUACUGUAUUGUUUU	666

Duplex ID	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-2055958	csasuauuGfuUfAfUfuuucugucauL96	397	asUfsgacAfgAfAfaauaAfcAfauaugsasc	532	GUCAUAUUGUUAUUUUCUGUCAU	667
AD-2055973	gsuscaucUfuUfUfUfcaagucuuuuL96	398	asAfsaagAfcUfUfgaaaAfaGfaugacsasg	533	CUGUCAUCUUUUUCAAGUCUUUU	668
AD-2055995	csasuccaCfaGfUfUfgguugaauuuL96	399	asAfsauuCfaAfCfcaacUfgUfggaugsgsa	534	UCCAUCCACAGUUGGUUGAAUUU	669
AD-2056048	ascsuguaUfuUfAfGfgauaauuucuL96	400	asGfsaaaUfuAfUfccuaAfaUfacagususg	535	CAACUGUAUUUAGGAUAAUUUCA	670
AD-2056062	csasucacUfuUfUfAfauucaaaccuL96	401	asGfsguuUfgAfAfuuaaAfaGfugaugsasa	536	UUCAUCACUUUUAAUUCAAACCA	671
AD-2056077	asasaccaCfaAfUfAfugugaauaauL96	402	asUfsuauUfcAfCfauauUfgUfgguuusgsa	537	UCAAACCACAAUAUGUGAAUAAG	672
AD-2056096	asgscagaUfaGfAfAfagaaucuuuuL96	403	asAfsaagAfuUfCfuuucUfaUfcugcususa	538	UAAGCAGAUAGAAAGAAUCUUUU	673
AD-2056121	gsuscgauGfuUfCfAfacuauuuuuuL96	404	asAfsaaaAfuAfGfuugaAfcAfucgacsasu	539	AUGUCGAUGUUCAACUAUUUUUG	674
AD-2056154	asascaugGfuUfGfCfuuucuauuuuL96	405	asAfsaauAfgAfAfagcaAfcCfauguuscsu	540	AGAACAUGGUUGCUUUCUAUUUU	675
AD-2056174	uscsuuggAfuAfUfGfgagguuucuuL96	406	asAfsgaaAfcCfUfccauAfuCfcaagasasa	541	UUUCUUGGAUAUGGAGGUUUCUU	676
AD-2056190	ususcuugAfaGfAfCfcuagaacauuL96	407	asAfsuguUfcUfAfggucUfuCfaagaasasc	542	GUUUCUUGAAGACCUAGAACAUA	677
AD-2056206	ascsauagAfaGfAfAfaugccuaguuuL96	408	asAfsacuAfgGfCfauucUfuCfuaugususc	543	GAACAUAGAAGAAUGCCUAGUUU	678
AD-2056234	usasugagUfuUfUfAfaggccaaaucuL96	409	asGfsauuUfgGfCfcuaaAfaCfucauasgsu	544	ACUAUGAGUUUUAGGCCAAAUCU	679
AD-2056249	asasaucuGfaGfAfAfaaagaucaaauL96	410	asUfsuugAfuCfUfuuucUfcAfgauuusgsg	545	CCAAAUCUGAGAAAAGAUCAAAG	680
AD-2056292	usasagcaUfaUfCfAfgguuagaacuL96	411	asGfsuucUfaAfCfcugaUfaUfgcuuascsu	546	AGUAAGCAUAUCAGGUUAGAACU	681
AD-2056307	asgsaacuCfuCfAfUfcacauguucuL96	412	asGfsaacAfuGfUfgaugAfgAfguucusasa	547	UUAGAACUCUCAUCACAUGUUCG	682
AD-2056338	usgsgagcAfaAfAfGfaguaaauaauL96	413	asUfsuauUfuAfCfucuuUfuGfcuccascsa	548	UGUGGAGCAAAAGAGUAAAUAAG	683

Table 6. Additional Modified Sense and Antisense Strand Sequences of Human PLG dsRNA Agents

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:
AD-2134523.1	csasguccCfaAfAfAfuggaacauaaL96	691	VPusUfsaugUfuccauuuUfgGfgacugsgsc	971
AD-2222854.1	csasguccCfaAfAfAfugguacauaaL96	692	VPusUfsaugUfaccauuuUfgGfgacugsgsc	972
AD-2134574.1	asgsucccAfaAfAfUfggaacauaaaL96	693	VPusUfsuauGfuuccauuUfuGfggacusgsg	973
AD-2222855.1	asgsucccAfaAfAfUfggaucauaaaL96	694	VPusUfsuauGfauccauuUfuGfggacusgsg	974

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:
AD-2134577.1	cscscaaaAfuGfGfAfacauaaggaaL96	695	VPusUfsccuUfauguuccAfuUfuugggsasc	975
AD-2134687.1	cscsucugGfaUfGfAfcuaugugaaaL96	696	VPusUfsucaCfauagucaUfcCfagaggscsu	976
AD-2222856.1	cscsucugGfaUfGfAfcuauuugaaaL96	697	VPusUfsucaAfauagucaUfcCfagaggscsu	977
AD-2134898.1	csasauauCfaCfAfGfuaaagagcaaL96	698	VPusUfsgcuCfuuuacugUfgAfuauugsgsa	978
AD-2222857.1	csasauauCfaCfAfGfuaaugagcaaL96	699	VPusUfsgcuCfauuacugUfgAfuauugsgsa	979
AD-2134900.1	asusaucaCfaGfUfAfaagagcaacaL96	700	VPusGfsuugCfucuuuacUfgUfgauaususg	980
AD-2222858.1	asusaucaCfaGfUfAfaagugcaacaL96	701	VPusGfsuugCfacuuuacUfgUfgauaususg	981
AD-2134906.1	csasguaaAfgAfGfCfaacaaugugaL96	702	VPusCfsacaUfuguugcuCfuUfuacugsusg	982
AD-2134907.1	asgsuaaaGfaGfCfAfacaauguguaL96	703	VPusAfscacAfuuguugcUfcUfuuacusgsu	983
AD-2135487.1	asasuguaUfgCfAfUfugcaguggaaL96	704	VPusUfsccaCfugcaaugCfaUfacauuscsc	984
AD-2222859.1	asasuguaUfgCfAfUfugcuguggaaL96	705	VPusUfsccaCfagcaaugCfaUfacauuscsc	985
AD-2135518.1	csgsgcaaAfaUfUfUfccaagaccaaL96	706	VPusUfsgguCfuuggaaaUfuUfugccgsusc	986
AD-2222860.1	csgsgcaaAfaUfUfUfccaugaccaaL96	707	VPusUfsgguCfauggaaaUfuUfugccgsusc	987
AD-2135519.1	gsgscaaaAfuUfUfCfcaagaccauaL96	708	VPusAfsuggUfcuuggaaAfuUfuugccsgsu	988
AD-2222861.1	gsgscaaaAfuUfUfCfcaauaccauaL96	709	VPusAfsuggUfauuggaaAfuUfuugccsgsu	989
AD-2135520.1	gscsaaaaUfuUfCfCfaagaccaugaL96	710	VPusCfsaugGfucuuggaAfaUfuuugcscsg	990
AD-2222862.1	gscsaaaaUfuUfCfCfaaguccaugaL96	711	VPusCfsaugGfacuuggaAfaUfuuugcscsg	991
AD-2135708.1	gsgsauacAfuUfCfCfuuccaaauuaL96	712	VPusAfsauuUfggaaggaAfuGfuauccsasu	992
AD-2222863.1	gsgsauacAfuUfCfCfuucuaaauuaL96	713	VPusAfsauuUfagaaggaAfuGfuauccsasu	993
AD-2135712.1	ascsauucCfuUfCfCfaaauuuccaaL96	714	VPusUfsggaAfauuuggaAfgGfaaugusasu	994
AD-2135713.1	csasuuccUfuCfCfAfaauuuccaaaL96	715	VPusUfsuggAfaauuuggAfaGfgaaugsusa	995
AD-2135716.1	uscscuucCfaAfAfUfuuccaaacaaL96	716	VPusUfsguuUfggaaauuUfgGfaaggasasu	996
AD-2222864.1	uscscuucCfaAfAfUfuucuaaacaaL96	717	VPusUfsguuUfagaaauuUfgGfaaggasasu	997
AD-2135717.1	cscsuuccAfaAfUfUfuccaaacaaaL96	718	VPusUfsuguUfuggaaauUfuGfgaaggsasa	998

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:
AD-2222865.1	cscsuuccAfaAfUfUfuccuaacaaaL96	719	VPusUfsuguUfaggaaauUfuGfgaaggsasa	999
AD-2135718.1	csususccaAfaUfUfUfccaaacaagaL96	720	VPusCfsuugUfuuggaaaUfuUfggaagsgsa	1000
AD-2135719.1	ususccaaAfuUfUfUfCfcaaacaagaaL96	721	VPusUfscuuGfuuuggaaAfuUfuggaasgsg	1001
AD-2222866.1	ususccaaAfuUfUfUfCfcaaucaagaaL96	722	VPusUfscuuGfauuggaaAfuUfuggaasgsg	1002
AD-2135721.1	cscsaaauUfuCfCfAfaacaagaacaL96	723	VPusGfsuucUfuguuuggAfaAfuuuggsasa	1003
AD-2222867.1	cscsaaauUfuCfCfAfaacuagaacaL96	724	VPusGfsuucUfaguuuggAfaAfuuuggsasa	1004
AD-2135730.1	csasaacaAfgAfAfCfcugaagaagaL96	725	VPusCfsuucUfucagguuCfuUfguuugsgsa	1005
AD-2135731.1	asasacaaGfaAfCfCfugaagaagaaL96	726	VPusUfscuuCfuucagguUfcUfuguuusgsg	1006
AD-2222868.1	asasacaaGfaAfCfCfugaugaagaaL96	727	VPusUfscuuCfaucagguUfcUfuguuusgsg	1007
AD-2135732.1	asascaagAfaCfCfUfgaagaagaaaL96	728	VPusUfsucuUfcuucaggUfuCfuuguususg	1008
AD-2222869.1	asascaagAfaCfCfUfgaauaagaaaL96	729	VPusUfsucuUfauucaggUfuCfuuguususg	1009
AD-2135734.1	csasagaaCfcUfGfAfagaagaauuaL96	730	VPusAfsauuCfuucuucaGfgUfucuugsusu	1010
AD-2222870.1	csasagaaCfcUfGfAfagaugaauuaL96	731	VPusAfsauuCfaucuucaGfgUfucuugsusu	1011
AD-2135736.1	asgsaaccUfgAfAfGfaagaauuacaL96	732	VPusGfsuaaUfucuucuuCfaGfguucususg	1012
AD-2135737.1	gsasaccuGfaAfGfAfagaauuacuaL96	733	VPusAfsguaAfuucuucuUfcAfgguucsusu	1013
AD-2135738.1	asasccugAfaGfAfAfgaauuacugaL96	734	VPusCfsaguAfauucuucUfuCfagguuscsu	1014
AD-2135786.1	csasccucCfaCfCfAfucuucugguaL96	735	VPusAfsccaGfaagauggUfgGfaggugsusu	1015
AD-2135788.1	cscsuccaCfcAfUfCfuucugguccaL96	736	VPusGfsgacCfagaagauGfgUfggaggsusg	1016
AD-2222871.1	cscsuccaCfcAfUfCfuucuuguccaL96	737	VPusGfsgacAfagaagauGfgUfggaggsusg	1017
AD-2135789.1	csusccacCfaUfCfUfucuggucccaL96	738	VPusGfsggaCfcagaagaUfgGfuggagsgsu	1018
AD-2222872.1	csusccacCfaUfCfUfucuugucccaL96	739	VPusGfsggaCfaagaagaUfgGfuggagsgsu	1019
AD-2135821.1	csusgaagGfgAfAfCfaggugaaaaaL96	740	VPusUfsuuuCfaccuguuCfcCfuucagsasc	1020
AD-2222873.1	csusgaagGfgAfAfCfagguuaaaaaL96	741	VPusUfsuuuAfaccuguuCfcCfuucagsasc	1021
AD-2135896.1	usasacagGfaCfAfCfcagaaaacuaL96	742	VPusAfsguuUfucuggugUfcCfuguuasusg	1022

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:
AD-2135897.1	asascaggAfcAfCfCfagaaaacuuaL96	743	VPusAfsaguUfuucugguGfuCfcuguusasu	1023
AD-2222874.1	cscsugcaAfaAfAfUfuuguaugaaaL96	744	VPusUfsucaUfacaaauuUfuUfgcaggsgsg	1024
AD-2222875.1	cscsugcaAfaAfAfUfuuggaugaaaL96	745	VPusUfsucaUfccaaauuUfuUfgcaggsgsg	1025
AD-2135900.1	csusgcaaAfaAfUfUfuggaugaaaaL96	746	VPusUfsuucAfuccaaauUfuUfugcagsgsg	1026
AD-2222876.1	csusgcaaAfaAfUfUfugguugaaaaL96	747	VPusUfsuucAfaccaaauUfuUfugcagsgsg	1027
AD-2135901.1	usgscaaaAfaUfUfUfggaugaaaaaL96	748	VPusUfsuuuCfauccaaaUfuUfuugcasgsg	1028
AD-2222877.1	usgscaaaAfaUfUfUfggauuaaaaaL96	749	VPusUfsuuuAfauccaaaUfuUfuugcasgsg	1029
AD-2135904.1	asasaaauUfuGfGfAfugaaaacuaaL96	750	VPusUfsaguUfuucauccAfaAfuuuuusgsc	1030
AD-2135907.1	asasuuugGfaUfGfAfaaacuacugaL96	751	VPusCfsaguAfguuuucaUfcCfaaauususu	1031
AD-2135962.1	csgsguggGfaGfUfAfcuguaagauaL96	752	VPusAfsucuUfacaguacUfcCfcaccgscsa	1032
AD-2135964.1	gsusgggaGfuAfCfUfguaagauacaL96	753	VPusGfsuauCfuuacaguAfcUfcccacscsg	1033
AD-2222878.1	gsusgggaGfuAfCfUfguaugauacaL96	754	VPusGfsuauCfauacaguAfcUfcccacscsg	1034
AD-2135965.1	usgsggagUfaCfUfGfuaagauaccaL96	755	VPusGfsguaUfcuuacagUfaCfucccascsc	1035
AD-2222879.1	usgsggagUfaCfUfGfuaauauaccaL96	756	VPusGfsguaUfauuacagUfaCfucccascsc	1036
AD-2135967.1	gsgsaguaCfuGfUfAfagauaccguaL96	757	VPusAfscggUfaucuuacAfgUfacuccscsa	1037
AD-2135973.1	csusguaaGfaUfAfCfcguccugugaL96	758	VPusCfsacaGfgacgguaUfcUfuacagsusa	1038
AD-2136060.1	csasccacCfaCfCfAfcaggaaagaaL96	759	VPusUfscuuUfccuguggUfgGfuggugsgsa	1039
AD-2222880.1	csasccacCfaCfCfAfcaguaaagaaL96	760	VPusUfscuuUfacuguggUfgGfuggugsgsa	1040
AD-2136066.1	csasccacAfgGfAfAfagaagugucaL96	761	VPusGfsacaCfuucuuucCfuGfuggugsgsu	1041
AD-2222881.1	csasccacAfgGfAfAfagaugugucaL96	762	VPusGfsacaCfaucuuucCfuGfuggugsgsu	1042
AD-2136068.1	cscsacagGfaAfAfGfaagugucagaL96	763	VPusCfsugaCfacuucuuUfcCfuguggsusg	1043
AD-2136069.1	csascaggAfaAfGfAfagugucaguaL96	764	VPusAfscugAfcacuucuUfuCfcugugsgsu	1044
AD-2222882.1	csascaggAfaAfGfAfaguuucaguaL96	765	VPusAfscugAfaacuucuUfuCfcugugsgsu	1045
AD-2136072.1	asgsgaaaGfaAfGfUfgucagucuuaL96	766	VPusAfsagaCfugacacuUfcUfuuccusgsu	1046

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:
AD-2222883.1	asgsgaaaGfaAfGfUfgucugucuuaL96	767	VPusAfsagaCfagacacuUfcUfuuccusgsu	1047
AD-2136073.1	gsgsaaagAfaGfUfGfucagucuugaL96	768	VPusCfsaagAfcugacacUfuCfuuuccsusg	1048
AD-2136074.1	gsasaagaAfgUfGfUfcagucuuggaL96	769	VPusCfscaaGfacugacaCfuUfcuuucscsu	1049
AD-2136075.1	asasagaaGfuGfUfCfagucuugguaL96	770	VPusAfsccaAfgacugacAfcUfucuuuscsc	1050
AD-2136077.1	asgsaaguGfuCfAfGfucuuggucaaL96	771	VPusUfsgacCfaagacugAfcAfcuucususu	1051
AD-2136079.1	asasguguCfaGfUfCfuuggucaucaL96	772	VPusGfsaugAfccaagacUfgAfcacuuscsu	1052
AD-2222884.1	asasguguCfaGfUfCfuuguucaucaL96	773	VPusGfsaugAfacaagacUfgAfcacuuscsu	1053
AD-2136080.1	asgsugucAfgUfCfUfuggucaucuaL96	774	VPusAfsgauGfaccaagaCfuGfacacususc	1054
AD-2222885.1	asgsugucAfgUfCfUfugguuaucuaL96	775	VPusAfsgauAfaccaagaCfuGfacacususc	1055
AD-2136083.1	gsuscaguCfuUfGfGfucaucuaugaL96	776	VPusCfsauaGfaugaccaAfgAfcugacsasc	1056
AD-2136164.1	gsgsugggAfgUfAfCfugcaaccugaL96	777	VPusCfsaggUfugcaguaCfuCfccaccsusg	1057
AD-2136166.1	usgsggagUfaCfUfGfcaaccugaaaL96	778	VPusUfsucaGfguugcagUfaCfucccascsc	1058
AD-2222886.1	usgsggagUfaCfUfGfcaaucugaaaL96	779	VPusUfsucaGfauugcagUfaCfucccascsc	1059
AD-2136168.1	gsgsaguaCfuGfCfAfaccugaaaaaL96	780	VPusUfsuuuCfagguugcAfgUfacucccsca	1060
AD-2222887.1	gsgsaguaCfuGfCfAfaccuuaaaaaL96	781	VPusUfsuuuAfagguugcAfgUfacucccsca	1061
AD-2136171.1	gsusacugCfaAfCfCfugaaaaaauaL96	782	VPusAfsuuuUfuucagguUfgCfaguacsusc	1062
AD-2136172.1	usascugcAfaCfCfUfgaaaaaaugaL96	783	VPusCfsauuUfuuucaggUfuGfcaguascsu	1063
AD-2136179.1	ascscugaAfaAfAfAfugcucaggaaL96	784	VPusUfsccuGfagcauuuUfuUfcaggususg	1064
AD-2222888.1	ascscugaAfaAfAfAfugcuuaggaaL96	785	VPusUfsccuAfagcauuuUfuUfcaggususg	1065
AD-2136183.1	gsasaaaaAfuGfCfUfcaggaacagaL96	786	VPusCfsuguUfccugagcAfuUfuuuucsasg	1066
AD-2136263.1	asasgaagAfcUfGfUfauguuugggaL96	787	VPusCfsccaAfacauacaGfuCfuucuuscsg	1067
AD-2136347.1	csasgcauUfuUfCfAfcuccagagaaL96	788	VPusUfscucUfggagugaAfaAfugcugsusg	1068
AD-2222889.1	csasgcauUfuUfCfAfcucuagagaaL96	789	VPusUfscucUfagagugaAfaAfugcugsusg	1069
AD-2136348.1	asgscauuUfuCfAfCfuccagagacaL96	790	VPusGfsucuCfuggagugAfaAfaugcusgsu	1070

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:
AD-2222890.1	asgscauuUfuCfAfCfuccugagacaL96	791	VPusGfsucuCfaggagugAfaAfaugcusgsu	1071
AD-2136349.1	gscsauuuUfcAfCfUfccagagacaaL96	792	VPusUfsgucUfcuggaguGfaAfaaugcsusg	1072
AD-2222891.1	gscsauuuUfcAfCfUfccauagacaaL96	793	VPusUfsgucUfauggaguGfaAfaaugcsusg	1073
AD-2136355.1	uscsacucCfaGfAfGfacaaauccaaL96	794	VPusUfsggaUfuugucucUfgGfagugasasa	1074
AD-2136421.1	usasggugGfuCfCfCfuggugcuacaL96	795	VPusGfsuagCfaccagggAfcCfaccuascsa	1075
AD-2222892.1	usasggugGfuCfCfCfugguucuacaL96	796	VPusGfsuagAfaccagggAfcCfaccuascsa	1076
AD-2136431.1	csusggugCfuAfCfAfcgacaaaucaL96	797	VPusGfsauuUfgucguguAfgCfaccagsgsg	1077
AD-2222893.1	csusggugCfuAfCfAfcgauaaaucaL96	798	VPusGfsauuUfaucguguAfgCfaccagsgsg	1078
AD-2136433.1	gsgsugcuAfcAfCfGfacaaauccaaL96	799	VPusUfsggaUfuugucguGfuAfgcaccsasg	1079
AD-2136434.1	gsusgcuaCfaCfGfAfcaaauccaaaL96	800	VPusUfsuggAfuuugucgUfgUfagcacscsa	1080
AD-2222894.1	gsusgcuaCfaCfGfAfcaauuccaaaL96	801	VPusUfsuggAfauugucgUfgUfagcacscsa	1081
AD-2136437.1	csusacacGfaCfAfAfauccaagaaaL96	802	VPusUfsucuUfggauuugUfcGfuguagscsa	1082
AD-2222895.1	csusacacGfaCfAfAfaucuaagaaaL96	803	VPusUfsucuUfagauuugUfcGfuguagscsa	1083
AD-2136438.1	usascacgAfcAfAfAfuccaagaaaaL96	804	VPusUfsuucUfuggauuuGfuCfguguasgsc	1084
AD-2222896.1	usascacgAfcAfAfAfuccuagaaaaL96	805	VPusUfsuucUfaggauuuGfuCfguguasgsc	1085
AD-2136439.1	ascsacgaCfaAfAfUfccaagaaaaaL96	806	VPusUfsuuuCfuuggauuUfgUfcgugusasg	1086
AD-2222897.1	ascsacgaCfaAfAfUfccaugaaaaaL96	807	VPusUfsuuuCfauggauuUfgUfcgugusasg	1087
AD-2136440.1	csascgacAfaAfUfCfcaagaaaacaL96	808	VPusGfsuuuUfcuuggauUfuGfucgugsusa	1088
AD-2222898.1	csascgacAfaAfUfCfcaauaaaacaL96	809	VPusGfsuuuUfauuggauUfuGfucgugsusa	1089
AD-2136442.1	csgsacaaAfuCfCfAfagaaaacuuaL96	810	VPusAfsaguUfuucuuggAfuUfugucgsusg	1090
AD-2136443.1	gsascaaaUfcCfAfAfgaaaacuuuaL96	811	VPusAfsaagUfuuucuugGfaUfuugucsgsu	1091
AD-2222899.1	gsascaaaUfcCfAfAfgaauacuuuaL96	812	VPusAfsaagUfauucuugGfaUfuugucsgsu	1092
AD-2136465.1	gsascuacUfgUfGfAfuguccccucaaL96	813	VPusUfsgagGfgacaucaCfaGfuagucsgsu	1093
AD-2222900.1	gsascuacUfgUfGfAfuguuccucaaL96	814	VPusUfsgagGfaacaucaCfaGfuagucsgsu	1094

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:
AD-2136470.1	csusgugaUfgUfCfCfcucagugugaL96	815	VPusCfsacaCfugagggaCfaUfcacagsusa	1095
AD-2136571.1	ususggaaUfgCfAfCfuucuguggaaL96	816	VPusUfsccaCfagaagugCfaUfuccaasasc	1096
AD-2222901.1	ususggaaUfgCfAfCfuucuuuggaaL96	817	VPusUfsccaAfagaagugCfaUfuccaasasc	1097
AD-2136606.1	usgscccaCfuGfCfUfuggagaaguaL96	818	VPusAfscuuCfuccaagcAfgUfgggcasgsc	1098
AD-2222902.1	usgscccaCfuGfCfUfuggugaaguaL96	819	VPusAfscuuCfaccaagcAfgUfgggcasgsc	1099
AD-2136716.1	asasagauAfuUfGfCfcuugcuaaaaL96	820	VPusUfsuuaGfcaaggcaAfuAfucuuususc	1100
AD-2222903.1	asasagauAfuUfGfCfcuuucuaaaaL96	821	VPusUfsuuaGfaaaggcaAfuAfucuuususc	1101
AD-2136717.1	asasgauaUfuGfCfCfuugcuaaagaL96	822	VPusCfsuuuAfgcaaggcAfaUfaucuususu	1102
AD-2136718.3	asgsauauUfgCfCfUfugcuaaagcaL96	823	VPusGfscuuUfagcaaggCfaAfuaucususu	1103
AD-2136721.1	usasuugcCfuUfGfCfuaaagcuaaaL96	824	VPusUfsuagCfuuuagcaAfgGfcaauasusc	1104
AD-2136726.1	cscsuugcUfaAfAfGfcuaagcaguaL96	825	VPusAfscugCfuuagcuuUfaGfcaaggscsa	1105
AD-2222905.1	cscsuugcUfaAfAfGfcuaugcaguaL96	826	VPusAfscugCfauagcuuUfaGfcaaggscsa	1106
AD-2136729.1	usgscuaaAfgCfUfAfagcaguccuaL96	827	VPusAfsggaCfugcuuagCfuUfuagcasasg	1107
AD-2222906.1	usgscuaaAfgCfUfAfagcuguccuaL96	828	VPusAfsggaCfagcuuagCfuUfuagcasasg	1108
AD-2136753.1	uscsaucaCfuGfAfCfaaaguaaucaL96	829	VPusGfsauuAfcuuugucAfgUfgaugascsg	1109
AD-2136754.1	csasucacUfgAfCfAfaaguaauccaL96	830	VPusGfsgauUfacuuuguCfaGfugaugsasc	1110
AD-2136755.1	asuscacuGfaCfAfAfaguaaucccaL96	831	VPusGfsggaUfuacuuugUfcAfgugausgsa	1111
AD-2136756.1	uscsacugAfcAfAfAfguaaucccaaL96	832	VPusUfsgggAfuuacuuuGfuCfagugasusg	1112
AD-2222907.1	uscsacugAfcAfAfAfguauucccaaL96	833	VPusUfsgggAfauacuuuGfuCfagugasusg	1113
AD-2136757.1	csascugaCfaAfAfGfuaaucccagaL96	834	VPusCfsuggGfauuacuuUfgUfcagugsasu	1114
AD-2222908.1	csascugaCfaAfAfGfuaauuccagaL96	835	VPusCfsuggAfauuacuuUfgUfcagugsasu	1115
AD-2136758.1	ascsugacAfaAfGfUfaaucccagcaL96	836	VPusGfscugGfgauuacuUfuGfucagusgsa	1116
AD-2222909.1	ascsugacAfaAfGfUfaauuccagcaL96	837	VPusGfscugGfaauuacuUfuGfucagusgsa	1117
AD-2136760.1	usgsacaaAfgUfAfAfucccagcuuaL96	838	VPusAfsagcUfgggauuaCfuUfugucasgsu	1118

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:
AD-2222910.1	usgsacaaAfgUfAfAfuccuagcuuaL96	839	VPusAfsagcUfaggauuaCfuUfugucasgsu	1119
AD-2136761.1	gsascaaaGfuAfAfUfcccagcuugaL96	840	VPusCfsaagCfugggauuAfcUfuugucsasg	1120
AD-2136762.1	ascsaaagUfaAfUfCfccagcuuguaL96	841	VPusAfscaaGfcugggauUfaCfuuuguscsa	1121
AD-2222911.1	ascsaaagUfaAfUfCfccaucuuguaL96	842	VPusAfscaaGfaugggauUfaCfuuuguscsa	1122
AD-2136763.1	csasaaguAfaUfCfCfcagcuugucaL96	843	VPusGfsacaAfgcugggaUfuAfcuuugsusc	1123
AD-2136764.1	asasaguaAfuCfCfCfagcuugucuaL96	844	VPusAfsgacAfagcugggAfuUfacuuusgsu	1124
AD-2136787.1	csusgaccGfgAfCfCfgaauguuucaL96	845	VPusGfsaaaCfauucgguCfcGfgucagscsg	1125
AD-2222912.1	csusgaccGfgAfCfCfgaauuuuucaL96	846	VPusGfsaaaAfauucgguCfcGfgucagscsg	1126
AD-2136790.1	ascscggaCfcGfAfAfuguuucaucaL96	847	VPusGfsaugAfaacauucGfgUfccgguscsa	1127
AD-2136791.1	cscsggacCfgAfAfUfguuucaucaaL96	848	VPusUfsgauGfaaacauuCfgGfuccggsusc	1128
AD-2222913.1	cscsggacCfgAfAfUfguuuuaucaaL96	849	VPusUfsgauAfaaacauuCfgGfuccggsusc	1129
AD-2136792.1	csgsgaccGfaAfUfGfuuucaucacaL96	850	VPusGfsugaUfgaaacauUfcGfguccgsgsu	1130
AD-2222914.1	csgsgaccGfaAfUfGfuuuuaucacaL96	851	VPusGfsugaUfaaaacauUfcGfguccgsgsu	1131
AD-2136793.1	gsgsaccgAfaUfGfUfuucaucacuaL96	852	VPusAfsgugAfugaaacaUfuCfgguccsgsg	1132
AD-2222915.1	gsgsaccgAfaUfGfUfuucuucacuaL96	853	VPusAfsgugAfagaaacaUfuCfgguccsgsg	1133
AD-2136794.1	gsasccgaAfuGfUfUfucaucacugaL96	854	VPusCfsaguGfaugaaacAfuUfcggucscsg	1134
AD-2222916.1	gsasccgaAfuGfUfUfucauuacugaL96	855	VPusCfsaguAfaugaaacAfuUfcggucscsg	1135
AD-2136797.1	csgsaaugUfuUfCfAfucacuggcuaL96	856	VPusAfsgccAfgugaugaAfaCfauucgsgsu	1136
AD-2222917.1	csgsaaugUfuUfCfAfucauuggcuaL96	857	VPusAfsgccAfaugaugaAfaCfauucgsgsu	1137
AD-2136851.1	csusgugaUfuGfAfGfaauaaagugaL96	858	VPusCfsacuUfuauucucAfaUfcacagsgsg	1138
AD-2136852.1	usgsugauUfgAfGfAfauaaaguguaL96	859	VPusAfscacUfuuauucuCfaAfucacasgsg	1139
AD-2136853.1	gsusgauuGfaGfAfAfuaaagugugaL96	860	VPusCfsacaCfuuuauucUfcAfaucacsasg	1140
AD-2136854.1	usgsauugAfgAfAfUfaaagugugcaL96	861	VPusGfscacAfcuuuauuCfuCfaaucascsa	1141
AD-2136855.1	gsasuugaGfaAfUfAfaagugugcaaL96	862	VPusUfsgcaCfacuuuauUfcUfcaaucsasc	1142

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:
AD-2222918.1	gsasuugaGfaAfUfAfaaguuugcaaL96	863	VPusUfsgcaAfacuuuauUfcUfcaaucsasc	1143
AD-2136857.1	ususgagaAfuAfAfAfgugugcaauaL96	864	VPusAfsuugCfacacuuuAfuUfcucaasusc	1144
AD-2222919.1	ususgagaAfuAfAfAfguguucaauaL96	865	VPusAfsuugAfacacuuuAfuUfcucaasusc	1145
AD-2136859.1	gsasgaauAfaAfGfUfgugcaaucgaL96	866	VPusCfsgauUfgcacacuUfuAfuucucsasa	1146
AD-2222920.1	gsasgaauAfaAfGfUfguguaaucgaL96	867	VPusCfsgauUfacacacuUfuAfuucucsasa	1147
AD-2136861.1	gsasauaaAfgUfGfUfgcaaucgcuaL96	868	VPusAfsgcgAfuugcacaCfuUfuauucsusc	1148
AD-2136862.1	asasuaaaGfuGfUfGfcaaucgcuaaL96	869	VPusUfsagcGfauugcacAfcUfuuauuscsu	1149
AD-2136864.1	usasaaguGfuGfCfAfaucgcuaugaL96	870	VPusCfsauaGfcgauugcAfcAfcuuuasusu	1150
AD-2136865.1	asasagugUfgCfAfAfucgcuaugaaL96	871	VPusUfscauAfgcgauugCfaCfacuuusasu	1151
AD-2222921.1	asasagugUfgCfAfAfucguuaugaaL96	872	VPusUfscauAfacgauugCfaCfacuuusasu	1152
AD-2136866.1	asasguguGfcAfAfUfcgcuaugagaL96	873	VPusCfsucaUfagcgauuGfcAfcacuususa	1153
AD-2136867.1	asgsugugCfaAfUfCfgcuaugaguaL96	874	VPusAfscucAfuagcgauUfgCfacacususu	1154
AD-2136868.1	gsusgugcAfaUfCfGfcuaugaguuaL96	875	VPusAfsacuCfauagcgaUfuGfcacacsusu	1155
AD-2222922.1	gsusgugcAfaUfCfGfcuauuaguuaL96	876	VPusAfsacuAfauagcgaUfuGfcacacsusu	1156
AD-2136869.1	usgsugcaAfuCfGfCfuaugaguuuaL96	877	VPusAfsaacUfcauagcgAfuUfgcacascsu	1157
AD-2222923.1	usgsugcaAfuCfGfCfuauuaguuuaL96	878	VPusAfsaacUfaauagcgAfuUfgcacascsu	1158
AD-2136870.1	gsusgcaaUfcGfCfUfaugaguuucaL96	879	VPusGfsaaaCfucauagcGfaUfugcacsasc	1159
AD-2222924.1	gsusgcaaUfcGfCfUfauguguuucaL96	880	VPusGfsaaaCfacauagcGfaUfugcacsasc	1160
AD-2136871.1	usgscaauCfgCfUfAfugaguuucuaL96	881	VPusAfsgaaAfcucauagCfgAfuugcascsa	1161
AD-2136873.1	csasaucgCfuAfUfGfaguuucugaaL96	882	VPusUfscagAfaacucauAfgCfgauugscsa	1162
AD-2136874.1	asasucgcUfaUfGfAfguuucugaaaL96	883	VPusUfsucaGfaaacucaUfaGfcgauusgsc	1163
AD-2222925.1	asasucgcUfaUfGfAfguuuuugaaaL96	884	VPusUfsucaAfaaacucaUfaGfcgauusgsc	1164
AD-2136875.1	asuscgcuAfuGfAfGfuuucugaauaL96	885	VPusAfsuucAfgaaacucAfuAfgcgaususg	1165
AD-2222926.1	asuscgcuAfuGfAfGfuuuuugaauaL96	886	VPusAfsuucAfaaaacucAfuAfgcgaususg	1166

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:
AD-2136876.1	uscsgcuaUfgAfGfUfuucugaaugaL96	887	VPusCfsauuCfagaaacuCfaUfagcgasusu	1167
AD-2222927.1	uscsgcuaUfgAfGfUfuucuuaaugaL96	888	VPusCfsauuAfagaaacuCfaUfagcgasusu	1168
AD-2136877.1	csgscuauGfaGfUfUfucugaauggaL96	889	VPusCfscauUfcagaaacUfcAfuagcgsasu	1169
AD-2136878.1	gscsuaugAfgUfUfUfcugaauggaaL96	890	VPusUfsccaUfucagaaaCfuCfauagcsgsa	1170
AD-2136879.1	csusaugaGfuUfUfCfugaauggaaaL96	891	VPusUfsuccAfuucagaaAfcUfcauagscsg	1171
AD-2222928.1	csusaugaGfuUfUfCfugauuggaaaL96	892	VPusUfsuccAfaucagaaAfcUfcauagscsg	1172
AD-2136880.1	usasugagUfuUfCfUfgaauggaagaL96	893	VPusCfsuucCfauucagaAfaCfucauasgsc	1173
AD-2222929.1	usasugagUfuUfCfUfgaauugaagaL96	894	VPusCfsuucAfauucagaAfaCfucauasgsc	1174
AD-2136882.1	usgsaguuUfcUfGfAfauggaagagaL96	895	VPusCfsucuUfccauucaGfaAfacucasusa	1175
AD-2136883.1	gsasguuuCfuGfAfAfuggaagaguaL96	896	VPusAfscucUfuccauucAfgAfaacucsasu	1176
AD-2222930.1	gsasguuuCfuGfAfAfugguagaguaL96	897	VPusAfscucUfaccauucAfgAfaacucsasu	1177
AD-2136992.1	csusucgaGfaAfGfGfacaaauacaaL96	898	VPusUfsguaUfuuguccuUfcUfcgaagscsa	1178
AD-2136993.1	ususcgagAfaGfGfAfcaaauacauaL96	899	VPusAfsuguAfuuuguccUfuCfucgaasgsc	1179
AD-2136994.1	uscsgagaAfgGfAfCfaaauacauuaL96	900	VPusAfsaugUfauuugucCfuUfcucgasasg	1180
AD-2222931.1	uscsgagaAfgGfAfCfaaauucauuaL96	901	VPusAfsaugAfauuugucCfuUfcucgasasg	1181
AD-2136995.1	csgsagaaGfgAfCfAfaauacauuuaL96	902	VPusAfsaauGfuauuuguCfcUfucucgsasa	1182
AD-2222932.1	csgsagaaGfgAfCfAfaauucauuuaL96	903	VPusAfsaauGfaauuuguCfcUfucucgsasa	1183
AD-2136996.1	gsasgaagGfaCfAfAfauacauuuuaL96	904	VPusAfsaaaUfguauuugUfcCfuucucsgsa	1184
AD-2136997.1	asgsaaggAfcAfAfAfuacauuuuaaL96	905	VPusUfsaaaAfuguauuuGfuCfcuucuscsg	1185
AD-2136998.1	gsasaggaCfaAfAfUfacauuuuacaL96	906	VPusGfsuaaAfauguauuUfgUfccuucsusc	1186
AD-2136999.1	asasggacAfaAfUfAfcauuuuacaaL96	907	VPusUfsguaAfaauguauUfuGfuccuuscsu	1187
AD-2137000.1	asgsgacaAfaUfAfCfauuuuacaaaL96	908	VPusUfsuguAfaaauguaUfuUfguccususc	1188
AD-2137001.1	gsgsacaaAfuAfCfAfuuuuacaagaL96	909	VPusCfsuugUfaaaauguAfuUfuguccsusu	1189
AD-2137002.1	gsascaaaUfaCfAfUfuuuacaaggaL96	910	VPusCfscuuGfuaaaaugUfaUfuugucscsu	1190

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:
AD-2222933.1	gsascaaaUfaCfAfUfuuuucaaggaL96	911	VPusCfscuuGfaaaaaugUfaUfuugucscsu	1191
AD-2137016.3	csusggugUfcUfAfUfguucguguuaL96	912	VPusAfsacaCfgaacauaGfaCfaccagsgsc	1192
AD-2137017.3	usgsguguCfuAfUfGfuucguguuuaL96	913	VPusAfsaacAfcgaacauAfgAfcaccasgsg	1193
AD-2137018.5	gsgsugucUfaUfGfUfucguguuucaL96	914	VPusGfsaaaCfacgaacaUfaGfacaccsasg	1194
AD-2222934.1	gsgsugucUfaUfGfUfucguuuuucaL96	915	VPusGfsaaaAfacgaacaUfaGfacaccsasg	1195
AD-2137019.1	gsusgucuAfuGfUfUfcguguuucaaL96	916	VPusUfsgaaAfcacgaacAfuAfgacacscsa	1196
AD-2137020.1	usgsucuaUfgUfUfCfguguuucaaaL96	917	VPusUfsugaAfacacgaaCfaUfagacascsc	1197
AD-2137021.1	gsuscuauGfuUfCfGfuguuucaagaL96	918	VPusCfsuugAfaacacgaAfcAfuagacsasc	1198
AD-2137022.1	uscsuaugUfuCfGfUfguuucaaggaL96	919	VPusCfscuuGfaaacacgAfaCfauagascsa	1199
AD-2137023.1	csusauguUfcGfUfGfuuucaagguaL96	920	VPusAfsccuUfgaaacacGfaAfcauagsasc	1200
AD-2137024.1	usasuguuCfgUfGfUfuucaagguuaL96	921	VPusAfsaccUfugaaacaCfgAfacauasgsa	1201
AD-2137025.1	asusguucGfuGfUfUfucaagguuuaL96	922	VPusAfsaacCfuugaaacAfcGfaacausasg	1202
AD-2137026.1	usgsuucgUfgUfUfUfcaagguuugaL96	923	VPusCfsaaaCfcuugaaaCfaCfgaacasusa	1203
AD-2137027.1	gsusucguGfuUfUfCfaagguuuguaL96	924	VPusAfscaaAfccuugaaAfcAfcgaacsasu	1204
AD-2137055.1	ususgaggGfaGfUfGfaugagaaauaL96	925	VPusAfsuuuCfucaucacUfcCfcucaasusc	1205
AD-2222935.1	ususgaggGfaGfUfGfaugugaaauaL96	926	VPusAfsuuuCfacaucacUfcCfcucaasusc	1206
AD-2137056.1	usgsagggAfgUfGfAfugagaaauaaL96	927	VPusUfsauuUfcucaucaCfuCfccucasasu	1207
AD-2222936.1	usgsagggAfgUfGfAfugauaaauaaL96	928	VPusUfsauuUfaucaucaCfuCfccucasasu	1208
AD-2137057.1	gsasgggaGfuGfAfUfgagaaauaaaL96	929	VPusUfsuauUfucucaucAfcUfcccucsasa	1209
AD-2222937.1	gsasgggaGfuGfAfUfgaguaauaaaL96	930	VPusUfsuauUfacucaucAfcUfcccucsasa	1210
AD-2137059.1	gsgsgaguGfaUfGfAfgaaauaauuaL96	931	VPusAfsauuAfuuucucaUfcAfcucccsusc	1211
AD-2137061.1	gsasgugaUfgAfGfAfaauaauuaaaL96	932	VPusUfsuaaUfuauuucuCfaUfcacucscsc	1212
AD-2222939.1	gsusgaugAfgAfAfAfuaauuaauuaL96	933	VPusAfsauuAfauuauuuCfuCfaucacsusc	1213
AD-2222940.1	usgsaugaGfaAfAfUfaauuaauugaL96	934	VPusCfsaauUfaauuauuUfcUfcaucascsu	1214

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:
AD-2137062.1	gsasugagAfaAfUfAfauuaauuggaL96	935	VPusCfscaaUfuaauuauUfuCfucaucsasc	1215
AD-2137063.1	asusgagaAfaUfAfAfuuaauuggaaL96	936	VPusUfsccaAfuuaauuaUfuUfcucauscsa	1216
AD-2137101.1	ascsugacUfcAfCfCfuagaggcugaL96	937	VPusCfsagcCfucuagguGfaGfucagusgsc	1217
AD-2137128.1	gsgsuaggGfaUfUfUfagcaugcugaL96	938	VPusCfsagcAfugcuaaaUfcCfcuaccscsa	1218
AD-2137130.1	usasgggaUfuUfAfGfcaugcuggaaL96	939	VPusUfsccaGfcaugcuaAfaUfcccuascsc	1219
AD-2137138.1	usasgcauGfcUfGfGfaaauaacugaL96	940	VPusCfsaguUfauuuccaGfcAfugcuasasa	1220
AD-2137196.1	usgsuuauUfuUfCfUfgacugcuggaL96	941	VPusCfscagCfagucagaAfaAfuaacascsa	1221
AD-2222942.1	usgsuuauUfuUfCfUfgacuucuggaL96	942	VPusCfscagAfagucagaAfaAfuaacascsa	1222
AD-2137197.1	gsusuauuUfuCfUfGfacugcuggaaL96	943	VPusUfsccaGfcagucagAfaAfauaacsasc	1223
AD-2222943.1	gsusuauuUfuCfUfGfacuucuggaaL96	944	VPusUfsccaGfaagucagAfaAfauaacsasc	1224
AD-2137198.1	ususauuuUfcUfGfAfcugcuggauaL96	945	VPusAfsuccAfgcagucaGfaAfaauaascsa	1225
AD-2222944.1	ususauuuUfcUfGfAfcuguuggauaL96	946	VPusAfsuccAfacagucaGfaAfaauaascsa	1226
AD-2137199.1	usasuuuuCfuGfAfCfugcuggauuaL96	947	VPusAfsaucCfagcagucAfgAfaaauasasc	1227
AD-2222945.1	usasuuuuCfuGfAfCfugcuugauuaL96	948	VPusAfsaucAfagcagucAfgAfaaauasasc	1228
AD-2137200.1	asususuucUfgAfCfUfgcuggauucaL96	949	VPusGfsaauCfcagcaguCfaGfaaaausasa	1229
AD-2222946.1	asususuucUfgAfCfUfgcuugauucaL96	950	VPusGfsaauCfaagcaguCfaGfaaaausasa	1230
AD-2137204.1	uscsugacUfgCfUfGfgauucuguaaL96	951	VPusUfsacaGfaauccagCfaGfucagasasa	1231
AD-2137223.1	asgsuaagGfuGfAfCfauagcuaugaL96	952	VPusCfsauaGfcuaugucAfcCfuuacusasc	1232
AD-2137224.1	gsusaaggUfgAfCfAfuagcuaugaaL96	953	VPusUfscauAfgcuauguCfaCfcuuacsusa	1233
AD-2222947.1	gsusaaggUfgAfCfAfuaguuaugaaL96	954	VPusUfscauAfacuauguCfaCfcuuacsusa	1234
AD-2137225.1	usasagguGfaCfAfUfagcuaugacaL96	955	VPusGfsucaUfagcuaugUfcAfccuuascsu	1235
AD-2222949.1	ascsauuuGfuUfAfAfaaauaaacuaL96	956	VPusAfsguuUfauuuuuaAfcAfaauguscsa	1236
AD-2138055	ccucugGfaUfGfAfcuaugugaaa	957	PuUfucaCfauagucaUfcCfagaggcu	1237
AD-2138237	acauucCfuUfCfCfaaauuuccaa	958	PuUfggaAfauuuggaAfgGfaauguau	1238

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:
AD-2138262	gaaccuGfaAfGfAfagaauuacua	959	PuAfguaAfuucuucuUfcAfgguucuu	1239
AD-2138349	ccugcaAfaAfAfUfuuggaugaaa	960	PuUfucaUfccaaauuUfuUfgcagggg	1240
AD-2138441	aggaaaGfaAfGfUfgucagucuua	961	PuAfagaCfugacacuUfcUfuuccugu	1241
AD-2138656	cugaccGfgAfCfCfgaauguuuca	962	PuGfaaaCfauucgguCfcGfgucagcg	1242
AD-2138710	ugcaauCfgCfUfAfugaguuucua	963	PuAfgaaAfcucauagCfgAfuugcaca	1243
AD-2138754	ggugucUfaUfGfUfucguguuuca	964	PuGfaaaCfacgaacaUfaGfacaccag	1244
AD-2138755	gugucuAfuGfUfUfcguguuucaa	965	PuUfgaaAfcacgaacAfuAfgacacca	1245
AD-2138756	ugucuaUfgUfUfCfguguuucaaa	966	PuUfugaAfacacgaaCfaUfagacacc	1246
AD-2138789	gagugaUfgAfGfAfaauaauuaaa	967	PuUfuaaUfuauuucuCfaUfcacuccc	1247
AD-2138792	ugaugaGfaAfAfUfaauuaauuga	968	PuCfaauUfaauuauuUfcUfcaucacu	1248
AD-2138794	augagaAfaUfAfAfuuaauuggaa	969	PuUfccaAfuuaauuaUfuUfcucauca	1249
AD-2138742	aaggacAfaAfUfAfcauuuuacaa	970	PuUfguaAfaauguauUfuGfuccuucu	1250
AD-2315876	cscsucugGfaUfGfAfcuaugugaaaL96	696	usUfsucaCfauagucaUfcCfagaggscsu	1251
AD-2315885	ascsauucCfuUfCfCfaaauuuccaaL96	714	usUfsggaAfauuuggaAfgGfaaugusasu	1252
AD-2315882	gsasaccuGfaAfGfAfagaauuacuaL96	733	usAfsguaAfuucuucuUfcAfgguucsusu	1253
AD-2315883	cscsugcaAfaAfAfUfuuguaugaaaL96	744	usUfsucaUfacaaauuUfuUfgcaggsgsg	1254
AD-2315887	asgsgaaaGfaAfGfUfgucagucuuaL96	766	usAfsagaCfugacacuUfcUfuuccusgsu	1255
AD-2315880	csusgaccGfgAfCfCfgaauguuucaL96	845	usGfsaaaCfauucgguCfcGfgucagscsg	1256
AD-2315878	usgscaauCfgCfUfAfugaguuucuaL96	881	usAfsgaaAfcucauagCfgAfuugcascsa	1257
AD-2315874	gsgsugucUfaUfGfUfucguguuucaL96	914	usGfsaaaCfacgaacaUfaGfacaccsasg	1258
AD-2315884	gsusgucuAfuGfUfUfcguguuucaaL96	916	usUfsgaaAfcacgaacAfuAfgacacscsa	1259
AD-2315886	usgsucuaUfgUfUfCfguguuucaaaL96	917	usUfsugaAfacacgaaCfaUfagacascsc	1260
AD-2315877	gsasgugaUfgAfGfAfaauaauuaaaL96	932	usUfsuaaUfuauuucuCfaUfcacucscsc	1261
AD-2315881	usgsaugaGfaAfAfUfaauuaauugaL96	934	usCfsaauUfaauuauuUfcUfcaucascsu	1262

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:
AD-2315879	asusgagaAfaUfAfAfuuaauuggaaL96	936	usUfsccaAfuuaauuaUfuUfcucauscsa	1263
AD-2315875	asasggacAfaAfUfAfcauuuuacaaL96	907	usUfsguaAfaauguauUfuGfuccuuscsu	1264

Table 7. Unmodified Sense and Antisense Strand Sequences of Selected Human PLG dsRNA Agents

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:
AD-2137018.5/ AD-2315874	GGUGUCUAUGU UCGUGUUUCA	1273	UGAAACACGAAC AUAGACACCAG	1287
AD-2136999.1/ AD-2315875	AAGGACAAAUAC AUUUUACAA	1274	UUGUAAAAUGUA UUUGUCCUUCU	1288
AD-2134687.1/ AD-2315876	CCUCUGGAUGAC UAUGUGAAA	1275	UUUCACAUAGUC AUCCAGAGGCU	1289
AD-2137061.1/ AD-2315877	GAGUGAUGAGA AAUAAUUAAA	1276	UUUAAUUAUUUC UCAUCACUCCC	1290
AD-2136871.1/ AD-2315878	UGCAAUCGCUAU GAGUUUCUA	1277	UAGAAACUCAUA GCGAUUGCACA	1291
AD-2137063.1/ AD-2315879	AUGAGAAAUAA UUAAUUGGAA	1278	UUCCAAUUAAUU AUUUCUCAUCA	1292
AD-2136787.1/ AD-2315880	CUGACCGGACCG AAUGUUUCA	1279	UGAAACAUUCGG UCCGGUCAGCG	1293
AD-2222940.1/ AD-2315881	UGAUGAGAAAU AAUUAAUUGA	1280	UCAAUUAAUUAU UUCUCAUCACU	1294
AD-2135737.1/ AD-2315882	GAACCUGAAGAA GAAUUACUA	1281	UAGUAAUUCUUC UUCAGGUUCUU	1295
AD-2222874.1/ AD-2315883	CCUGCAAAAAUU UGUAUGAAA	1282	UUUCAUACAAAU UUUUGCAGGGG	1296
AD-2137019.1/ AD-2315884	GUGUCUAUGUUC GUGUUUCAA	1283	UUGAAACACGAA CAUAGACACCA	1297
AD-2135712.1/ AD-2315885	ACAUUCCUUCCA AAUUUCCAA	1284	UUGGAAAUUUGG AAGGAAUGUAU	1298
AD-2137020.1/ AD-2315886	UGUCUAUGUUCG UGUUUCAAA	1285	UUUGAAACACGA ACAUAGACACC	1299
AD-2136072.1/ AD-2315887	AGGAAAGAAGU GUCAGUCUUA	1286	UAAGACUGACAC UUCUUUCCUGU	1300

Table 8A. Additional Unmodified Sense and Antisense Strands of Human PLG dsRNA Agents

Duplex ID	Sense Sequence	SEQ ID NO	Antisense Sequence	SEQ ID NO
AD-2138040.1	GGACCCACUUUCUGGGCACUA	1265	UAGUGCCCAGAAAGUGGGUCCCA	1815
AD-2138041.1	GACCCACUUUCUGGGCACUGA	1266	UCAGUGCCCAGAAAGUGGGUCCC	1816
AD-2138042.1	ACCCACUUUCUGGGCACUGCA	1267	UGCAGUGCCCAGAAAGUGGGUCC	1817
AD-2138043.1	CAGUCCCAAAAUGGAACAUAA	1268	UUAUGUUCCAUUUUGGGACUGGC	1818
AD-2138044.1	AGUCCCAAAAUGGAACAUAAA	1269	UUUAUGUUCCAUUUUGGGACUGG	1819
AD-2138045.1	GUCCCAAAAUGGAACAUAAGA	1270	UCUUAUGUUCCAUUUUGGGACUG	1820
AD-2138046.1	UCCCAAAAUGGAACAUAAGGA	1271	UCCUUAUGUUCCAUUUUGGGACU	1821
AD-2138047.1	CCCAAAAUGGAACAUAAGGAA	1272	UUCCUUAUGUUCCAUUUUGGGAC	1822
AD-2138048.1	CCAAAAUGGAACAUAAGGAAA	1273	UUUCCUUAUGUUCCAUUUUGGGA	1823
AD-2138049.1	CAAAAUGGAACAUAAGGAAGA	1274	UCUUCCUUAUGUUCCAUUUUGGG	1824
AD-2138050.1	AAAAUGGAACAUAAGGAAGUA	1275	UACUUCCUUAUGUUCCAUUUUGG	1825
AD-2138051.1	AAAUGGAACAUAAGGAAGUGA	1276	UCACUUCCUUAUGUUCCAUUUUG	1826
AD-2138052.1	AAUGGAACAUAAGGAAGUGGA	1277	UCCACUUCCUUAUGUUCCAUUUU	1827
AD-2138053.1	AUGGAACAUAAGGAAGUGGUA	1278	UACCACUUCCUUAUGUUCCAUUU	1828
AD-2138054.1	UGGAACAUAAGGAAGUGGUUA	1279	UAACCACUUCCUUAUGUUCCAUU	1829
AD-2138055.1	CCUCUGGAUGACUAUGUGAAA	1280	UUUCACAUAGUCAUCCAGAGGCU	1830
AD-2138056.1	UAAGAAGCAGCUGGGAGCAGA	1281	UCUGCUCCCAGCUGCUUCUUAGU	1831
AD-2138057.1	AGCAGCUGGGAGCAGGAAGUA	1282	UACUUCCUGCUCCCAGCUGCUUC	1832
AD-2138059.1	AGCUGGGAGCAGGAAGUAUAA	1283	UUAUACUUCCUGCUCCCAGCUGC	1833
AD-2138060.1	CUGGGAGCAGGAAGUAUAGAA	1284	UUCUAUACUUCCUGCUCCCAGCU	1834
AD-2138061.1	UGGGAGCAGGAAGUAUAGAAA	1285	UUUCUAUACUUCCUGCUCCCAGC	1835
AD-2138062.1	GGGAGCAGGAAGUAUAGAAGA	1286	UCUUCUAUACUUCCUGCUCCCAG	1836
AD-2138063.1	GGAGCAGGAAGUAUAGAAGAA	1287	UUCUUCUAUACUUCCUGCUCCCA	1837
AD-2138064.1	GAGCAGGAAGUAUAGAAGAAA	1288	UUUCUUCUAUACUUCCUGCUCCC	1838
AD-2138065.1	AGCAGGAAGUAUAGAAGAAUA	1289	UAUUCUUCUAUACUUCCUGCUCC	1839
AD-2138066.1	GCAGGAAGUAUAGAAGAAUGA	1290	UCAUUCUUCUAUACUUCCUGCUC	1840
AD-2138067.1	CAGGAAGUAUAGAAGAAUGUA	1291	UACAUUCUUCUAUACUUCCUGCU	1841
AD-2138068.1	AGGAAGUAUAGAAGAAUGUGA	1292	UCACAUUCUUCUAUACUUCCUGC	1842
AD-2138069.1	GGAAGUAUAGAAGAAUGUGCA	1293	UGCACAUUCUUCUAUACUUCCUG	1843
AD-2138070.1	GAAGUAUAGAAGAAUGUGCAA	1294	UUGCACAUUCUUCUAUACUUCCU	1844
AD-2138071.1	AAGUAUAGAAGAAUGUGCAGA	1295	UCUGCACAUUCUUCUAUACUUCC	1845
AD-2138072.1	AGUAUAGAAGAAUGUGCAGCA	1296	UGCUGCACAUUCUUCUAUACUUC	1846
AD-2138073.1	GUAUAGAAGAAUGUGCAGCAA	1297	UUGCUGCACAUUCUUCUAUACUU	1847
AD-2138074.1	UAUAGAAGAAUGUGCAGCAAA	1298	UUUGCUGCACAUUCUUCUAUACU	1848
AD-2138075.1	UCCAAUAUCACAGUAAAGAGA	1299	UCUCUUUACUGUGAUAUUGGAAU	1849
AD-2138076.1	CCAAUAUCACAGUAAAGAGCA	1300	UGCUCUUUACUGUGAUAUUGGAA	1850
AD-2138077.1	CAAUAUCACAGUAAAGAGCAA	1301	UUGCUCUUUACUGUGAUAUUGGA	1851
AD-2138078.1	AAUAUCACAGUAAAGAGCAAA	1302	UUUGCUCUUUACUGUGAUAUUGG	1852
AD-2138079.1	AUAUCACAGUAAAGAGCAACA	1303	UGUUGCUCUUUACUGUGAUAUUG	1853
AD-2138080.1	UAUCACAGUAAAGAGCAACAA	1304	UUGUUGCUCUUUACUGUGAUAUU	1854

Duplex ID	Sense Sequence	SEQ ID NO	Antisense Sequence	SEQ ID NO
AD-2138081.1	AUCACAGUAAAGAGCAACAAA	1305	UUUGUUGCUCUUUACUGUGAUAU	1855
AD-2138082.1	UCACAGUAAAGAGCAACAAUA	1306	UAUUGUUGCUCUUUACUGUGAUA	1856
AD-2138083.1	CACAGUAAAGAGCAACAAUGA	1307	UCAUUGUUGCUCUUUACUGUGAU	1857
AD-2138084.1	ACAGUAAAGAGCAACAAUGUA	1308	UACAUUGUUGCUCUUUACUGUGA	1858
AD-2138085.1	CAGUAAAGAGCAACAAUGUGA	1309	UCACAUUGUUGCUCUUUACUGUG	1859
AD-2138086.1	AGUAAAGAGCAACAAUGUGUA	1310	UACACAUUGUUGCUCUUUACUGU	1860
AD-2138087.1	GGAUGAGAGAUGUAGUUUUAA	1311	UUAAAACUACAUCUCUCAUCCUA	1861
AD-2138088.1	GAUGAGAGAUGUAGUUUUAUA	1312	UAUAAAACUACAUCUCUCAUCCU	1862
AD-2138089.1	AUGAGAGAUGUAGUUUUAUUA	1313	UAAUAAAACUACAUCUCUCAUCC	1863
AD-2138090.1	UGAGAGAUGUAGUUUUAUUUA	1314	UAAAUAAAACUACAUCUCUCAUC	1864
AD-2138091.1	GAGAGAUGUAGUUUUAUUUGA	1315	UCAAAUAAAACUACAUCUCUCAU	1865
AD-2138092.1	AGAGAUGUAGUUUUAUUUGAA	1316	UUCAAAUAAAACUACAUCUCUCA	1866
AD-2138093.1	GAGAUGUAGUUUUAUUUGAAA	1317	UUUCAAAUAAAACUACAUCUCUC	1867
AD-2138094.1	AGAUGUAGUUUUAUUUGAAAA	1318	UUUUCAAAUAAAACUACAUCUCU	1868
AD-2138095.1	GAUGUAGUUUUAUUUGAAAAA	1319	UUUUUCAAAUAAAACUACAUCUC	1869
AD-2138096.1	AUGUAGUUUUAUUUGAAAAGA	1320	UCUUUUCAAAUAAAACUACAUCU	1870
AD-2138097.1	UGUAGUUUUAUUUGAAAAGAA	1321	UUCUUUUCAAAUAAAACUACAUC	1871
AD-2138098.1	GUAGUUUUAUUUGAAAAGAAA	1322	UUUCUUUUCAAAUAAAACUACAU	1872
AD-2138099.1	UGAAAAGAAAGUGUAUCUCUA	1323	UAGAGAUACACUUUCUUUUCAAA	1873
AD-2138100.1	GAAAAGAAAGUGUAUCUCUCA	1324	UGAGAGAUACACUUUCUUUUCAA	1874
AD-2138101.1	AAAAGAAAGUGUAUCUCUCAA	1325	UUGAGAGAUACACUUUCUUUUCA	1875
AD-2138102.1	AAAGAAAGUGUAUCUCUCAGA	1326	UCUGAGAGAUACACUUUCUUUUC	1876
AD-2138103.1	AAGAAAGUGUAUCUCUCAGAA	1327	UUCUGAGAGAUACACUUUCUUUU	1877
AD-2138104.1	AGAAAGUGUAUCUCUCAGAGA	1328	UCUCUGAGAGAUACACUUUCUUU	1878
AD-2138105.1	GAAAGUGUAUCUCUCAGAGUA	1329	UACUCUGAGAGAUACACUUUCUU	1879
AD-2138106.1	AAAGUGUAUCUCUCAGAGUGA	1330	UCACUCUGAGAGAUACACUUUCU	1880
AD-2138107.1	AAGUGUAUCUCUCAGAGUGCA	1331	UGCACUCUGAGAGAUACACUUUC	1881
AD-2138108.1	AGUGUAUCUCUCAGAGUGCAA	1332	UUGCACUCUGAGAGAUACACUUU	1882
AD-2138109.1	GUGUAUCUCUCAGAGUGCAAA	1333	UUUGCACUCUGAGAGAUACACUU	1883
AD-2138110.1	UGUAUCUCUCAGAGUGCAAGA	1334	UCUUGCACUCUGAGAGAUACACU	1884
AD-2138111.1	GUAUCUCUCAGAGUGCAAGAA	1335	UUCUUGCACUCUGAGAGAUACAC	1885
AD-2138112.1	AUCUCUCAGAGUGCAAGACUA	1336	UAGUCUUGCACUCUGAGAGAUAC	1886
AD-2138113.1	ACAGAGGGACGAUGUCCAAAA	1337	UUUUGGACAUCGUCCCUCUGUAG	1887
AD-2138114.1	CAGAGGGACGAUGUCCAAAAA	1338	UUUUUGGACAUCGUCCCUCUGUA	1888
AD-2138115.1	AGAGGGACGAUGUCCAAAACA	1339	UGUUUUGGACAUCGUCCCUCUGU	1889
AD-2138116.1	GAGGGACGAUGUCCAAAACAA	1340	UUGUUUUGGACAUCGUCCCUCUG	1890
AD-2138117.1	AGGGACGAUGUCCAAAACAAA	1341	UUUGUUUUGGACAUCGUCCCUCU	1891
AD-2138118.1	GGGACGAUGUCCAAAACAAAA	1342	UUUUGUUUUGGACAUCGUCCCUC	1892
AD-2138119.1	GGACGAUGUCCAAAACAAAAA	1343	UUUUUGUUUUGGACAUCGUCCCU	1893
AD-2138120.1	GACGAUGUCCAAAACAAAAAA	1344	UUUUUUGUUUUGGACAUCGUCCC	1894
AD-2138121.1	ACGAUGUCCAAAACAAAAAAA	1345	UUUUUUUGUUUUGGACAUCGUCC	1895
AD-2138122.1	CGAUGUCCAAAACAAAAAAUA	1346	UAUUUUUUGUUUUGGACAUCGUC	1896

Duplex ID	Sense Sequence	SEQ ID NO	Antisense Sequence	SEQ ID NO
AD-2138123.1	GAUGUCCAAAACAAAAAAUGA	1347	UCAUUUUUUGUUUUGGACAUCGU	1897
AD-2138124.1	AUGUCCAAAACAAAAAAUGGA	1348	UCCAUUUUUUGUUUUGGACAUCG	1898
AD-2138125.1	CACAGACCUAGAUUCUCACCA	1349	UGGUGAGAAUCUAGGUCUGUGGG	1899
AD-2138126.1	ACAGACCUAGAUUCUCACCUA	1350	UAGGUGAGAAUCUAGGUCUGUGG	1900
AD-2138127.1	CAGACCUAGAUUCUCACCUGA	1351	UCAGGUGAGAAUCUAGGUCUGUG	1901
AD-2138128.1	GACCUAGAUUCUCACCUGCUA	1352	UAGCAGGUGAGAAUCUAGGUCUG	1902
AD-2138129.1	ACCUAGAUUCUCACCUGCUAA	1353	UUAGCAGGUGAGAAUCUAGGUCU	1903
AD-2138130.1	CCUAGAUUCUCACCUGCUACA	1354	UGUAGCAGGUGAGAAUCUAGGUC	1904
AD-2138131.1	CUCAGAGGGACUGGAGGAGAA	1355	UUCUCCUCCAGUCCCUCUGAGGG	1905
AD-2138132.1	UCAGAGGGACUGGAGGAGAAA	1356	UUUCUCCUCCAGUCCCUCUGAGG	1906
AD-2138133.1	CAGAGGGACUGGAGGAGAACA	1357	UGUUCUCCUCCAGUCCCUCUGAG	1907
AD-2138134.1	AGAGGGACUGGAGGAGAACUA	1358	UAGUUCUCCUCCAGUCCCUCUGA	1908
AD-2138135.1	GAGGGACUGGAGGAGAACUAA	1359	UUAGUUCUCCUCCAGUCCCUCUG	1909
AD-2138136.1	AGGGACUGGAGGAGAACUACA	1360	UGUAGUUCUCCUCCAGUCCCUCU	1910
AD-2138137.1	GGGACUGGAGGAGAACUACUA	1361	UAGUAGUUCUCCUCCAGUCCCUC	1911
AD-2138138.1	GGACUGGAGGAGAACUACUGA	1362	UCAGUAGUUCUCCUCCAGUCCCU	1912
AD-2138139.1	ACUGGAGGAGAACUACUGCAA	1363	UUGCAGUAGUUCUCCUCCAGUCC	1913
AD-2138140.1	CUGGAGGAGAACUACUGCAGA	1364	UCUGCAGUAGUUCUCCUCCAGUC	1914
AD-2138141.1	UGGAGGAGAACUACUGCAGGA	1365	UCCUGCAGUAGUUCUCCUCCAGU	1915
AD-2138142.1	GAGGAGAACUACUGCAGGAAA	1366	UUUCCUGCAGUAGUUCUCCUCCA	1916
AD-2138143.1	AAUCCAGACAACGAUCCGCAA	1367	UUGCGGAUCGUUGUCUGGAUUCC	1917
AD-2138144.1	UCCAGACAACGAUCCGCAGGA	1368	UCCUGCGGAUCGUUGUCUGGAUU	1918
AD-2138145.1	UGCUAUACUACUGAUCCAGAA	1369	UUCUGGAUCAGUAGUAUAGCACC	1919
AD-2138146.1	GCUAUACUACUGAUCCAGAAA	1370	UUUCUGGAUCAGUAGUAUAGCAC	1920
AD-2138147.1	CUAUACUACUGAUCCAGAAAA	1371	UUUUCUGGAUCAGUAGUAUAGCA	1921
AD-2138148.1	UAUACUACUGAUCCAGAAAAA	1372	UUUUUCUGGAUCAGUAGUAUAGC	1922
AD-2138149.1	AUACUACUGAUCCAGAAAAGA	1373	UCUUUUCUGGAUCAGUAGUAUAG	1923
AD-2138150.1	UACUACUGAUCCAGAAAAGAA	1374	UUCUUUUCUGGAUCAGUAGUAUA	1924
AD-2138151.1	ACUACUGAUCCAGAAAAGAGA	1375	UCUCUUUUCUGGAUCAGUAGUAU	1925
AD-2138152.1	CUACUGAUCCAGAAAAGAGAA	1376	UUCUCUUUUCUGGAUCAGUAGUA	1926
AD-2138153.1	UACUGAUCCAGAAAAGAGAUA	1377	UAUCUCUUUUCUGGAUCAGUAGU	1927
AD-2138154.1	ACUGAUCCAGAAAAGAGAUAA	1378	UUAUCUCUUUUCUGGAUCAGUAG	1928
AD-2138155.1	CUGAUCCAGAAAAGAGAUAUA	1379	UAUAUCUCUUUUCUGGAUCAGUA	1929
AD-2138156.1	UGAUCCAGAAAAGAGAUAUGA	1380	UCAUAUCUCUUUUCUGGAUCAGU	1930
AD-2138157.1	GAUCCAGAAAAGAGAUAUGAA	1381	UUCAUAUCUCUUUUCUGGAUCAG	1931
AD-2138158.1	AUCCAGAAAAGAGAUAUGACA	1382	UGUCAUAUCUCUUUUCUGGAUCA	1932
AD-2138159.1	UCCAGAAAAGAGAUAUGACUA	1383	UAGUCAUAUCUCUUUUCUGGAUC	1933
AD-2138160.1	CCAGAAAAGAGAUAUGACUAA	1384	UUAGUCAUAUCUCUUUUCUGGAU	1934
AD-2138161.1	CAGAAAAGAGAUAUGACUACA	1385	UGUAGUCAUAUCUCUUUUCUGGA	1935
AD-2138162.1	AGAAAAGAGAUAUGACUACUA	1386	UAGUAGUCAUAUCUCUUUUCUGG	1936
AD-2138163.1	GAAAAGAGAUAUGACUACUGA	1387	UCAGUAGUCAUAUCUCUUUUCUG	1937
AD-2138164.1	AAAAGAGAUAUGACUACUGCA	1388	UGCAGUAGUCAUAUCUCUUUUCU	1938

Duplex ID	Sense Sequence	SEQ ID NO	Antisense Sequence	SEQ ID NO
AD-2138165.1	UAUGACUACUGCGACAUUCUA	1389	UAGAAUGUCGCAGUAGUCAUAUC	1939
AD-2138166.1	AUGACUACUGCGACAUUCUUA	1390	UAAGAAUGUCGCAGUAGUCAUAU	1940
AD-2138167.1	UGACUACUGCGACAUUCUUGA	1391	UCAAGAAUGUCGCAGUAGUCAUA	1941
AD-2138168.1	GACUACUGCGACAUUCUUGAA	1392	UUCAAGAAUGUCGCAGUAGUCAU	1942
AD-2138169.1	CUACUGCGACAUUCUUGAGUA	1393	UACUCAAGAAUGUCGCAGUAGUC	1943
AD-2138170.1	UACUGCGACAUUCUUGAGUGA	1394	UCACUCAAGAAUGUCGCAGUAGU	1944
AD-2138171.1	ACUGCGACAUUCUUGAGUGUA	1395	UACACUCAAGAAUGUCGCAGUAG	1945
AD-2138172.1	CUGCGACAUUCUUGAGUGUGA	1396	UCACACUCAAGAAUGUCGCAGUA	1946
AD-2138173.1	UGCGACAUUCUUGAGUGUGAA	1397	UUCACACUCAAGAAUGUCGCAGU	1947
AD-2138174.1	GCGACAUUCUUGAGUGUGAAA	1398	UUUCACACUCAAGAAUGUCGCAG	1948
AD-2138175.1	CGACAUUCUUGAGUGUGAAGA	1399	UCUUCACACUCAAGAAUGUCGCA	1949
AD-2138176.1	GACAUUCUUGAGUGUGAAGAA	1400	UUCUUCACACUCAAGAAUGUCGC	1950
AD-2138177.1	ACAUUCUUGAGUGUGAAGAGA	1401	UCUCUUCACACUCAAGAAUGUCG	1951
AD-2138178.1	AUUCUUGAGUGUGAAGAGGAA	1402	UUCCUCUUCACACUCAAGAAUGU	1952
AD-2138179.1	UUCUUGAGUGUGAAGAGGAAA	1403	UUUCCUCUUCACACUCAAGAAUG	1953
AD-2138180.1	UCUUGAGUGUGAAGAGGAAUA	1404	UAUUCCUCUUCACACUCAAGAAU	1954
AD-2138181.1	CUUGAGUGUGAAGAGGAAUGA	1405	UCAUUCCUCUUCACACUCAAGAA	1955
AD-2138182.1	UUGAGUGUGAAGAGGAAUGUA	1406	UACAUUCCUCUUCACACUCAAGA	1956
AD-2138183.1	UGAGUGUGAAGAGGAAUGUAA	1407	UUACAUUCCUCUUCACACUCAAG	1957
AD-2138184.1	GAGUGUGAAGAGGAAUGUAUA	1408	UAUACAUUCCUCUUCACACUCAA	1958
AD-2138185.1	AGUGUGAAGAGGAAUGUAUGA	1409	UCAUACAUUCCUCUUCACACUCA	1959
AD-2138186.1	GUGUGAAGAGGAAUGUAUGCA	1410	UGCAUACAUUCCUCUUCACACUC	1960
AD-2138187.1	UGUGAAGAGGAAUGUAUGCAA	1411	UUGCAUACAUUCCUCUUCACACU	1961
AD-2138188.1	GUGAAGAGGAAUGUAUGCAUA	1412	UAUGCAUACAUUCCUCUUCACAC	1962
AD-2138189.1	UGAAGAGGAAUGUAUGCAUUA	1413	UAAUGCAUACAUUCCUCUUCACA	1963
AD-2138190.1	GAAGAGGAAUGUAUGCAUUGA	1414	UCAAUGCAUACAUUCCUCUUCAC	1964
AD-2138191.1	AAGAGGAAUGUAUGCAUUGCA	1415	UGCAAUGCAUACAUUCCUCUUCA	1965
AD-2138192.1	AGAGGAAUGUAUGCAUUGCAA	1416	UUGCAAUGCAUACAUUCCUCUUC	1966
AD-2138193.1	GAGGAAUGUAUGCAUUGCAGA	1417	UCUGCAAUGCAUACAUUCCUCUU	1967
AD-2138195.1	GGAAUGUAUGCAUUGCAGUGA	1418	UCACUGCAAUGCAUACAUUCCUC	1968
AD-2138196.1	GAAUGUAUGCAUUGCAGUGGA	1419	UCCACUGCAAUGCAUACAUUCCU	1969
AD-2138197.1	AAUGUAUGCAUUGCAGUGGAA	1420	UUCCACUGCAAUGCAUACAUUCC	1970
AD-2138198.1	AUGUAUGCAUUGCAGUGGAGA	1421	UCUCCACUGCAAUGCAUACAUUC	1971
AD-2138199.1	UGUAUGCAUUGCAGUGGAGAA	1422	UUCUCCACUGCAAUGCAUACAUU	1972
AD-2138200.1	GUAUGCAUUGCAGUGGAGAAA	1423	UUUCUCCACUGCAAUGCAUACAU	1973
AD-2138201.1	UAUGCAUUGCAGUGGAGAAAA	1424	UUUUCUCCACUGCAAUGCAUACA	1974
AD-2138202.1	AUGCAUUGCAGUGGAGAAAAA	1425	UUUUUCUCCACUGCAAUGCAUAC	1975
AD-2138203.1	UGCAUUGCAGUGGAGAAAACA	1426	UGUUUUCUCCACUGCAAUGCAUA	1976
AD-2138204.1	GCAUUGCAGUGGAGAAAACUA	1427	UAGUUUUCUCCACUGCAAUGCAU	1977
AD-2138205.1	CAUUGCAGUGGAGAAAACUAA	1428	UUAGUUUUCUCCACUGCAAUGCA	1978
AD-2138206.1	AUUGCAGUGGAGAAAACUAUA	1429	UAUAGUUUUCUCCACUGCAAUGC	1979
AD-2138207.1	UUGCAGUGGAGAAAACUAUGA	1430	UCAUAGUUUUCUCCACUGCAAUG	1980

Duplex ID	Sense Sequence	SEQ ID NO	Antisense Sequence	SEQ ID NO
AD-2138208.1	UGCAGUGGAGAAAACUAUGAA	1431	UUCAUAGUUUUCUCCACUGCAAU	1981
AD-2138209.1	ACGGCAAAAUUUCCAAGACCA	1432	UGGUCUUGGAAAUUUUGCCGUCA	1982
AD-2138210.1	CGGCAAAAUUUCCAAGACCAA	1433	UUGGUCUUGGAAAUUUUGCCGUC	1983
AD-2138211.1	GGCAAAAUUUCCAAGACCAUA	1434	UAUGGUCUUGGAAAUUUUGCCGU	1984
AD-2138212.1	GCAAAAUUUCCAAGACCAUGA	1435	UCAUGGUCUUGGAAAUUUUGCCG	1985
AD-2138213.1	CAAAAUUUCCAAGACCAUGUA	1436	UACAUGGUCUUGGAAAUUUUGCC	1986
AD-2138214.1	AAAAUUUCCAAGACCAUGUCA	1437	UGACAUGGUCUUGGAAAUUUUGC	1987
AD-2138215.1	AAAUUUCCAAGACCAUGUCUA	1438	UAGACAUGGUCUUGGAAAUUUUG	1988
AD-2138216.1	AAUUUCCAAGACCAUGUCUGA	1439	UCAGACAUGGUCUUGGAAAUUUU	1989
AD-2138217.1	AUUUCCAAGACCAUGUCUGGA	1440	UCCAGACAUGGUCUUGGAAAUUU	1990
AD-2138218.1	UUUCCAAGACCAUGUCUGGAA	1441	UUCCAGACAUGGUCUUGGAAAUU	1991
AD-2138219.1	AAUGCCAGGCCUGGGACUCUA	1442	UAGAGUCCCAGGCCUGGCAUUCC	1992
AD-2138220.1	GCCAGGCCUGGGACUCUCAGA	1443	UCUGAGAGUCCCAGGCCUGGCAU	1993
AD-2138221.1	CCAGGCCUGGGACUCUCAGAA	1444	UUCUGAGAGUCCCAGGCCUGGCA	1994
AD-2138222.1	AGCCCACACGCUCAUGGAUAA	1445	UUAUCCAUGAGCGUGUGGGCUCU	1995
AD-2138223.1	CCACACGCUCAUGGAUACAUA	1446	UAUGUAUCCAUGAGCGUGUGGGC	1996
AD-2138224.1	CACACGCUCAUGGAUACAUUA	1447	UAAUGUAUCCAUGAGCGUGUGGG	1997
AD-2138225.1	ACGCUCAUGGAUACAUUCCUA	1448	UAGGAAUGUAUCCAUGAGCGUGU	1998
AD-2138226.1	CGCUCAUGGAUACAUUCCUUA	1449	UAAGGAAUGUAUCCAUGAGCGUG	1999
AD-2138227.1	GCUCAUGGAUACAUUCCUUCA	1450	UGAAGGAAUGUAUCCAUGAGCGU	2000
AD-2138228.1	CUCAUGGAUACAUUCCUUCCA	1451	UGGAAGGAAUGUAUCCAUGAGCG	2001
AD-2138229.1	UCAUGGAUACAUUCCUUCCAA	1452	UUGGAAGGAAUGUAUCCAUGAGC	2002
AD-2138230.1	CAUGGAUACAUUCCUUCCAAA	1453	UUUGGAAGGAAUGUAUCCAUGAG	2003
AD-2138231.1	AUGGAUACAUUCCUUCCAAAA	1454	UUUUGGAAGGAAUGUAUCCAUGA	2004
AD-2138232.1	UGGAUACAUUCCUUCCAAAUA	1455	UAUUUGGAAGGAAUGUAUCCAUG	2005
AD-2138233.1	GGAUACAUUCCUUCCAAAUUA	1456	UAAUUUGGAAGGAAUGUAUCCAU	2006
AD-2138234.1	GAUACAUUCCUUCCAAAUUUA	1457	UAAAUUUGGAAGGAAUGUAUCCA	2007
AD-2138235.1	AUACAUUCCUUCCAAAUUUCA	1458	UGAAAUUUGGAAGGAAUGUAUCC	2008
AD-2138236.1	UACAUUCCUUCCAAAUUUCCA	1459	UGGAAAUUUGGAAGGAAUGUAUC	2009
AD-2138237.1	ACAUUCCUUCCAAAUUUCCAA	1460	UUGGAAAUUUGGAAGGAAUGUAU	2010
AD-2138238.1	CAUUCCUUCCAAAUUUCCAAA	1461	UUUGGAAAUUUGGAAGGAAUGUA	2011
AD-2138239.1	AUUCCUUCCAAAUUUCCAAAA	1462	UUUUGGAAAUUUGGAAGGAAUGU	2012
AD-2138240.1	UUCCUUCCAAAUUUCCAAACA	1463	UGUUUGGAAAUUUGGAAGGAAUG	2013
AD-2138241.1	UCCUUCCAAAUUUCCAAACAA	1464	UUGUUUGGAAAUUUGGAAGGAAU	2014
AD-2138242.1	CCUUCCAAAUUUCCAAACAAA	1465	UUUGUUUGGAAAUUUGGAAGGAA	2015
AD-2138243.1	CUUCCAAAUUUCCAAACAAGA	1466	UCUUGUUUGGAAAUUUGGAAGGA	2016
AD-2138244.1	UUCCAAAUUUCCAAACAAGAA	1467	UUCUUGUUUGGAAAUUUGGAAGG	2017
AD-2138245.1	UCCAAAUUUCCAAACAAGAAA	1468	UUUCUUGUUUGGAAAUUUGGAAG	2018
AD-2138246.1	CCAAAUUUCCAAACAAGAACA	1469	UGUUCUUGUUUGGAAAUUUGGAA	2019
AD-2138247.1	CAAAUUUCCAAACAAGAACCA	1470	UGGUUCUUGUUUGGAAAUUUGGA	2020
AD-2138248.1	AAAUUUCCAAACAAGAACCUA	1471	UAGGUUCUUGUUUGGAAAUUUGG	2021
AD-2138249.1	AAUUUCCAAACAAGAACCUGA	1472	UCAGGUUCUUGUUUGGAAAUUUG	2022

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AD-2138250.1	AUUUCCAAACAAGAACCUGAA	1473	UUCAGGUUCUUGUUUGGAAAUUU	2023
AD-2138251.1	UUUCCAAACAAGAACCUGAAA	1474	UUUCAGGUUCUUGUUUGGAAAUU	2024
AD-2138252.1	UUCCAAACAAGAACCUGAAGA	1475	UCUUCAGGUUCUUGUUUGGAAAU	2025
AD-2138253.1	UCCAAACAAGAACCUGAAGAA	1476	UUCUUCAGGUUCUUGUUUGGAAA	2026
AD-2138254.1	CCAAACAAGAACCUGAAGAAA	1477	UUUCUUCAGGUUCUUGUUUGGAA	2027
AD-2138255.1	CAAACAAGAACCUGAAGAAGA	1478	UCUUCUUCAGGUUCUUGUUUGGA	2028
AD-2138256.1	AAACAAGAACCUGAAGAAGAA	1479	UUCUUCUUCAGGUUCUUGUUUGG	2029
AD-2138257.1	AACAAGAACCUGAAGAAGAAA	1480	UUUCUUCUUCAGGUUCUUGUUUG	2030
AD-2138258.1	ACAAGAACCUGAAGAAGAAUA	1481	UAUUCUUCUUCAGGUUCUUGUUU	2031
AD-2138259.1	CAAGAACCUGAAGAAGAAUUA	1482	UAAUUCUUCUUCAGGUUCUUGUU	2032
AD-2138260.1	AAGAACCUGAAGAAGAAUUAA	1483	UUAAUUCUUCUUCAGGUUCUUGU	2033
AD-2138261.1	AGAACCUGAAGAAGAAUUACA	1484	UGUAAUUCUUCUUCAGGUUCUUG	2034
AD-2138262.1	GAACCUGAAGAAGAAUUACUA	1485	UAGUAAUUCUUCUUCAGGUUCUU	2035
AD-2138263.1	AACCUGAAGAAGAAUUACUGA	1486	UCAGUAAUUCUUCUUCAGGUUCU	2036
AD-2138264.1	ACCUGAAGAAGAAUUACUGUA	1487	UACAGUAAUUCUUCUUCAGGUUC	2037
AD-2138265.1	CCUGAAGAAGAAUUACUGUCA	1488	UGACAGUAAUUCUUCUUCAGGUU	2038
AD-2138266.1	CUGAAGAAGAAUUACUGUCGA	1489	UCGACAGUAAUUCUUCUUCAGGU	2039
AD-2138267.1	UGAAGAAGAAUUACUGUCGUA	1490	UACGACAGUAAUUCUUCUUCAGG	2040
AD-2138268.1	GAAGAAGAAUUACUGUCGUAA	1491	UUACGACAGUAAUUCUUCUUCAG	2041
AD-2138269.1	AAGAAGAAUUACUGUCGUAAA	1492	UUUACGACAGUAAUUCUUCUUCA	2042
AD-2138270.1	AGGGAGCUGCGGCCUUGGUGA	1493	UCACCAAGGCCGCAGCUCCCUAU	2043
AD-2138271.1	GGAGCUGCGGCCUUGGUGUUA	1494	UAACACCAAGGCCGCAGCUCCCU	2044
AD-2138272.1	GAGCUGCGGCCUUGGUGUUUA	1495	UAAACACCAAGGCCGCAGCUCCC	2045
AD-2138273.1	AGCUGCGGCCUUGGUGUUUCA	1496	UGAAACACCAAGGCCGCAGCUCC	2046
AD-2138274.1	UGCGGCCUUGGUGUUUCACCA	1497	UGGUGAAACACCAAGGCCGCAGC	2047
AD-2138275.1	CGGCCUUGGUGUUUCACCACA	1498	UGUGGUGAAACACCAAGGCCGCA	2048
AD-2138276.1	GGCCUUGGUGUUUCACCACCA	1499	UGGUGGUGAAACACCAAGGCCGC	2049
AD-2138277.1	GCCUUGGUGUUUCACCACCGA	1500	UCGGUGGUGAAACACCAAGGCCG	2050
AD-2138278.1	CAACAAGCGCUGGGAACUUUA	1501	UAAAGUUCCCAGCGCUUGUUGGG	2051
AD-2138279.1	AACAAGCGCUGGGAACUUUGA	1502	UCAAAGUUCCCAGCGCUUGUUGG	2052
AD-2138280.1	GCUGCACAACACCUCCACCAA	1503	UUGGUGGAGGUGUUGUGCAGCGG	2053
AD-2138281.1	CUGCACAACACCUCCACCAUA	1504	UAUGGUGGAGGUGUUGUGCAGCG	2054
AD-2138282.1	UGCACAACACCUCCACCAUCA	1505	UGAUGGUGGAGGUGUUGUGCAGC	2055
AD-2138283.1	GCACAACACCUCCACCAUCUA	1506	UAGAUGGUGGAGGUGUUGUGCAG	2056
AD-2138284.1	CACAACACCUCCACCAUCUUA	1507	UAAGAUGGUGGAGGUGUUGUGCA	2057
AD-2138285.1	ACAACACCUCCACCAUCUUCA	1508	UGAAGAUGGUGGAGGUGUUGUGC	2058
AD-2138286.1	CAACACCUCCACCAUCUUCUA	1509	UAGAAGAUGGUGGAGGUGUUGUG	2059
AD-2138287.1	CACCUCCACCAUCUUCUGGUA	1510	UACCAGAAGAUGGUGGAGGUGUU	2060
AD-2138288.1	ACCUCCACCAUCUUCUGGUCA	1511	UGACCAGAAGAUGGUGGAGGUGU	2061
AD-2138289.1	CCUCCACCAUCUUCUGGUCCA	1512	UGGACCAGAAGAUGGUGGAGGUG	2062
AD-2138290.1	CUCCACCAUCUUCUGGUCCCA	1513	UGGGACCAGAAGAUGGUGGAGGU	2063
AD-2138291.1	UCCACCAUCUUCUGGUCCCAA	1514	UUGGGACCAGAAGAUGGUGGAGG	2064

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AD-2138293.1	CACCAUCUUCUGGUCCCACCA	1516	UGGUGGGACCAGAAGAUGGUGGA	2066
AD-2138295.1	CAUCUUCUGGUCCCACCUACA	1517	UGUAGGUGGGACCAGAAGAUGGU	2067
AD-2138296.1	UUCUGGUCCCACCUACCAGUA	1518	UACUGGUAGGUGGGACCAGAAGA	2068
AD-2138297.1	UCUGGUCCCACCUACCAGUGA	1519	UCACUGGUAGGUGGGACCAGAAG	2069
AD-2138298.1	CUGGUCCCACCUACCAGUGUA	1520	UACACUGGUAGGUGGGACCAGAA	2070
AD-2138299.1	UGGUCCCACCUACCAGUGUCA	1521	UGACACUGGUAGGUGGGACCAGA	2071
AD-2138300.1	CCCACCUACCAGUGUCUGAAA	1522	UUUCAGACACUGGUAGGUGGGAC	2072
AD-2138301.1	CCACCUACCAGUGUCUGAAGA	1523	UCUUCAGACACUGGUAGGUGGGA	2073
AD-2138302.1	ACCUACCAGUGUCUGAAGGGA	1524	UCCCUUCAGACACUGGUAGGUGG	2074
AD-2138303.1	CCUACCAGUGUCUGAAGGGAA	1525	UUCCCUUCAGACACUGGUAGGUG	2075
AD-2138304.1	CUACCAGUGUCUGAAGGGAAA	1526	UUUCCCUUCAGACACUGGUAGGU	2076
AD-2138305.1	UACCAGUGUCUGAAGGGAACA	1527	UGUUCCCUUCAGACACUGGUAGG	2077
AD-2138306.1	GUGUCUGAAGGGAACAGGUGA	1528	UCACCUGUUCCCUUCAGACACUG	2078
AD-2138307.1	GUCUGAAGGGAACAGGUGAAA	1529	UUUCACCUGUUCCCUUCAGACAC	2079
AD-2138308.1	UCUGAAGGGAACAGGUGAAAA	1530	UUUUCACCUGUUCCCUUCAGACA	2080
AD-2138309.1	CUGAAGGGAACAGGUGAAAAA	1531	UUUUUCACCUGUUCCCUUCAGAC	2081
AD-2138310.1	UGAAGGGAACAGGUGAAAACA	1532	UGUUUUCACCUGUUCCCUUCAGA	2082
AD-2138311.1	GAAGGGAACAGGUGAAAACUA	1533	UAGUUUUCACCUGUUCCCUUCAG	2083
AD-2138312.1	AAGGGAACAGGUGAAAACUAA	1534	UUAGUUUUCACCUGUUCCCUUCA	2084
AD-2138313.1	AGGGAACAGGUGAAAACUAUA	1535	UAUAGUUUUCACCUGUUCCCUUC	2085
AD-2138314.1	GGGAACAGGUGAAAACUAUCA	1536	UGAUAGUUUUCACCUGUUCCCUU	2086
AD-2138315.1	GGAACAGGUGAAAACUAUCGA	1537	UCGAUAGUUUUCACCUGUUCCCU	2087
AD-2138316.1	GAACAGGUGAAAACUAUCGCA	1538	UGCGAUAGUUUUCACCUGUUCCC	2088
AD-2138317.1	GUGAAAACUAUCGCGGGAAUA	1539	UAUUCCCGCGAUAGUUUUCACCU	2089
AD-2138318.1	GAAAACUAUCGCGGGAAUGUA	1540	UACAUUCCCGCGAUAGUUUUCAC	2090
AD-2138319.1	AAAACUAUCGCGGGAAUGUGA	1541	UCACAUUCCCGCGAUAGUUUUCA	2091
AD-2138320.1	UAUCGCGGGAAUGUGGCUGUA	1542	UACAGCCACAUUCCCGCGAUAGU	2092
AD-2138321.1	AUCGCGGGAAUGUGGCUGUUA	1543	UAACAGCCACAUUCCCGCGAUAG	2093
AD-2138322.1	UCGCGGGAAUGUGGCUGUUAA	1544	UUAACAGCCACAUUCCCGCGAUA	2094
AD-2138323.1	CGCGGGAAUGUGGCUGUUACA	1545	UGUAACAGCCACAUUCCCGCGAU	2095
AD-2138324.1	GGGAAUGUGGCUGUUACCGUA	1546	UACGGUAACAGCCACAUUCCCGC	2096
AD-2138325.1	GAAUGUGGCUGUUACCGUGUA	1547	UACACGGUAACAGCCACAUUCCC	2097
AD-2138326.1	AAUGUGGCUGUUACCGUGUCA	1548	UGACACGGUAACAGCCACAUUCC	2098
AD-2138327.1	CCGUGUCCGGGCACACCUGUA	1549	UACAGGUGUGCCCGGACACGGUA	2099
AD-2138328.1	UCCGGGCACACCUGUCAGCAA	1550	UUGCUGACAGGUGUGCCCGGACA	2100
AD-2138329.1	CGGGCACACCUGUCAGCACUA	1551	UAGUGCUGACAGGUGUGCCCGGA	2101
AD-2138330.1	GCACACCUGUCAGCACUGGAA	1552	UUCCAGUGCUGACAGGUGUGCCC	2102
AD-2138331.1	CACACCUGUCAGCACUGGAGA	1553	UCUCCAGUGCUGACAGGUGUGCC	2103
AD-2138332.1	ACACCUGUCAGCACUGGAGUA	1554	UACUCCAGUGCUGACAGGUGUGC	2104
AD-2138333.1	CCUGUCAGCACUGGAGUGCAA	1555	UUGCACUCCAGUGCUGACAGGUG	2105
AD-2138334.1	UGUCAGCACUGGAGUGCACAA	1556	UUGUGCACUCCAGUGCUGACAGG	2106

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AD-2138336.1	CAGCACUGGAGUGCACAGACA	1558	UGUCUGUGCACUCCAGUGCUGAC	2108
AD-2138337.1	AGCACUGGAGUGCACAGACCA	1559	UGGUCUGUGCACUCCAGUGCUGA	2109
AD-2138338.1	CUCACACACAUAACAGGACAA	1560	UUGUCCUGUUAUGUGUGUGAGGG	2110
AD-2138339.1	CACACACAUAACAGGACACCA	1561	UGGUGUCCUGUUAUGUGUGUGAG	2111
AD-2138340.1	ACACACAUAACAGGACACCAA	1562	UUGGUGUCCUGUUAUGUGUGUGA	2112
AD-2138341.1	CACACAUAACAGGACACCAGA	1563	UCUGGUGUCCUGUUAUGUGUGUG	2113
AD-2138342.1	ACACAUAACAGGACACCAGAA	1564	UUCUGGUGUCCUGUUAUGUGUGU	2114
AD-2138343.1	CACAUAACAGGACACCAGAAA	1565	UUUCUGGUGUCCUGUUAUGUGUG	2115
AD-2138344.1	ACAUAACAGGACACCAGAAAA	1566	UUUUCUGGUGUCCUGUUAUGUGU	2116
AD-2138345.1	CAUAACAGGACACCAGAAAAA	1567	UUUUUCUGGUGUCCUGUUAUGUG	2117
AD-2138346.1	AUAACAGGACACCAGAAAACA	1568	UGUUUUCUGGUGUCCUGUUAUGU	2118
AD-2138347.1	UAACAGGACACCAGAAAACUA	1569	UAGUUUUCUGGUGUCCUGUUAUG	2119
AD-2138348.1	AACAGGACACCAGAAAACUUA	1570	UAAGUUUUCUGGUGUCCUGUUAU	2120
AD-2138349.1	CCUGCAAAAAUUUGGAUGAAA	1571	UUUCAUCCAAAUUUUUGCAGGGG	2121
AD-2138350.1	CUGCAAAAAUUUGGAUGAAAA	1572	UUUUCAUCCAAAUUUUUGCAGGG	2122
AD-2138351.1	UGCAAAAAUUUGGAUGAAAAA	1573	UUUUUCAUCCAAAUUUUUGCAGG	2123
AD-2138352.1	GCAAAAAUUUGGAUGAAAACA	1574	UGUUUUCAUCCAAAUUUUUGCAG	2124
AD-2138353.1	CAAAAAUUUGGAUGAAAACUA	1575	UAGUUUUCAUCCAAAUUUUUGCA	2125
AD-2138354.1	AAAAAUUUGGAUGAAAACUAA	1576	UUAGUUUUCAUCCAAAUUUUUGC	2126
AD-2138355.1	AAAAUUUGGAUGAAAACUACA	1577	UGUAGUUUUCAUCCAAAUUUUUG	2127
AD-2138356.1	AAAUUUGGAUGAAAACUACUA	1578	UAGUAGUUUUCAUCCAAAUUUUU	2128
AD-2138357.1	AAUUUGGAUGAAAACUACUGA	1579	UCAGUAGUUUUCAUCCAAAUUUU	2129
AD-2138358.1	AUUUGGAUGAAAACUACUGCA	1580	UGCAGUAGUUUUCAUCCAAAUUU	2130
AD-2138359.1	UUUGGAUGAAAACUACUGCCA	1581	UGGCAGUAGUUUUCAUCCAAAUU	2131
AD-2138360.1	UUGGAUGAAAACUACUGCCGA	1582	UCGGCAGUAGUUUUCAUCCAAAU	2132
AD-2138361.1	UGGAUGAAAACUACUGCCGCA	1583	UGCGGCAGUAGUUUUCAUCCAAA	2133
AD-2138362.1	GGAUGAAAACUACUGCCGCAA	1584	UUGCGGCAGUAGUUUUCAUCCAA	2134
AD-2138363.1	GAUGAAAACUACUGCCGCAAA	1585	UUUGCGGCAGUAGUUUUCAUCCA	2135
AD-2138364.1	AUGAAAACUACUGCCGCAAUA	1586	UAUUGCGGCAGUAGUUUUCAUCC	2136
AD-2138365.1	UGAAAACUACUGCCGCAAUCA	1587	UGAUUGCGGCAGUAGUUUUCAUC	2137
AD-2138366.1	GAAAACUACUGCCGCAAUCCA	1588	UGGAUUGCGGCAGUAGUUUUCAU	2138
AD-2138367.1	AAAACUACUGCCGCAAUCCUA	1589	UAGGAUUGCGGCAGUAGUUUUCA	2139
AD-2138368.1	AAACUACUGCCGCAAUCCUGA	1590	UCAGGAUUGCGGCAGUAGUUUUC	2140
AD-2138369.1	AACUACUGCCGCAAUCCUGAA	1591	UUCAGGAUUGCGGCAGUAGUUUU	2141
AD-2138370.1	UACUGCCGCAAUCCUGACGGA	1592	UCCGUCAGGAUUGCGGCAGUAGU	2142
AD-2138371.1	ACUGCCGCAAUCCUGACGGAA	1593	UUCCGUCAGGAUUGCGGCAGUAG	2143
AD-2138372.1	CUGCCGCAAUCCUGACGGAAA	1594	UUUCCGUCAGGAUUGCGGCAGUA	2144
AD-2138373.1	UGCCGCAAUCCUGACGGAAAA	1595	UUUUCCGUCAGGAUUGCGGCAGU	2145
AD-2138374.1	GCCGCAAUCCUGACGGAAAAA	1596	UUUUUCCGUCAGGAUUGCGGCAG	2146
AD-2138375.1	CCGCAAUCCUGACGGAAAAAA	1597	UUUUUUCCGUCAGGAUUGCGGCA	2147
AD-2138376.1	CGCAAUCCUGACGGAAAAAGA	1598	UCUUUUUCCGUCAGGAUUGCGGC	2148

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AD-2138379.1	AAUCCUGACGGAAAAAGGGCA	1601	UGCCCUUUUUCCGUCAGGAUUGC	2151
AD-2138380.1	AUCCUGACGGAAAAAGGGCCA	1602	UGGCCCUUUUUCCGUCAGGAUUG	2152
AD-2138381.1	CAUGGUGCCAUACAACCAACA	1603	UGUUGGUUGUAUGGCACCAUGGG	2153
AD-2138383.1	UGGUGCCAUACAACCAACAGA	1604	UCUGUUGGUUGUAUGGCACCAUG	2154
AD-2138384.1	GUGCCAUACAACCAACAGCCA	1605	UGGCUGUUGGUUGUAUGGCACCA	2155
AD-2138385.1	GCCAUACAACCAACAGCCAAA	1606	UUUGGCUGUUGGUUGUAUGGCAC	2156
AD-2138386.1	CCAUACAACCAACAGCCAAGA	1607	UCUUGGCUGUUGGUUGUAUGGCA	2157
AD-2138387.1	CAUACAACCAACAGCCAAGUA	1608	UACUUGGCUGUUGGUUGUAUGGC	2158
AD-2138388.1	AUACAACCAACAGCCAAGUGA	1609	UCACUUGGCUGUUGGUUGUAUGG	2159
AD-2138389.1	UACAACCAACAGCCAAGUGCA	1610	UGCACUUGGCUGUUGGUUGUAUG	2160
AD-2138390.1	ACAACCAACAGCCAAGUGCGA	1611	UCGCACUUGGCUGUUGGUUGUAU	2161
AD-2138391.1	GCCAAGUGCGGUGGGAGUACA	1612	UGUACUCCCACCGCACUUGGCUG	2162
AD-2138392.1	AAGUGCGGUGGGAGUACUGUA	1613	UACAGUACUCCCACCGCACUUGG	2163
AD-2138393.1	AGUGCGGUGGGAGUACUGUAA	1614	UUACAGUACUCCCACCGCACUUG	2164
AD-2138394.1	GUGCGGUGGGAGUACUGUAAA	1615	UUUACAGUACUCCCACCGCACUU	2165
AD-2138395.1	UGCGGUGGGAGUACUGUAAGA	1616	UCUUACAGUACUCCCACCGCACU	2166
AD-2138396.1	GCGGUGGGAGUACUGUAAGAA	1617	UUCUUACAGUACUCCCACCGCAC	2167
AD-2138397.1	CGGUGGGAGUACUGUAAGAUA	1618	UAUCUUACAGUACUCCCACCGCA	2168
AD-2138398.1	GGUGGGAGUACUGUAAGAUAA	1619	UUAUCUUACAGUACUCCCACCGC	2169
AD-2138399.1	GUGGGAGUACUGUAAGAUACA	1620	UGUAUCUUACAGUACUCCCACCG	2170
AD-2138400.1	UGGGAGUACUGUAAGAUACCA	1621	UGGUAUCUUACAGUACUCCCACC	2171
AD-2138401.1	GGAGUACUGUAAGAUACCGUA	1622	UACGGUAUCUUACAGUACUCCCA	2172
AD-2138402.1	GAGUACUGUAAGAUACCGUCA	1623	UGACGGUAUCUUACAGUACUCCC	2173
AD-2138403.1	AGUACUGUAAGAUACCGUCCA	1624	UGGACGGUAUCUUACAGUACUCC	2174
AD-2138405.1	ACUGUAAGAUACCGUCCUGUA	1625	UACAGGACGGUAUCUUACAGUAC	2175
AD-2138406.1	CUGUAAGAUACCGUCCUGUGA	1626	UCACAGGACGGUAUCUUACAGUA	2176
AD-2138407.1	GUAAGAUACCGUCCUGUGACA	1627	UGUCACAGGACGGUAUCUUACAG	2177
AD-2138408.1	UUGGCUCCCACAGCACCACCA	1628	UGGUGGUGCUGUGGGAGCCAAUU	2178
AD-2138409.1	GGCUCCCACAGCACCACCUGA	1629	UCAGGUGGUGCUGUGGGAGCCAA	2179
AD-2138410.1	GCUCCCACAGCACCACCUGAA	1630	UUCAGGUGGUGCUGUGGGAGCCA	2180
AD-2138412.1	ACAGCACCACCUGAGCUAACA	1631	UGUUAGCUCAGGUGGUGCUGUGG	2181
AD-2138413.1	CAGCACCACCUGAGCUAACCA	1632	UGGUUAGCUCAGGUGGUGCUGUG	2182
AD-2138414.1	CAUGGUGAUGGACAGAGCUAA	1633	UUAGCUCUGUCCAUCACCAUGGU	2183
AD-2138415.1	GACAGAGCUACCGAGGCACAA	1634	UUGUGCCUCGGUAGCUCUGUCCA	2184
AD-2138416.1	ACAGAGCUACCGAGGCACAUA	1635	UAUGUGCCUCGGUAGCUCUGUCC	2185
AD-2138417.1	CAGAGCUACCGAGGCACAUCA	1636	UGAUGUGCCUCGGUAGCUCUGUC	2186
AD-2138418.1	GAGCUACCGAGGCACAUCCUA	1637	UAGGAUGUGCCUCGGUAGCUCUG	2187
AD-2138419.1	ACCGAGGCACAUCCUCCACCA	1638	UGGUGGAGGAUGUGCCUCGGUAG	2188
AD-2138420.1	CGAGGCACAUCCUCCACCACA	1639	UGUGGUGGAGGAUGUGCCUCGGU	2189
AD-2138421.1	AGGCACAUCCUCCACCACCAA	1640	UUGGUGGUGGAGGAUGUGCCUCG	2190

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AD-2138422.1	GCACAUCCUCCACCACCACCA	1641	UGGUGGUGGUGGAGGAUGUGCCU	2191
AD-2138423.1	CAUCCUCCACCACCACCACAA	1642	UUGUGGUGGUGGUGGAGGAUGUG	2192
AD-2138424.1	AUCCUCCACCACCACCACAGA	1643	UCUGUGGUGGUGGUGGAGGAUGU	2193
AD-2138425.1	UCCUCCACCACCACCACAGGA	1644	UCCUGUGGUGGUGGUGGAGGAUG	2194
AD-2138426.1	CCUCCACCACCACCACAGGAA	1645	UUCCUGUGGUGGUGGUGGAGGAU	2195
AD-2138427.1	CUCCACCACCACCACAGGAAA	1646	UUUCCUGUGGUGGUGGUGGAGGA	2196
AD-2138428.1	UCCACCACCACCACAGGAAAA	1647	UUUUCCUGUGGUGGUGGUGGAGG	2197
AD-2138429.1	CCACCACCACCACAGGAAAGA	1648	UCUUUCCUGUGGUGGUGGUGGAG	2198
AD-2138430.1	CACCACCACCACAGGAAAGAA	1649	UUCUUUCCUGUGGUGGUGGUGGA	2199
AD-2138431.1	ACCACCACCACAGGAAAGAAA	1650	UUUCUUUCCUGUGGUGGUGGUGG	2200
AD-2138432.1	CCACCACCACAGGAAAGAAGA	1651	UCUUCUUUCCUGUGGUGGUGGUG	2201
AD-2138433.1	CACCACCACAGGAAAGAAGUA	1652	UACUUCUUUCCUGUGGUGGUGGU	2202
AD-2138434.1	CCACCACAGGAAAGAAGUGUA	1653	UACACUUCUUUCCUGUGGUGGUG	2203
AD-2138435.1	CACCACAGGAAAGAAGUGUCA	1654	UGACACUUCUUUCCUGUGGUGGU	2204
AD-2138436.1	ACCACAGGAAAGAAGUGUCAA	1655	UUGACACUUCUUUCCUGUGGUGG	2205
AD-2138437.1	CCACAGGAAAGAAGUGUCAGA	1656	UCUGACACUUCUUUCCUGUGGUG	2206
AD-2138438.1	CACAGGAAAGAAGUGUCAGUA	1657	UACUGACACUUCUUUCCUGUGGU	2207
AD-2138439.1	ACAGGAAAGAAGUGUCAGUCA	1658	UGACUGACACUUCUUUCCUGUGG	2208
AD-2138440.1	CAGGAAAGAAGUGUCAGUCUA	1659	UAGACUGACACUUCUUUCCUGUG	2209
AD-2138441.1	AGGAAAGAAGUGUCAGUCUUA	1660	UAAGACUGACACUUCUUUCCUGU	2210
AD-2138442.1	GGAAAGAAGUGUCAGUCUUGA	1661	UCAAGACUGACACUUCUUUCCUG	2211
AD-2138443.1	GAAAGAAGUGUCAGUCUUGGA	1662	UCCAAGACUGACACUUCUUUCCU	2212
AD-2138444.1	AAAGAAGUGUCAGUCUUGGUA	1663	UACCAAGACUGACACUUCUUUCC	2213
AD-2138445.1	AGAAGUGUCAGUCUUGGUCAA	1664	UUGACCAAGACUGACACUUCUUU	2214
AD-2138446.1	GAAGUGUCAGUCUUGGUCAUA	1665	UAUGACCAAGACUGACACUUCUU	2215
AD-2138447.1	AAGUGUCAGUCUUGGUCAUCA	1666	UGAUGACCAAGACUGACACUUCU	2216
AD-2138448.1	AGUGUCAGUCUUGGUCAUCUA	1667	UAGAUGACCAAGACUGACACUUC	2217
AD-2138449.1	GUGUCAGUCUUGGUCAUCUAA	1668	UUAGAUGACCAAGACUGACACUU	2218
AD-2138450.1	UGUCAGUCUUGGUCAUCUAUA	1669	UAUAGAUGACCAAGACUGACACU	2219
AD-2138451.1	GUCAGUCUUGGUCAUCUAUGA	1670	UCAUAGAUGACCAAGACUGACAC	2220
AD-2138452.1	UCAGUCUUGGUCAUCUAUGAA	1671	UUCAUAGAUGACCAAGACUGACA	2221
AD-2138453.1	CAGUCUUGGUCAUCUAUGACA	1672	UGUCAUAGAUGACCAAGACUGAC	2222
AD-2138454.1	AGUCUUGGUCAUCUAUGACAA	1673	UUGUCAUAGAUGACCAAGACUGA	2223
AD-2138455.1	GGAAUCCAGAUGCCGAUAAAA	1674	UUUUAUCGGCAUCUGGAUUCCUG	2224
AD-2138456.1	GAAUCCAGAUGCCGAUAAAGA	1675	UCUUUAUCGGCAUCUGGAUUCCU	2225
AD-2138457.1	GGUGGGAGUACUGCAACCUGA	1676	UCAGGUUGCAGUACUCCCACCUG	2226
AD-2138458.1	GUGGGAGUACUGCAACCUGAA	1677	UUCAGGUUGCAGUACUCCCACCU	2227
AD-2138459.1	UGGGAGUACUGCAACCUGAAA	1678	UUUCAGGUUGCAGUACUCCCACC	2228
AD-2138460.1	GGGAGUACUGCAACCUGAAAA	1679	UUUUCAGGUUGCAGUACUCCCAC	2229
AD-2138461.1	GGAGUACUGCAACCUGAAAAA	1680	UUUUUCAGGUUGCAGUACUCCCA	2230
AD-2138462.1	GAGUACUGCAACCUGAAAAAA	1681	UUUUUUCAGGUUGCAGUACUCCC	2231
AD-2138463.1	AGUACUGCAACCUGAAAAAAA	1682	UUUUUUUCAGGUUGCAGUACUCC	2232

Duplex ID	Sense Sequence	SEQ ID NO	Antisense Sequence	SEQ ID NO
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AD-2138465.1	UACUGCAACCUGAAAAAAUGA	1684	UCAUUUUUUCAGGUUGCAGUACU	2234
AD-2138466.1	ACUGCAACCUGAAAAAAUGCA	1685	UGCAUUUUUUCAGGUUGCAGUAC	2235
AD-2138467.1	CUGCAACCUGAAAAAAUGCUA	1686	UAGCAUUUUUUCAGGUUGCAGUA	2236
AD-2138468.1	UGCAACCUGAAAAAAUGCUCA	1687	UGAGCAUUUUUUCAGGUUGCAGU	2237
AD-2138469.1	GCAACCUGAAAAAAUGCUCAA	1688	UUGAGCAUUUUUUCAGGUUGCAG	2238
AD-2138470.1	CAACCUGAAAAAAUGCUCAGA	1689	UCUGAGCAUUUUUUCAGGUUGCA	2239
AD-2138471.1	AACCUGAAAAAAUGCUCAGGA	1690	UCCUGAGCAUUUUUUCAGGUUGC	2240
AD-2138472.1	ACCUGAAAAAAUGCUCAGGAA	1691	UUCCUGAGCAUUUUUUCAGGUUG	2241
AD-2138473.1	CCUGAAAAAAUGCUCAGGAAA	1692	UUUCCUGAGCAUUUUUUCAGGUU	2242
AD-2138474.1	CUGAAAAAAUGCUCAGGAACA	1693	UGUUCCUGAGCAUUUUUUCAGGU	2243
AD-2138475.1	UGAAAAAAUGCUCAGGAACAA	1694	UUGUUCCUGAGCAUUUUUUCAGG	2244
AD-2138476.1	GAAAAAAUGCUCAGGAACAGA	1695	UCUGUUCCUGAGCAUUUUUUCAG	2245
AD-2138477.1	AAAAAAUGCUCAGGAACAGAA	1696	UUCUGUUCCUGAGCAUUUUUUCA	2246
AD-2138478.1	AAAAAUGCUCAGGAACAGAAA	1697	UUUCUGUUCCUGAGCAUUUUUUC	2247
AD-2138479.1	AAAAUGCUCAGGAACAGAAGA	1698	UCUUCUGUUCCUGAGCAUUUUUU	2248
AD-2138480.1	AAAUGCUCAGGAACAGAAGCA	1699	UGCUUCUGUUCCUGAGCAUUUUU	2249
AD-2138481.1	GCACCUCCGCCUGUUGUCCUA	1700	UAGGACAACAGGCGGAGGUGCUA	2250
AD-2138482.1	CACCUCCGCCUGUUGUCCUGA	1701	UCAGGACAACAGGCGGAGGUGCU	2251
AD-2138483.1	CCUCCGCCUGUUGUCCUGCUA	1702	UAGCAGGACAACAGGCGGAGGUG	2252
AD-2138484.1	CUCCGCCUGUUGUCCUGCUUA	1703	UAAGCAGGACAACAGGCGGAGGU	2253
AD-2138485.1	UCCGCCUGUUGUCCUGCUUCA	1704	UGAAGCAGGACAACAGGCGGAGG	2254
AD-2138486.1	CCGCCUGUUGUCCUGCUUCCA	1705	UGGAAGCAGGACAACAGGCGGAG	2255
AD-2138487.1	CGCCUGUUGUCCUGCUUCCAA	1706	UUGGAAGCAGGACAACAGGCGGA	2256
AD-2138488.1	CCGAAGAAGACUGUAUGUUUA	1707	UAAACAUACAGUCUUCUUCGGAA	2257
AD-2138489.1	CGAAGAAGACUGUAUGUUUGA	1708	UCAAACAUACAGUCUUCUUCGGA	2258
AD-2138490.1	GAAGAAGACUGUAUGUUUGGA	1709	UCCAAACAUACAGUCUUCUUCGG	2259
AD-2138491.1	AAGAAGACUGUAUGUUUGGGA	1710	UCCCAAACAUACAGUCUUCUUCG	2260
AD-2138492.1	GCGACCACUGUUACUGGGACA	1711	UGUCCCAGUAACAGUGGUCGCCC	2261
AD-2138493.1	CUGGGACGCCAUGCCAGGACA	1712	UGUCCUGGCAUGGCGUCCCAGUA	2262
AD-2138494.1	UGGGACGCCAUGCCAGGACUA	1713	UAGUCCUGGCAUGGCGUCCCAGU	2263
AD-2138495.1	CAUAGACACAGCAUUUUCACA	1714	UGUGAAAAUGCUGUGUCUAUGGG	2264
AD-2138496.1	AUAGACACAGCAUUUUCACUA	1715	UAGUGAAAAUGCUGUGUCUAUGG	2265
AD-2138497.1	UAGACACAGCAUUUUCACUCA	1716	UGAGUGAAAAUGCUGUGUCUAUG	2266
AD-2138498.1	AGACACAGCAUUUUCACUCCA	1717	UGGAGUGAAAAUGCUGUGUCUAU	2267
AD-2138499.1	GACACAGCAUUUUCACUCCAA	1718	UUGGAGUGAAAAUGCUGUGUCUA	2268
AD-2138500.1	ACACAGCAUUUUCACUCCAGA	1719	UCUGGAGUGAAAAUGCUGUGUCU	2269
AD-2138501.1	CACAGCAUUUUCACUCCAGAA	1720	UUCUGGAGUGAAAAUGCUGUGUC	2270
AD-2138502.1	ACAGCAUUUUCACUCCAGAGA	1721	UCUCUGGAGUGAAAAUGCUGUGU	2271
AD-2138503.1	CAGCAUUUUCACUCCAGAGAA	1722	UUCUCUGGAGUGAAAAUGCUGUG	2272
AD-2138504.1	AGCAUUUUCACUCCAGAGACA	1723	UGUCUCUGGAGUGAAAAUGCUGU	2273
AD-2138505.1	GCAUUUUCACUCCAGAGACAA	1724	UUGUCUCUGGAGUGAAAAUGCUG	2274

Duplex ID	Sense Sequence	SEQ ID NO	Antisense Sequence	SEQ ID NO
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AD-2138507.1	AUUUUCACUCCAGAGACAAAA	1726	UUUUGUCUCUGGAGUGAAAAUGC	2276
AD-2138508.1	UUUUCACUCCAGAGACAAAUA	1727	UAUUUGUCUCUGGAGUGAAAAUG	2277
AD-2138509.1	UUUCACUCCAGAGACAAAUCA	1728	UGAUUUGUCUCUGGAGUGAAAAU	2278
AD-2138510.1	UUCACUCCAGAGACAAAUCCA	1729	UGGAUUUGUCUCUGGAGUGAAAA	2279
AD-2138511.1	UCACUCCAGAGACAAAUCCAA	1730	UUGGAUUUGUCUCUGGAGUGAAA	2280
AD-2138512.1	ACGGGCGGGUCUGGAAAAAAA	1731	UUUUUUUCCAGACCCGCCCGUGG	2281
AD-2138513.1	CGGGCGGGUCUGGAAAAAAAA	1732	UUUUUUUUCCAGACCCGCCCGUG	2282
AD-2138514.1	GGGCGGGUCUGGAAAAAAAUA	1733	UAUUUUUUUCCAGACCCGCCCGU	2283
AD-2138515.1	GGCGGGUCUGGAAAAAAAUUA	1734	UAAUUUUUUUCCAGACCCGCCCG	2284
AD-2138516.1	GCGGGUCUGGAAAAAAAUUAA	1735	UUAAUUUUUUUCCAGACCCGCCC	2285
AD-2138517.1	CGGGUCUGGAAAAAAAUUACA	1736	UGUAAUUUUUUUCCAGACCCGCC	2286
AD-2138518.1	GGGUCUGGAAAAAAAUUACUA	1737	UAGUAAUUUUUUUCCAGACCCGC	2287
AD-2138519.1	GGUCUGGAAAAAAAUUACUGA	1738	UCAGUAAUUUUUUUCCAGACCCG	2288
AD-2138520.1	GUCUGGAAAAAAAUUACUGCA	1739	UGCAGUAAUUUUUUUCCAGACCC	2289
AD-2138521.1	UCUGGAAAAAAAUUACUGCCA	1740	UGGCAGUAAUUUUUUUCCAGACC	2290
AD-2138522.1	CUGGAAAAAAAUUACUGCCGA	1741	UCGGCAGUAAUUUUUUUCCAGAC	2291
AD-2138523.1	UGGAAAAAAAUUACUGCCGUA	1742	UACGGCAGUAAUUUUUUUCCAGA	2292
AD-2138524.1	CGUAACCCUGAUGGUGAUGUA	1743	UACAUCACCAUCAGGGUUACGGC	2293
AD-2138525.1	AACCCUGAUGGUGAUGUAGGA	1744	UCCUACAUCACCAUCAGGGUUAC	2294
AD-2138526.1	CCCUGAUGGUGAUGUAGGUGA	1745	UCACCUACAUCACCAUCAGGGUU	2295
AD-2138527.1	CCUGAUGGUGAUGUAGGUGGA	1746	UCCACCUACAUCACCAUCAGGGU	2296
AD-2138528.1	UAGGUGGUCCCUGGUGCUACA	1747	UGUAGCACCAGGGACCACCUACA	2297
AD-2138529.1	AGGUGGUCCCUGGUGCUACAA	1748	UUGUAGCACCAGGGACCACCUAC	2298
AD-2138530.1	GUGGUCCCUGGUGCUACACGA	1749	UCGUGUAGCACCAGGGACCACCU	2299
AD-2138531.1	CUGGUGCUACACGACAAAUCA	1750	UGAUUUGUCGUGUAGCACCAGGG	2300
AD-2138532.1	GGUGCUACACGACAAAUCCAA	1751	UUGGAUUUGUCGUGUAGCACCAG	2301
AD-2138533.1	GUGCUACACGACAAAUCCAAA	1752	UUUGGAUUUGUCGUGUAGCACCA	2302
AD-2138534.1	UGCUACACGACAAAUCCAAGA	1753	UCUUGGAUUUGUCGUGUAGCACC	2303
AD-2138535.1	GCUACACGACAAAUCCAAGAA	1754	UUCUUGGAUUUGUCGUGUAGCAC	2304
AD-2138536.1	CUACACGACAAAUCCAAGAAA	1755	UUUCUUGGAUUUGUCGUGUAGCA	2305
AD-2138537.1	UACACGACAAAUCCAAGAAAA	1756	UUUUCUUGGAUUUGUCGUGUAGC	2306
AD-2138538.1	ACACGACAAAUCCAAGAAAAA	1757	UUUUUCUUGGAUUUGUCGUGUAG	2307
AD-2138539.1	CACGACAAAUCCAAGAAAACA	1758	UGUUUUCUUGGAUUUGUCGUGUA	2308
AD-2138540.1	ACGACAAAUCCAAGAAAACUA	1759	UAGUUUUCUUGGAUUUGUCGUGU	2309
AD-2138541.1	CGACAAAUCCAAGAAAACUUA	1760	UAAGUUUUCUUGGAUUUGUCGUG	2310
AD-2138542.1	GACAAAUCCAAGAAAACUUUA	1761	UAAAGUUUUCUUGGAUUUGUCGU	2311
AD-2138543.1	ACAAAUCCAAGAAAACUUUAA	1762	UUAAAGUUUUCUUGGAUUUGUCG	2312
AD-2138544.1	CAAAUCCAAGAAAACUUUACA	1763	UGUAAAGUUUUCUUGGAUUUGUC	2313
AD-2138545.1	AAAUCCAAGAAAACUUUACGA	1764	UCGUAAAGUUUUCUUGGAUUUGU	2314
AD-2138546.1	AAUCCAAGAAAACUUUACGAA	1765	UUCGUAAAGUUUUCUUGGAUUUG	2315
AD-2138547.1	AUCCAAGAAAACUUUACGACA	1766	UGUCGUAAAGUUUUCUUGGAUUU	2316

Duplex ID	Sense Sequence	SEQ ID NO	Antisense Sequence	SEQ ID NO
AD-2138548.1	UCCAAGAAAACUUUACGACUA	1767	UAGUCGUAAAGUUUUCUUGGAUU	2317
AD-2138549.1	CCAAGAAAACUUUACGACUAA	1768	UUAGUCGUAAAGUUUUCUUGGAU	2318
AD-2138550.1	AAGAAAACUUUACGACUACUA	1769	UAGUAGUCGUAAAGUUUUCUUGG	2319
AD-2138551.1	AGAAAACUUUACGACUACUGA	1770	UCAGUAGUCGUAAAGUUUUCUUG	2320
AD-2138552.1	GAAAACUUUACGACUACUGUA	1771	UACAGUAGUCGUAAAGUUUUCUU	2321
AD-2138553.1	AAAACUUUACGACUACUGUGA	1772	UCACAGUAGUCGUAAAGUUUUCU	2322
AD-2138554.1	AAACUUUACGACUACUGUGAA	1773	UUCACAGUAGUCGUAAAGUUUUC	2323
AD-2138555.1	AACUUUACGACUACUGUGAUA	1774	UAUCACAGUAGUCGUAAAGUUUU	2324
AD-2138556.1	ACUUUACGACUACUGUGAUGA	1775	UCAUCACAGUAGUCGUAAAGUUU	2325
AD-2138557.1	CUUUACGACUACUGUGAUGUA	1776	UACAUCACAGUAGUCGUAAAGUU	2326
AD-2138558.1	UUUACGACUACUGUGAUGUCA	1777	UGACAUCACAGUAGUCGUAAAGU	2327
AD-2138559.1	GACUACUGUGAUGUCCCUCAA	1778	UUGAGGGACAUCACAGUAGUCGU	2328
AD-2138560.1	CUGUGAUGUCCCUCAGUGUGA	1779	UCACACUGAGGGACAUCACAGUA	2329
AD-2138561.1	AUGUCCCUCAGUGUGCGGCCA	1780	UGGCCGCACACUGAGGGACAUCA	2330
AD-2138562.1	AAGAAAUGUCCUGGAAGGGUA	1781	UACCCUUCCAGGACAUUUCUUCG	2331
AD-2138563.1	GCCCUGGCAAGUCAGUCUUAA	1782	UUAAGACUGACUUGCCAGGGCCA	2332
AD-2138564.1	CCUGGCAAGUCAGUCUUAGAA	1783	UUCUAAGACUGACUUGCCAGGGC	2333
AD-2138565.1	CUGGCAAGUCAGUCUUAGAAA	1784	UUUCUAAGACUGACUUGCCAGGG	2334
AD-2138566.1	UGGCAAGUCAGUCUUAGAACA	1785	UGUUCUAAGACUGACUUGCCAGG	2335
AD-2138567.1	GGCAAGUCAGUCUUAGAACAA	1786	UUGUUCUAAGACUGACUUGCCAG	2336
AD-2138568.1	GCAAGUCAGUCUUAGAACAAA	1787	UUUGUUCUAAGACUGACUUGCCA	2337
AD-2138569.1	CAAGUCAGUCUUAGAACAAGA	1788	UCUUGUUCUAAGACUGACUUGCC	2338
AD-2138570.1	AAGUCAGUCUUAGAACAAGGA	1789	UCCUUGUUCUAAGACUGACUUGC	2339
AD-2138571.1	AGUCAGUCUUAGAACAAGGUA	1790	UACCUUGUUCUAAGACUGACUUG	2340
AD-2138572.1	GUCAGUCUUAGAACAAGGUUA	1791	UAACCUUGUUCUAAGACUGACUU	2341
AD-2138573.1	UCAGUCUUAGAACAAGGUUUA	1792	UAAACCUUGUUCUAAGACUGACU	2342
AD-2138574.1	CAGUCUUAGAACAAGGUUUGA	1793	UCAAACCUUGUUCUAAGACUGAC	2343
AD-2138575.1	AGUCUUAGAACAAGGUUUGGA	1794	UCCAAACCUUGUUCUAAGACUGA	2344
AD-2138576.1	GUCUUAGAACAAGGUUUGGAA	1795	UUCCAAACCUUGUUCUAAGACUG	2345
AD-2138577.1	UCUUAGAACAAGGUUUGGAAA	1796	UUUCCAAACCUUGUUCUAAGACU	2346
AD-2138578.1	CUUAGAACAAGGUUUGGAAUA	1797	UAUUCCAAACCUUGUUCUAAGAC	2347
AD-2138579.1	UUAGAACAAGGUUUGGAAUGA	1798	UCAUUCCAAACCUUGUUCUAAGA	2348
AD-2138580.1	UAGAACAAGGUUUGGAAUGCA	1799	UGCAUUCCAAACCUUGUUCUAAG	2349
AD-2138581.1	AGAACAAGGUUUGGAAUGCAA	1800	UUGCAUUCCAAACCUUGUUCUAA	2350
AD-2138582.1	GAACAAGGUUUGGAAUGCACA	1801	UGUGCAUUCCAAACCUUGUUCUA	2351
AD-2138583.1	AACAAGGUUUGGAAUGCACUA	1802	UAGUGCAUUCCAAACCUUGUUCU	2352
AD-2138584.1	ACAAGGUUUGGAAUGCACUUA	1803	UAAGUGCAUUCCAAACCUUGUUC	2353
AD-2138585.1	CAAGGUUUGGAAUGCACUUCA	1804	UGAAGUGCAUUCCAAACCUUGUU	2354
AD-2138586.1	AAGGUUUGGAAUGCACUUCUA	1805	UAGAAGUGCAUUCCAAACCUUGU	2355
AD-2138587.1	AGGUUUGGAAUGCACUUCUGA	1806	UCAGAAGUGCAUUCCAAACCUUG	2356
AD-2138588.1	GGUUUGGAAUGCACUUCUGUA	1807	UACAGAAGUGCAUUCCAAACCUU	2357
AD-2138589.1	UUGGAAUGCACUUCUGUGGAA	1808	UUCCACAGAAGUGCAUUCCAAAC	2358

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AD-2138591.1	GAAUGCACUUCUGUGGAGGCA	1810	UGCCUCCACAGAAGUGCAUUCCA	2360
AD-2138592.1	CUGUGGAGGCACCUUGAUAUA	1811	UAUAUCAAGGUGCCUCCACAGAA	2361
AD-2138593.1	UGUGGAGGCACCUUGAUAUCA	1812	UGAUAUCAAGGUGCCUCCACAGA	2362
AD-2138594.1	GUGGAGGCACCUUGAUAUCCA	1813	UGGAUAUCAAGGUGCCUCCACAG	2363
AD-2138595.1	UUGACUGCUGCCCACUGCUUA	1814	UAAGCAGUGGGCAGCAGUCAACA	2364
AD-2138596.1	UGACUGCUGCCCACUGCUUGA	2365	UCAAGCAGUGGGCAGCAGUCAAC	2915
AD-2138597.1	ACUGCUGCCCACUGCUUGGAA	2366	UUCCAAGCAGUGGGCAGCAGUCA	2916
AD-2138598.1	CUGCUGCCCACUGCUUGGAGA	2367	UCUCCAAGCAGUGGGCAGCAGUC	2917
AD-2138599.1	UGCUGCCCACUGCUUGGAGAA	2368	UUCUCCAAGCAGUGGGCAGCAGU	2918
AD-2138600.1	CUGCCCACUGCUUGGAGAAGA	2369	UCUUCUCCAAGCAGUGGGCAGCA	2919
AD-2138601.1	UGCCCACUGCUUGGAGAAGUA	2370	UACUUCUCCAAGCAGUGGGCAGC	2920
AD-2138602.1	CCCACUGCUUGGAGAAGUCCA	2371	UGGACUUCUCCAAGCAGUGGGCA	2921
AD-2138603.1	GUGCACACCAAGAAGUGAAUA	2372	UAUUCACUUCUUGGUGUGCACCC	2922
AD-2138604.1	GCACACCAAGAAGUGAAUCUA	2373	UAGAUUCACUUCUUGGUGUGCAC	2923
AD-2138605.1	ACACCAAGAAGUGAAUCUCGA	2374	UCGAGAUUCACUUCUUGGUGUGC	2924
AD-2138606.1	CACCAAGAAGUGAAUCUCGAA	2375	UUCGAGAUUCACUUCUUGGUGUG	2925
AD-2138607.1	ACCAAGAAGUGAAUCUCGAAA	2376	UUUCGAGAUUCACUUCUUGGUGU	2926
AD-2138608.1	UGAAUCUCGAACCGCAUGUUA	2377	UAACAUGCGGUUCGAGAUUCACU	2927
AD-2138609.1	AAUCUCGAACCGCAUGUUCAA	2378	UUGAACAUGCGGUUCGAGAUUCA	2928
AD-2138610.1	CGAACCGCAUGUUCAGGAAAA	2379	UUUUCCUGAACAUGCGGUUCGAG	2929
AD-2138611.1	GAACCGCAUGUUCAGGAAAUA	2380	UAUUUCCUGAACAUGCGGUUCGA	2930
AD-2138612.1	AACCGCAUGUUCAGGAAAUAA	2381	UUAUUUCCUGAACAUGCGGUUCG	2931
AD-2138613.1	ACCGCAUGUUCAGGAAAUAGA	2382	UCUAUUUCCUGAACAUGCGGUUC	2932
AD-2138614.1	CCGCAUGUUCAGGAAAUAGAA	2383	UUCUAUUUCCUGAACAUGCGGUU	2933
AD-2138615.1	UUGGAGCCCACACGAAAAGAA	2384	UUCUUUUCGUGUGGGCUCCAAGA	2934
AD-2138616.1	UGGAGCCCACACGAAAAGAUA	2385	UAUCUUUUCGUGUGGGCUCCAAG	2935
AD-2138617.1	GAGCCCACACGAAAAGAUAUA	2386	UAUAUCUUUUCGUGUGGGCUCCA	2936
AD-2138618.1	AGCCCACACGAAAAGAUAUUA	2387	UAAUAUCUUUUCGUGUGGGCUCC	2937
AD-2138619.1	GCCCACACGAAAAGAUAUUGA	2388	UCAAUAUCUUUUCGUGUGGGCUC	2938
AD-2138620.1	CCCACACGAAAAGAUAUUGCA	2389	UGCAAUAUCUUUUCGUGUGGGCU	2939
AD-2138621.1	CCACACGAAAAGAUAUUGCCA	2390	UGGCAAUAUCUUUUCGUGUGGGC	2940
AD-2138622.1	CACACGAAAAGAUAUUGCCUA	2391	UAGGCAAUAUCUUUUCGUGUGGG	2941
AD-2138623.1	ACACGAAAAGAUAUUGCCUUA	2392	UAAGGCAAUAUCUUUUCGUGUGG	2942
AD-2138624.1	CACGAAAAGAUAUUGCCUUGA	2393	UCAAGGCAAUAUCUUUUCGUGUG	2943
AD-2138625.1	ACGAAAAGAUAUUGCCUUGCA	2394	UGCAAGGCAAUAUCUUUUCGUGU	2944
AD-2138626.1	CGAAAAGAUAUUGCCUUGCUA	2395	UAGCAAGGCAAUAUCUUUUCGUG	2945
AD-2138627.1	GAAAAGAUAUUGCCUUGCUAA	2396	UUAGCAAGGCAAUAUCUUUUCGU	2946
AD-2138628.1	AAAAGAUAUUGCCUUGCUAAA	2397	UUUAGCAAGGCAAUAUCUUUUCG	2947
AD-2138629.1	AAAGAUAUUGCCUUGCUAAAA	2398	UUUUAGCAAGGCAAUAUCUUUUC	2948
AD-2138630.1	AAGAUAUUGCCUUGCUAAAGA	2399	UCUUUAGCAAGGCAAUAUCUUUU	2949
AD-2138631.1	AGAUAUUGCCUUGCUAAAGCA	2400	UGCUUUAGCAAGGCAAUAUCUUU	2950

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AD-2138632.1	GAUAUUGCCUUGCUAAAGCUA	2401	UAGCUUUAGCAAGGCAAUAUCUU	2951
AD-2138633.1	AUAUUGCCUUGCUAAAGCUAA	2402	UUAGCUUUAGCAAGGCAAUAUCU	2952
AD-2138634.1	UAUUGCCUUGCUAAAGCUAAA	2403	UUUAGCUUUAGCAAGGCAAUAUC	2953
AD-2138635.1	CCUUGCUAAAGCUAAGCAGUA	2404	UACUGCUUAGCUUUAGCAAGGCA	2954
AD-2138636.1	CUUGCUAAAGCUAAGCAGUCA	2405	UGACUGCUUAGCUUUAGCAAGGC	2955
AD-2138637.1	UGCUAAAGCUAAGCAGUCCUA	2406	UAGGACUGCUUAGCUUUAGCAAG	2956
AD-2138638.1	CUAAGCAGUCCUGCCGUCAUA	2407	UAUGACGGCAGGACUGCUUAGCU	2957
AD-2138639.1	AGCAGUCCUGCCGUCAUCACA	2408	UGUGAUGACGGCAGGACUGCUUA	2958
AD-2138640.1	GCAGUCCUGCCGUCAUCACUA	2409	UAGUGAUGACGGCAGGACUGCUU	2959
AD-2138641.1	CAGUCCUGCCGUCAUCACUGA	2410	UCAGUGAUGACGGCAGGACUGCU	2960
AD-2138642.1	UCAUCACUGACAAAGUAAUCA	2411	UGAUUACUUUGUCAGUGAUGACG	2961
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AD-2138646.1	CACUGACAAAGUAAUCCCAGA	2415	UCUGGGAUUACUUUGUCAGUGAU	2965
AD-2138647.1	ACUGACAAAGUAAUCCCAGCA	2416	UGCUGGGAUUACUUUGUCAGUGA	2966
AD-2138648.1	CUGACAAAGUAAUCCCAGCUA	2417	UAGCUGGGAUUACUUUGUCAGUG	2967
AD-2138649.1	UGACAAAGUAAUCCCAGCUUA	2418	UAAGCUGGGAUUACUUUGUCAGU	2968
AD-2138650.1	GACAAAGUAAUCCCAGCUUGA	2419	UCAAGCUGGGAUUACUUUGUCAG	2969
AD-2138651.1	ACAAAGUAAUCCCAGCUUGUA	2420	UACAAGCUGGGAUUACUUUGUCA	2970
AD-2138652.1	CAAAGUAAUCCCAGCUUGUCA	2421	UGACAAGCUGGGAUUACUUUGUC	2971
AD-2138653.1	AAAGUAAUCCCAGCUUGUCUA	2422	UAGACAAGCUGGGAUUACUUUGU	2972
AD-2138654.1	UAAUCCCAGCUUGUCUGCCAA	2423	UUGGCAGACAAGCUGGGAUUACU	2973
AD-2138655.1	AUCCCAGCUUGUCUGCCAUCA	2424	UGAUGGCAGACAAGCUGGGAUUA	2974
AD-2138656.1	CUGACCGGACCGAAUGUUUCA	2425	UGAAACAUUCGGUCCGGUCAGCG	2975
AD-2138657.1	GACCGGACCGAAUGUUUCAUA	2426	UAUGAAACAUUCGGUCCGGUCAG	2976
AD-2138658.1	ACCGGACCGAAUGUUUCAUCA	2427	UGAUGAAACAUUCGGUCCGGUCA	2977
AD-2138659.1	CCGGACCGAAUGUUUCAUCAA	2428	UUGAUGAAACAUUCGGUCCGGUC	2978
AD-2138660.1	CGGACCGAAUGUUUCAUCACA	2429	UGUGAUGAAACAUUCGGUCCGGU	2979
AD-2138661.1	GGACCGAAUGUUUCAUCACUA	2430	UAGUGAUGAAACAUUCGGUCCGG	2980
AD-2138662.1	GACCGAAUGUUUCAUCACUGA	2431	UCAGUGAUGAAACAUUCGGUCCG	2981
AD-2138663.1	CGAAUGUUUCAUCACUGGCUA	2432	UAGCCAGUGAUGAAACAUUCGGU	2982
AD-2138664.1	GAGAAACCCAAGGUACUUUUA	2433	UAAAAGUACCUUGGGUUUCUCCC	2983
AD-2138665.1	AGAAACCCAAGGUACUUUUGA	2434	UCAAAAGUACCUUGGGUUUCUCC	2984
AD-2138666.1	GAAACCCAAGGUACUUUUGGA	2435	UCCAAAAGUACCUUGGGUUUCUC	2985
AD-2138667.1	AAACCCAAGGUACUUUUGGAA	2436	UUCCAAAAGUACCUUGGGUUUCU	2986
AD-2138668.1	AACCCAAGGUACUUUUGGAGA	2437	UCUCCAAAAGUACCUUGGGUUUC	2987
AD-2138669.1	ACCCAAGGUACUUUUGGAGCA	2438	UGCUCCAAAAGUACCUUGGGUUU	2988
AD-2138670.1	CCCAAGGUACUUUUGGAGCUA	2439	UAGCUCCAAAAGUACCUUGGGUU	2989
AD-2138671.1	CAAGGUACUUUUGGAGCUGGA	2440	UCCAGCUCCAAAAGUACCUUGGG	2990
AD-2138672.1	ACUUUUGGAGCUGGCCUUCUA	2441	UAGAAGGCCAGCUCCAAAAGUAC	2991
AD-2138673.1	UUUGGAGCUGGCCUUCUCAAA	2442	UUUGAGAAGGCCAGCUCCAAAAG	2992

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AD-2138676.1	GGAGCUGGCCUUCUCAAGGAA	2445	UUCCUUGAGAAGGCCAGCUCCAA	2995
AD-2138677.1	GGAAGCCCAGCUCCCUGUGAA	2446	UUCACAGGGAGCUGGGCUUCCUU	2996
AD-2138678.1	GAAGCCCAGCUCCCUGUGAUA	2447	UAUCACAGGGAGCUGGGCUUCCU	2997
AD-2138679.1	AAGCCCAGCUCCCUGUGAUUA	2448	UAAUCACAGGGAGCUGGGCUUCC	2998
AD-2138680.1	AGCCCAGCUCCCUGUGAUUGA	2449	UCAAUCACAGGGAGCUGGGCUUC	2999
AD-2138681.1	GCCCAGCUCCCUGUGAUUGAA	2450	UUCAAUCACAGGGAGCUGGGCUU	3000
AD-2138682.1	CCCAGCUCCCUGUGAUUGAGA	2451	UCUCAAUCACAGGGAGCUGGGCU	3001
AD-2138683.1	CCAGCUCCCUGUGAUUGAGAA	2452	UUCUCAAUCACAGGGAGCUGGGC	3002
AD-2138684.1	CAGCUCCCUGUGAUUGAGAAA	2453	UUUCUCAAUCACAGGGAGCUGGG	3003
AD-2138685.1	AGCUCCCUGUGAUUGAGAAUA	2454	UAUUCUCAAUCACAGGGAGCUGG	3004
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AD-2138687.1	CUCCCUGUGAUUGAGAAUAAA	2456	UUUAUUCUCAAUCACAGGGAGCU	3006
AD-2138688.1	UCCCUGUGAUUGAGAAUAAAA	2457	UUUUAUUCUCAAUCACAGGGAGC	3007
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AD-2138690.1	CCUGUGAUUGAGAAUAAAGUA	2459	UACUUUAUUCUCAAUCACAGGGA	3009
AD-2138691.1	CUGUGAUUGAGAAUAAAGUGA	2460	UCACUUUAUUCUCAAUCACAGGG	3010
AD-2138692.1	UGUGAUUGAGAAUAAAGUGUA	2461	UACACUUUAUUCUCAAUCACAGG	3011
AD-2138693.1	GUGAUUGAGAAUAAAGUGUGA	2462	UCACACUUUAUUCUCAAUCACAG	3012
AD-2138694.1	UGAUUGAGAAUAAAGUGUGCA	2463	UGCACACUUUAUUCUCAAUCACA	3013
AD-2138695.1	GAUUGAGAAUAAAGUGUGCAA	2464	UUGCACACUUUAUUCUCAAUCAC	3014
AD-2138696.1	AUUGAGAAUAAAGUGUGCAAA	2465	UUUGCACACUUUAUUCUCAAUCA	3015
AD-2138697.1	UUGAGAAUAAAGUGUGCAAUA	2466	UAUUGCACACUUUAUUCUCAAUC	3016
AD-2138698.1	UGAGAAUAAAGUGUGCAAUCA	2467	UGAUUGCACACUUUAUUCUCAAU	3017
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AD-2138701.1	AAUAAAGUGUGCAAUCGCUAA	2470	UUAGCGAUUGCACACUUUAUUCU	3020
AD-2138702.1	AUAAAGUGUGCAAUCGCUAUA	2471	UAUAGCGAUUGCACACUUUAUUC	3021
AD-2138703.1	UAAAGUGUGCAAUCGCUAUGA	2472	UCAUAGCGAUUGCACACUUUAUU	3022
AD-2138704.1	AAAGUGUGCAAUCGCUAUGAA	2473	UUCAUAGCGAUUGCACACUUUAU	3023
AD-2138705.1	AAGUGUGCAAUCGCUAUGAGA	2474	UCUCAUAGCGAUUGCACACUUUA	3024
AD-2138706.1	AGUGUGCAAUCGCUAUGAGUA	2475	UACUCAUAGCGAUUGCACACUUU	3025
AD-2138707.1	GUGUGCAAUCGCUAUGAGUUA	2476	UAACUCAUAGCGAUUGCACACUU	3026
AD-2138708.1	UGUGCAAUCGCUAUGAGUUUA	2477	UAAACUCAUAGCGAUUGCACACU	3027
AD-2138709.1	GUGCAAUCGCUAUGAGUUUCA	2478	UGAAACUCAUAGCGAUUGCACAC	3028
AD-2138710.1	UGCAAUCGCUAUGAGUUUCUA	2479	UAGAAACUCAUAGCGAUUGCACA	3029
AD-2138711.1	CAAUCGCUAUGAGUUUCUGAA	2480	UUCAGAAACUCAUAGCGAUUGCA	3030
AD-2138712.1	AAUCGCUAUGAGUUUCUGAAA	2481	UUUCAGAAACUCAUAGCGAUUGC	3031
AD-2138713.1	AUCGCUAUGAGUUUCUGAAUA	2482	UAUUCAGAAACUCAUAGCGAUUG	3032
AD-2138714.1	UCGCUAUGAGUUUCUGAAUGA	2483	UCAUUCAGAAACUCAUAGCGAUU	3033
AD-2138715.1	CGCUAUGAGUUUCUGAAUGGA	2484	UCCAUUCAGAAACUCAUAGCGAU	3034

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AD-2138717.1	CUAUGAGUUUCUGAAUGGAAA	2486	UUUCCAUUCAGAAACUCAUAGCG	3036
AD-2138718.1	UAUGAGUUUCUGAAUGGAAGA	2487	UCUUCCAUUCAGAAACUCAUAGC	3037
AD-2138719.1	AUGAGUUUCUGAAUGGAAGAA	2488	UUCUUCCAUUCAGAAACUCAUAG	3038
AD-2138720.1	UGAGUUUCUGAAUGGAAGAGA	2489	UCUCUUCCAUUCAGAAACUCAUA	3039
AD-2138721.1	GAGUUUCUGAAUGGAAGAGUA	2490	UACUCUUCCAUUCAGAAACUCAU	3040
AD-2138722.1	GUUUCUGAAUGGAAGAGUCCA	2491	UGGACUCUUCCAUUCAGAAACUC	3041
AD-2138723.1	UUUCUGAAUGGAAGAGUCCAA	2492	UUGGACUCUUCCAUUCAGAAACU	3042
AD-2138724.1	UUCUGAAUGGAAGAGUCCAAA	2493	UUUGGACUCUUCCAUUCAGAAAC	3043
AD-2138725.1	UCUGAAUGGAAGAGUCCAAUA	2494	UAUUGGACUCUUCCAUUCAGAAA	3044
AD-2138726.1	CUGAAUGGAAGAGUCCAAUCA	2495	UGAUUGGACUCUUCCAUUCAGAA	3045
AD-2138727.1	GAAUGGAAGAGUCCAAUCCAA	2496	UUGGAUUGGACUCUUCCAUUCAG	3046
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AD-2138729.1	AACUCUGUGCUGGGCAUUUGA	2498	UCAAAUGCCCAGCACAGAGUUCG	3048
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AD-2138731.1	UCUGUGCUGGGCAUUUGGCCA	2500	UGGCCAAAUGCCCAGCACAGAGU	3050
AD-2138732.1	UGUGCUGGGCAUUUGGCCGGA	2501	UCCGGCCAAAUGCCCAGCACAGA	3051
AD-2138733.1	GUGCUGGGCAUUUGGCCGGAA	2502	UUCCGGCCAAAUGCCCAGCACAG	3052
AD-2138734.1	UGCUGGGCAUUUGGCCGGAGA	2503	UCUCCGGCCAAAUGCCCAGCACA	3053
AD-2138735.1	CUUCGAGAAGGACAAAUACAA	2504	UUGUAUUUGUCCUUCUCGAAGCA	3054
AD-2138736.1	UUCGAGAAGGACAAAUACAUA	2505	UAUGUAUUUGUCCUUCUCGAAGC	3055
AD-2138737.1	UCGAGAAGGACAAAUACAUUA	2506	UAAUGUAUUUGUCCUUCUCGAAG	3056
AD-2138738.1	CGAGAAGGACAAAUACAUUUA	2507	UAAAUGUAUUUGUCCUUCUCGAA	3057
AD-2138739.1	GAGAAGGACAAAUACAUUUUA	2508	UAAAAUGUAUUUGUCCUUCUCGA	3058
AD-2138740.1	AGAAGGACAAAUACAUUUUAA	2509	UUAAAAUGUAUUUGUCCUUCUCG	3059
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AD-2138746.1	ACAAAUACAUUUUACAAGGAA	2515	UUCCUUGUAAAAUGUAUUUGUCC	3065
AD-2138747.1	AAUAAGCCUGGUGUCUAUGUA	2516	UACAUAGACACCAGGCUUAUUGG	3066
AD-2138748.1	AUAAGCCUGGUGUCUAUGUUA	2517	UAACAUAGACACCAGGCUUAUUG	3067
AD-2138749.1	UAAGCCUGGUGUCUAUGUUCA	2518	UGAACAUAGACACCAGGCUUAUU	3068
AD-2138750.1	AGCCUGGUGUCUAUGUUCGUA	2519	UACGAACAUAGACACCAGGCUUA	3069
AD-2138751.1	CCUGGUGUCUAUGUUCGUGUA	2520	UACACGAACAUAGACACCAGGCU	3070
AD-2138752.1	CUGGUGUCUAUGUUCGUGUUA	2521	UAACACGAACAUAGACACCAGGC	3071
AD-2138753.1	UGGUGUCUAUGUUCGUGUUUA	2522	UAAACACGAACAUAGACACCAGG	3072
AD-2138754.1	GGUGUCUAUGUUCGUGUUUCA	2523	UGAAACACGAACAUAGACACCAG	3073
AD-2138755.1	GUGUCUAUGUUCGUGUUUCAA	2524	UUGAAACACGAACAUAGACACCA	3074
AD-2138756.1	UGUCUAUGUUCGUGUUUCAAA	2525	UUUGAAACACGAACAUAGACACC	3075
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AD-2138760.1	UAUGUUCGUGUUUCAAGGUUA	2529	UAACCUUGAAACACGAACAUAGA	3079
AD-2138761.1	AUGUUCGUGUUUCAAGGUUUA	2530	UAAACCUUGAAACACGAACAUAG	3080
AD-2138762.1	UGUUCGUGUUUCAAGGUUUGA	2531	UCAAACCUUGAAACACGAACAUA	3081
AD-2138763.1	GUUCGUGUUUCAAGGUUUGUA	2532	UACAAACCUUGAAACACGAACAU	3082
AD-2138764.1	UUCGUGUUUCAAGGUUUGUUA	2533	UAACAAACCUUGAAACACGAACA	3083
AD-2138765.1	UCGUGUUUCAAGGUUUGUUAA	2534	UUAACAAACCUUGAAACACGAAC	3084
AD-2138766.1	CGUGUUUCAAGGUUUGUUACA	2535	UGUAACAAACCUUGAAACACGAA	3085
AD-2138767.1	GUGUUUCAAGGUUUGUUACUA	2536	UAGUAACAAACCUUGAAACACGA	3086
AD-2138768.1	UGUUUCAAGGUUUGUUACUUA	2537	UAAGUAACAAACCUUGAAACACG	3087
AD-2138769.1	GUUUCAAGGUUUGUUACUUGA	2538	UCAAGUAACAAACCUUGAAACAC	3088
AD-2138770.1	UUUCAAGGUUUGUUACUUGGA	2539	UCCAAGUAACAAACCUUGAAACA	3089
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AD-2138772.1	UCAAGGUUUGUUACUUGGAUA	2541	UAUCCAAGUAACAAACCUUGAAA	3091
AD-2138773.1	UGUUACUUGGAUUGAGGGAGA	2542	UCUCCCUCAAUCCAAGUAACAAA	3092
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AD-2138779.1	UGGAUUGAGGGAGUGAUGAGA	2548	UCUCAUCACUCCCUCAAUCCAAG	3098
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AD-2138791.2	GUGAUGAGAAAUAAUUAAUUA	2558	UAAUUAAUUAUUUCUCAUCACUC	3108
AD-2138792.2	UGAUGAGAAAUAAUUAAUUGA	2559	UCAAUUAAUUAUUUCUCAUCACU	3109
AD-2138793.2	GAUGAGAAAUAAUUAAUUGGA	2560	UCCAAUUAAUUAUUUCUCAUCAC	3110
AD-2138794.2	AUGAGAAAUAAUUAAUUGGAA	2561	UUCCAAUUAAUUAUUUCUCAUCA	3111
AD-2138795.2	UGGACGGGAGACAGAGUGACA	2562	UGUCACUCUGUCUCCCGUCCAAU	3112
AD-2138796.2	GGACGGGAGACAGAGUGACGA	2563	UCGUCACUCUGUCUCCCGUCCAA	3113
AD-2138797.2	GACGGGAGACAGAGUGACGCA	2564	UGCGUCACUCUGUCUCCCGUCCA	3114
AD-2138798.2	ACGGGAGACAGAGUGACGCAA	2565	UUGCGUCACUCUGUCUCCCGUCC	3115
AD-2138800.2	AGACAGAGUGACGCACUGACA	2566	UGUCAGUGCGUCACUCUGUCUCC	3116
AD-2138802.2	ACAGAGUGACGCACUGACUCA	2567	UGAGUCAGUGCGUCACUCUGUCU	3117
AD-2138804.2	AGAGUGACGCACUGACUCACA	2568	UGUGAGUCAGUGCGUCACUCUGU	3118

Duplex ID	Sense Sequence	SEQ ID NO	Antisense Sequence	SEQ ID NO
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AD-2138807.2	UGACGCACUGACUCACCUAGA	2571	UCUAGGUGAGUCAGUGCGUCACU	3121
AD-2138808.2	GACGCACUGACUCACCUAGAA	2572	UUCUAGGUGAGUCAGUGCGUCAC	3122
AD-2138809.2	ACGCACUGACUCACCUAGAGA	2573	UCUCUAGGUGAGUCAGUGCGUCA	3123
AD-2138810.2	CGCACUGACUCACCUAGAGGA	2574	UCCUCUAGGUGAGUCAGUGCGUC	3124
AD-2138811.2	GCACUGACUCACCUAGAGGCA	2575	UGCCUCUAGGUGAGUCAGUGCGU	3125
AD-2138812.2	CACUGACUCACCUAGAGGCUA	2576	UAGCCUCUAGGUGAGUCAGUGCG	3126
AD-2138813.2	ACUGACUCACCUAGAGGCUGA	2577	UCAGCCUCUAGGUGAGUCAGUGC	3127
AD-2138814.2	GAACGUGGGUAGGGAUUUAGA	2578	UCUAAAUCCCUACCCACGUUCCA	3128
AD-2138816.2	ACGUGGGUAGGGAUUUAGCAA	2579	UUGCUAAAUCCCUACCCACGUUC	3129
AD-2138819.2	UGGGUAGGGAUUUAGCAUGCA	2580	UGCAUGCUAAAUCCCUACCCACG	3130
AD-2138820.2	GGGUAGGGAUUUAGCAUGCUA	2581	UAGCAUGCUAAAUCCCUACCCAC	3131
AD-2138821.2	GGUAGGGAUUUAGCAUGCUGA	2582	UCAGCAUGCUAAAUCCCUACCCA	3132
AD-2138822.2	GUAGGGAUUUAGCAUGCUGGA	2583	UCCAGCAUGCUAAAUCCCUACCC	3133
AD-2138823.2	UAGGGAUUUAGCAUGCUGGAA	2584	UUCCAGCAUGCUAAAUCCCUACC	3134
AD-2138824.2	UUUAGCAUGCUGGAAAUAACA	2585	UGUUAUUUCCAGCAUGCUAAAUC	3135
AD-2138825.2	UUAGCAUGCUGGAAAUAACUA	2586	UAGUUAUUUCCAGCAUGCUAAAU	3136
AD-2138826.2	UAGCAUGCUGGAAAUAACUGA	2587	UCAGUUAUUUCCAGCAUGCUAAA	3137
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AD-2138830.2	AUGCUGGAAAUAACUGGCAGA	2591	UCUGCCAGUUAUUUCCAGCAUGC	3141
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AD-2138836.2	GAAAUAACUGGCAGUAAUCAA	2597	UUGAUUACUGCCAGUUAUUUCCA	3147
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AD-2138843.2	UGGCAGUAAUCAAACGAAGAA	2604	UUCUUCGUUUGAUUACUGCCAGU	3154
AD-2138844.2	GGCAGUAAUCAAACGAAGACA	2605	UGUCUUCGUUUGAUUACUGCCAG	3155
AD-2138845.2	GCAGUAAUCAAACGAAGACAA	2606	UUGUCUUCGUUUGAUUACUGCCA	3156
AD-2138847.2	AGUAAUCAAACGAAGACACUA	2607	UAGUGUCUUCGUUUGAUUACUGC	3157
AD-2138848.2	AAUCAAACGAAGACACUGUCA	2608	UGACAGUGUCUUCGUUUGAUUAC	3158
AD-2138849.2	AUCAAACGAAGACACUGUCCA	2609	UGGACAGUGUCUUCGUUUGAUUA	3159
AD-2138850.2	ACGCCAAACCUCGGCAUUUUA	2610	UAAAAUGCCGAGGUUUGGCGUAG	3160

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AD-2138852.2	GCCAAACCUCGGCAUUUUUUA	2612	UAAAAAAUGCCGAGGUUUGGCGU	3162
AD-2138853.2	CCAAACCUCGGCAUUUUUUGA	2613	UCAAAAAAUGCCGAGGUUUGGCG	3163
AD-2138854.2	CAAACCUCGGCAUUUUUUGUA	2614	UACAAAAAAUGCCGAGGUUUGGC	3164
AD-2138855.2	AAACCUCGGCAUUUUUUGUGA	2615	UCACAAAAAAUGCCGAGGUUUGG	3165
AD-2138856.2	AACCUCGGCAUUUUUUGUGUA	2616	UACACAAAAAAUGCCGAGGUUUG	3166
AD-2138857.2	ACCUCGGCAUUUUUUGUGUUA	2617	UAACACAAAAAAUGCCGAGGUUU	3167
AD-2138858.2	CCUCGGCAUUUUUUGUGUUAA	2618	UUAACACAAAAAAUGCCGAGGUU	3168
AD-2138859.2	CUCGGCAUUUUUUGUGUUAUA	2619	UAUAACACAAAAAAUGCCGAGGU	3169
AD-2138860.2	UCGGCAUUUUUUGUGUUAUUA	2620	UAAUAACACAAAAAAUGCCGAGG	3170
AD-2138861.2	GGCAUUUUUUGUGUUAUUUUA	2621	UAAAAUAACACAAAAAAUGCCGA	3171
AD-2138862.2	GCAUUUUUUGUGUUAUUUUCA	2622	UGAAAAUAACACAAAAAAUGCCG	3172
AD-2138863.2	CAUUUUUUGUGUUAUUUUCUA	2623	UAGAAAAUAACACAAAAAAUGCC	3173
AD-2138864.2	UUUGUGUUAUUUUCUGACUGA	2624	UCAGUCAGAAAAUAACACAAAAA	3174
AD-2138865.2	UUGUGUUAUUUUCUGACUGCA	2625	UGCAGUCAGAAAAUAACACAAAA	3175
AD-2138866.2	UGUGUUAUUUUCUGACUGCUA	2626	UAGCAGUCAGAAAAUAACACAAA	3176
AD-2138867.2	GUGUUAUUUUCUGACUGCUGA	2627	UCAGCAGUCAGAAAAUAACACAA	3177
AD-2138868.2	UGUUAUUUUCUGACUGCUGGA	2628	UCCAGCAGUCAGAAAAUAACACA	3178
AD-2138869.2	GUUAUUUUCUGACUGCUGGAA	2629	UUCCAGCAGUCAGAAAAUAACAC	3179
AD-2138870.2	UUAUUUUCUGACUGCUGGAUA	2630	UAUCCAGCAGUCAGAAAAUAACA	3180
AD-2138871.2	UAUUUUCUGACUGCUGGAUUA	2631	UAAUCCAGCAGUCAGAAAAUAAC	3181
AD-2138872.2	AUUUUCUGACUGCUGGAUUCA	2632	UGAAUCCAGCAGUCAGAAAAUAA	3182
AD-2138873.2	UCUGACUGCUGGAUUCUGUAA	2633	UUACAGAAUCCAGCAGUCAGAAA	3183
AD-2138874.2	AGUAAGGUGACAUAGCUAUGA	2634	UCAUAGCUAUGUCACCUUACUAC	3184
AD-2138875.2	GUAAGGUGACAUAGCUAUGAA	2635	UUCAUAGCUAUGUCACCUUACUA	3185
AD-2138876.2	UAAGGUGACAUAGCUAUGACA	2636	UGUCAUAGCUAUGUCACCUUACU	3186
AD-2138877.2	AAGGUGACAUAGCUAUGACAA	2637	UUGUCAUAGCUAUGUCACCUUAC	3187
AD-2138878.2	AGGUGACAUAGCUAUGACAUA	2638	UAUGUCAUAGCUAUGUCACCUUA	3188
AD-2138879.2	GGUGACAUAGCUAUGACAUUA	2639	UAAUGUCAUAGCUAUGUCACCUU	3189
AD-2138880.2	GUGACAUAGCUAUGACAUUUA	2640	UAAAUGUCAUAGCUAUGUCACCU	3190
AD-2138881.2	UGACAUAGCUAUGACAUUUGA	2641	UCAAAUGUCAUAGCUAUGUCACC	3191
AD-2138882.2	ACAUAGCUAUGACAUUUGUUA	2642	UAACAAAUGUCAUAGCUAUGUCA	3192
AD-2138883.2	CAUAGCUAUGACAUUUGUUAA	2643	UUAACAAAUGUCAUAGCUAUGUC	3193
AD-2138884.2	AUAGCUAUGACAUUUGUUAAA	2644	UUUAACAAAUGUCAUAGCUAUGU	3194
AD-2138885.2	UAGCUAUGACAUUUGUUAAAA	2645	UUUUAACAAAUGUCAUAGCUAUG	3195
AD-2138886.2	AGCUAUGACAUUUGUUAAAAA	2646	UUUUUAACAAAUGUCAUAGCUAU	3196
AD-2138887.2	GCUAUGACAUUUGUUAAAAAA	2647	UUUUUUAACAAAUGUCAUAGCUA	3197
AD-2138888.2	CUAUGACAUUUGUUAAAAAUA	2648	UAUUUUUAACAAAUGUCAUAGCU	3198
AD-2138889.2	UAUGACAUUUGUUAAAAAUAA	2649	UUAUUUUUAACAAAUGUCAUAGC	3199
AD-2138890.2	AUGACAUUUGUUAAAAAUAAA	2650	UUUAUUUUUAACAAAUGUCAUAG	3200
AD-2138891.2	UGACAUUUGUUAAAAAUAAAA	2651	UUUUAUUUUUAACAAAUGUCAUA	3201
AD-2138892.2	GACAUUUGUUAAAAAUAAACA	2652	UGUUUAUUUUUAACAAAUGUCAU	3202

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AD-2138895.2	AUAAACUCUGUACUUAACUUA	2655	UAAGUUAAGUACAGAGUUUAUUU	3205
AD-2138896.2	UAAACUCUGUACUUAACUUUA	2656	UAAAGUUAAGUACAGAGUUUAUU	3206
AD-2138897.2	AAACUCUGUACUUAACUUUGA	2657	UCAAAGUUAAGUACAGAGUUUAU	3207
AD-2138898.2	AACUCUGUACUUAACUUUGAA	2658	UUCAAAGUUAAGUACAGAGUUUA	3208
AD-2138899.2	ACUCUGUACUUAACUUUGAUA	2659	UAUCAAAGUUAAGUACAGAGUUU	3209
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AD-2138901.2	UCUGUACUUAACUUUGAUUUA	2661	UAAAUCAAAGUUAAGUACAGAGU	3211
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AD-2138903.2	UGUACUUAACUUUGAUUUGAA	2663	UUCAAAUCAAAGUUAAGUACAGA	3213
AD-2138904.2	GUACUUAACUUUGAUUUGAGA	2664	UCUCAAAUCAAAGUUAAGUACAG	3214
AD-2138905.2	UACUUAACUUUGAUUUGAGUA	2665	UACUCAAAUCAAAGUUAAGUACA	3215
AD-2138906.2	ACUUAACUUUGAUUUGAGUAA	2666	UUACUCAAAUCAAAGUUAAGUAC	3216
AD-2138907.2	UUGAUUUGAGUAAAUUUUGGA	2667	UCCAAAAUUUACUCAAAUCAAAG	3217
AD-2138908.2	UGAGUAAAUUUUGGUUUUGGA	2668	UCCAAAACCAAAAUUUACUCAAA	3218
AD-2138909.2	GAGUAAAUUUUGGUUUUGGUA	2669	UACCAAAACCAAAAUUUACUCAA	3219
AD-2138910.2	AGUAAAUUUUGGUUUUGGUCA	2670	UGACCAAAACCAAAAUUUACUCA	3220
AD-2138911.2	GUAAAUUUUGGUUUUGGUCUA	2671	UAGACCAAAACCAAAAUUUACUC	3221
AD-2138912.2	UAAAUUUUGGUUUUGGUCUUA	2672	UAAGACCAAAACCAAAAUUUACU	3222
AD-2138913.2	AAAUUUUGGUUUUGGUCUUCA	2673	UGAAGACCAAAACCAAAAUUUAC	3223
AD-2138914.2	AUUUUGGUUUUGGUCUUCAAA	2674	UUUGAAGACCAAAACCAAAAUUU	3224
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AD-2138916.2	UUGGUUUUGGUCUUCAACAUA	2676	UAUGUUGAAGACCAAAACCAAAA	3226
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AD-2138923.2	UGGUCUUCAACAUUUUCAUGA	2683	UCAUGAAAAUGUUGAAGACCAAA	3233
AD-2138924.2	GGUCUUCAACAUUUUCAUGCA	2684	UGCAUGAAAAUGUUGAAGACCAA	3234
AD-2138925.2	GUCUUCAACAUUUUCAUGCUA	2685	UAGCAUGAAAAUGUUGAAGACCA	3235
AD-2138926.2	CUUCAACAUUUUCAUGCUCUA	2686	UAGAGCAUGAAAAUGUUGAAGAC	3236
AD-2138927.2	UUCAACAUUUUCAUGCUCUUA	2687	UAAGAGCAUGAAAAUGUUGAAGA	3237
AD-2138928.2	UCAACAUUUUCAUGCUCUUUA	2688	UAAAGAGCAUGAAAAUGUUGAAG	3238
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AD-2138930.2	AACAUUUUCAUGCUCUUUGUA	2690	UACAAAGAGCAUGAAAAUGUUGA	3240
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AD-2138932.2	CAUUUUCAUGCUCUUUGUUCA	2692	UGAACAAAGAGCAUGAAAAUGUU	3242
AD-2138933.2	AUUUUCAUGCUCUUUGUUCAA	2693	UUGAACAAAGAGCAUGAAAAUGU	3243
AD-2138934.2	UUUUCAUGCUCUUUGUUCACA	2694	UGUGAACAAAGAGCAUGAAAAUG	3244

Duplex ID	Sense Sequence	SEQ ID NO	Antisense Sequence	SEQ ID NO
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AD-2138937.2	AUUUAGCUGCUUUUGAUAAGA	2697	UCUUAUCAAAAGCAGCUAAAUCC	3247
AD-2138938.2	UUAGCUGCUUUUGAUAAGGAA	2698	UUCCUUAUCAAAAGCAGCUAAAU	3248
AD-2138939.2	UAGCUGCUUUUGAUAAGGAAA	2699	UUUCCUUAUCAAAAGCAGCUAAA	3249
AD-2138940.2	AGCUGCUUUUGAUAAGGAACA	2700	UGUUCCUUAUCAAAAGCAGCUAA	3250
AD-2138941.2	GCUGCUUUUGAUAAGGAACAA	2701	UUGUUCCUUAUCAAAAGCAGCUA	3251
AD-2138942.2	AUAAGGAACAGCUGCACAAAA	2702	UUUUGUGCAGCUGUUCCUUAUCA	3252
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AD-2138944.2	GCAUUUACCUCAUCAGCUAAA	2704	UUUAGCUGAUGAGGUAAAUGCGU	3254
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AD-2138947.2	CUUGACAUGCAUUUUUACUGA	2707	UCAGUAAAAAUGCAUGUCAAGCC	3257
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AD-2138949.2	UGACAUGCAUUUUUACUGUCA	2709	UGACAGUAAAAAUGCAUGUCAAG	3259
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AD-2138953.2	AUGCAUUUUUACUGUCUUUAA	2713	UUAAAGACAGUAAAAAUGCAUGU	3263
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AD-2138963.2	CUGUCUUUAUUCCUGACACUA	2723	UAGUGUCAGGAAUAAAGACAGUA	3273
AD-2138964.2	GUCUUUAUUCCUGACACUGAA	2724	UUCAGUGUCAGGAAUAAAGACAG	3274
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AD-2138966.2	ACACUGAGAUGAAUGUUUUCA	2726	UGAAAACAUUCAUCUCAGUGUCA	3276
AD-2138967.2	CACUGAGAUGAAUGUUUUCAA	2727	UUGAAAACAUUCAUCUCAGUGUC	3277
AD-2138968.2	ACUGAGAUGAAUGUUUUCAAA	2728	UUUGAAAACAUUCAUCUCAGUGU	3278
AD-2138969.2	CUGAGAUGAAUGUUUUCAAAA	2729	UUUUGAAAACAUUCAUCUCAGUG	3279
AD-2138970.2	UGAGAUGAAUGUUUUCAAAGA	2730	UCUUUGAAAACAUUCAUCUCAGU	3280
AD-2138971.2	GAGAUGAAUGUUUUCAAAGCA	2731	UGCUUUGAAAACAUUCAUCUCAG	3281
AD-2138972.2	AGAUGAAUGUUUUCAAAGCUA	2732	UAGCUUUGAAAACAUUCAUCUCA	3282
AD-2138973.2	AAUGUUUUCAAAGCUGCAACA	2733	UGUUGCAGCUUUGAAAACAUUCA	3283
AD-2138974.2	AUGUUUUCAAAGCUGCAACAA	2734	UUGUUGCAGCUUUGAAAACAUUC	3284
AD-2138975.2	UGUUUUCAAAGCUGCAACAUA	2735	UAUGUUGCAGCUUUGAAAACAUU	3285
AD-2138976.2	GUUUUCAAAGCUGCAACAUGA	2736	UCAUGUUGCAGCUUUGAAAACAU	3286

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AD-2138979.2	CCGAUUCUGUUAUUGGGAAUA	2739	UAUUCCCAAUAACAGAAUCGGUU	3289
AD-2138980.2	CGAUUCUGUUAUUGGGAAUGA	2740	UCAUUCCCAAUAACAGAAUCGGU	3290
AD-2138981.2	GAUUCUGUUAUUGGGAAUGAA	2741	UUCAUUCCCAAUAACAGAAUCGG	3291
AD-2138982.2	AUUCUGUUAUUGGGAAUGAAA	2742	UUUCAUUCCCAAUAACAGAAUCG	3292
AD-2138983.2	UUCUGUUAUUGGGAAUGAAAA	2743	UUUUCAUUCCCAAUAACAGAAUC	3293
AD-2138984.2	UCUGUUAUUGGGAAUGAAAUA	2744	UAUUUCAUUCCCAAUAACAGAAU	3294
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AD-2138987.2	GUUAUUGGGAAUGAAAUCUGA	2747	UCAGAUUUCAUUCCCAAUAACAG	3297
AD-2138988.2	UUAUUGGGAAUGAAAUCUGUA	2748	UACAGAUUUCAUUCCCAAUAACA	3298
AD-2138989.2	AUUGGGAAUGAAAUCUGUCAA	2749	UUGACAGAUUUCAUUCCCAAUAA	3299
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AD-2138994.2	GUGUAACACAAGACCAACUGA	2754	UCAGUUGGUCUUGUGUUACACAU	3304
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AD-2138996.2	UAACACAAGACCAACUGAGAA	2756	UUCUCAGUUGGUCUUGUGUUACA	3306
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AD-2139015.2	UAAAUGAACAACAAGCAAAUA	2775	UAUUUGCUUGUUGUUCAUUUACA	3325
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AD-2139017.2	AAUGAACAACAAGCAAAUAUA	2777	UAUAUUUGCUUGUUGUUCAUUUA	3327
AD-2139018.2	AUGAACAACAAGCAAAUAUUA	2778	UAAUAUUUGCUUGUUGUUCAUUU	3328

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AD-2139021.2	AACAACAAGCAAAUAUUGAAA	2781	UUUCAAUAUUUGCUUGUUGUUCA	3331
AD-2139022.2	ACAACAAGCAAAUAUUGAAGA	2782	UCUUCAAUAUUUGCUUGUUGUUC	3332
AD-2139023.2	CAACAAGCAAAUAUUGAAGGA	2783	UCCUUCAAUAUUUGCUUGUUGUU	3333
AD-2139024.2	AACAAGCAAAUAUUGAAGGUA	2784	UACCUUCAAUAUUUGCUUGUUGU	3334
AD-2139025.2	ACAAGCAAAUAUUGAAGGUGA	2785	UCACCUUCAAUAUUUGCUUGUUG	3335
AD-2139026.2	CACUUAUUUCCCAUUGCUAAA	2786	UUUAGCAAUGGGAAAUAAGUGGU	3336
AD-2139027.2	ACUUAUUUCCCAUUGCUAAUA	2787	UAUUAGCAAUGGGAAAUAAGUGG	3337
AD-2139028.2	CUUAUUUCCCAUUGCUAAUUA	2788	UAAUUAGCAAUGGGAAAUAAGUG	3338
AD-2139029.2	UUAUUUCCCAUUGCUAAUUGA	2789	UCAAUUAGCAAUGGGAAAUAAGU	3339
AD-2139030.2	AUUUCCCAUUGCUAAUUGCCA	2790	UGGCAAUUAGCAAUGGGAAAUAA	3340
AD-2139031.2	GCCUGCCCGGUUUUGAAACAA	2791	UUGUUUCAAAACCGGGCAGGCAA	3341
AD-2139032.2	UUUUGAAACAGUCUGCAGUAA	2792	UUACUGCAGACUGUUUCAAAACC	3342
AD-2139033.2	UUGAAACAGUCUGCAGUACAA	2793	UUGUACUGCAGACUGUUUCAAAA	3343
AD-2139034.2	GUGGGAGAGAUACAUGUUUAA	2794	UUAAACAUGUAUCUCUCCCACAG	3344
AD-2139035.2	GGGAGAGAUACAUGUUUAGAA	2795	UUCUAAACAUGUAUCUCUCCCAC	3345
AD-2139036.2	GGAGAGAUACAUGUUUAGAAA	2796	UUUCUAAACAUGUAUCUCUCCCA	3346
AD-2139037.2	GAGAGAUACAUGUUUAGAAGA	2797	UCUUCUAAACAUGUAUCUCUCCC	3347
AD-2139038.2	GAGAUACAUGUUUAGAAGGAA	2798	UUCCUUCUAAACAUGUAUCUCUC	3348
AD-2139039.2	AGAUACAUGUUUAGAAGGAAA	2799	UUUCCUUCUAAACAUGUAUCUCU	3349
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AD-2139047.2	AGAAGGAAGAGAAAGGACAAA	2807	UUUGUCCUUUCUCUUCCUUCUAA	3357
AD-2139048.2	GAAGGAAGAGAAAGGACAAAA	2808	UUUUGUCCUUUCUCUUCCUUCUA	3358
AD-2139049.2	AAGGCACACGUUUUACCAUUA	2809	UAAUGGUAAAACGUGUGCCUUUG	3359
AD-2139050.2	AGGCACACGUUUUACCAUUUA	2810	UAAAUGGUAAAACGUGUGCCUUU	3360
AD-2139051.2	GGCACACGUUUUACCAUUUAA	2811	UUAAAUGGUAAAACGUGUGCCUU	3361
AD-2139052.2	GCACACGUUUUACCAUUUAAA	2812	UUUAAAUGGUAAAACGUGUGCCU	3362
AD-2139053.2	CACACGUUUUACCAUUUAAAA	2813	UUUUAAAUGGUAAAACGUGUGCC	3363
AD-2139054.2	ACACGUUUUACCAUUUAAAAA	2814	UUUUUAAAUGGUAAAACGUGUGC	3364
AD-2139055.2	CACGUUUUACCAUUUAAAAUA	2815	UAUUUUAAAUGGUAAAACGUGUG	3365
AD-2139056.2	ACGUUUUACCAUUUAAAAUAA	2816	UUAUUUUAAAUGGUAAAACGUGU	3366
AD-2139057.2	CGUUUUACCAUUUAAAAUAUA	2817	UAUAUUUUAAAUGGUAAAACGUG	3367
AD-2139058.2	GUUUUACCAUUUAAAAUAUUA	2818	UAAUAUUUUAAAUGGUAAAACGU	3368
AD-2139059.2	UUUUACCAUUUAAAAUAUUGA	2819	UCAAUAUUUUAAAUGGUAAAACG	3369
AD-2139060.2	UUUACCAUUUAAAAUAUUGUA	2820	UACAAUAUUUUAAAUGGUAAAAC	3370

Duplex ID	Sense Sequence	SEQ ID NO	Antisense Sequence	SEQ ID NO
AD-2139061.2	UUUAAAAUAUUGUUACCAAAA	2821	UUUUGGUAACAAUAUUUUAAAUG	3371
AD-2139062.2	UUAAAAUAUUGUUACCAAACA	2822	UGUUUGGUAACAAUAUUUUAAAU	3372
AD-2139063.2	UAAAAUAUUGUUACCAAACAA	2823	UUGUUUGGUAACAAUAUUUUAAA	3373
AD-2139064.2	AAAAUAUUGUUACCAAACAAA	2824	UUUGUUUGGUAACAAUAUUUUAA	3374
AD-2139065.2	AAAUAUUGUUACCAAACAAAA	2825	UUUUGUUUGGUAACAAUAUUUUA	3375
AD-2139066.2	AAUAUUGUUACCAAACAAAAA	2826	UUUUUGUUUGGUAACAAUAUUUU	3376
AD-2139067.2	AUAUUGUUACCAAACAAAAAA	2827	UUUUUUGUUUGGUAACAAUAUUU	3377
AD-2139068.2	UAUUGUUACCAAACAAAAAUA	2828	UAUUUUUGUUUGGUAACAAUAUU	3378
AD-2139069.2	AUUGUUACCAAACAAAAAUAA	2829	UUAUUUUUGUUUGGUAACAAUAU	3379
AD-2139070.2	UUGUUACCAAACAAAAAUAUA	2830	UAUAUUUUUGUUUGGUAACAAUA	3380
AD-2139071.2	UGUUACCAAACAAAAAUAUCA	2831	UGAUAUUUUUGUUUGGUAACAAU	3381
AD-2139072.2	GUUACCAAACAAAAAUAUCCA	2832	UGGAUAUUUUUGUUUGGUAACAA	3382
AD-2139073.2	UUACCAAACAAAAAUAUCCAA	2833	UUGGAUAUUUUUGUUUGGUAACA	3383
AD-2139074.2	UACCAAACAAAAAUAUCCAUA	2834	UAUGGAUAUUUUUGUUUGGUAAC	3384
AD-2139075.2	CCAAACAAAAAUAUCCAUUCA	2835	UGAAUGGAUAUUUUUGUUUGGUA	3385
AD-2139076.2	CAAACAAAAAUAUCCAUUCAA	2836	UUGAAUGGAUAUUUUUGUUUGGU	3386
AD-2139077.2	AAACAAAAAUAUCCAUUCAAA	2837	UUUGAAUGGAUAUUUUUGUUUGG	3387
AD-2139078.2	AAAAUAUCCAUUCAAAAUACA	2838	UGUAUUUUGAAUGGAUAUUUUUG	3388
AD-2139079.2	AAAUAUCCAUUCAAAAUACAA	2839	UUGUAUUUUGAAUGGAUAUUUUU	3389
AD-2139080.2	AAUAUCCAUUCAAAAUACAAA	2840	UUUGUAUUUUGAAUGGAUAUUUU	3390
AD-2139081.2	AUAUCCAUUCAAAAUACAAUA	2841	UAUUGUAUUUUGAAUGGAUAUUU	3391
AD-2139082.2	UAUCCAUUCAAAAUACAAUUA	2842	UAAUUGUAUUUUGAAUGGAUAUU	3392
AD-2139083.2	AUCCAUUCAAAAUACAAUUUA	2843	UAAAUUGUAUUUUGAAUGGAUAU	3393
AD-2139084.2	UCCAUUCAAAAUACAAUUUAA	2844	UUAAAUUGUAUUUUGAAUGGAUA	3394
AD-2139085.2	CCAUUCAAAAUACAAUUUAAA	2845	UUUAAAUUGUAUUUUGAAUGGAU	3395
AD-2139086.2	CAUUCAAAAUACAAUUUAACA	2846	UGUUAAAUUGUAUUUUGAAUGGA	3396
AD-2139087.2	AUUCAAAAUACAAUUUAACAA	2847	UUGUUAAAUUGUAUUUUGAAUGG	3397
AD-2139088.2	UUCAAAAUACAAUUUAACAAA	2848	UUUGUUAAAUUGUAUUUUGAAUG	3398
AD-2139089.2	UCAAAAUACAAUUUAACAAUA	2849	UAUUGUUAAAUUGUAUUUUGAAU	3399
AD-2139090.2	CAAUUUAACAAUGCAACAGUA	2850	UACUGUUGCAUUGUUAAAUUGUA	3400
AD-2139091.2	UCAUCUUACAGCAGAGAAAUA	2851	UAUUUCUCUGCUGUAAGAUGACU	3401
AD-2139092.2	CAUCUUACAGCAGAGAAAUGA	2852	UCAUUUCUCUGCUGUAAGAUGAC	3402
AD-2139093.2	AUCUUACAGCAGAGAAAUGCA	2853	UGCAUUUCUCUGCUGUAAGAUGA	3403
AD-2139094.2	UCUUACAGCAGAGAAAUGCAA	2854	UUGCAUUUCUCUGCUGUAAGAUG	3404
AD-2139095.2	CUUACAGCAGAGAAAUGCAGA	2855	UCUGCAUUUCUCUGCUGUAAGAU	3405
AD-2139096.2	UUACAGCAGAGAAAUGCAGAA	2856	UUCUGCAUUUCUCUGCUGUAAGA	3406
AD-2139097.2	UACAGCAGAGAAAUGCAGAGA	2857	UCUCUGCAUUUCUCUGCUGUAAG	3407
AD-2139098.2	ACAGCAGAGAAAUGCAGAGAA	2858	UUCUCUGCAUUUCUCUGCUGUAA	3408
AD-2139099.2	CAGCAGAGAAAUGCAGAGAAA	2859	UUUCUCUGCAUUUCUCUGCUGUA	3409
AD-2139100.2	AGCAGAGAAAUGCAGAGAAAA	2860	UUUUCUCUGCAUUUCUCUGCUGU	3410
AD-2139101.2	GCAGAGAAAUGCAGAGAAAAA	2861	UUUUUCUCUGCAUUUCUCUGCUG	3411
AD-2139102.2	CAGAGAAAUGCAGAGAAAAGA	2862	UCUUUUCUCUGCAUUUCUCUGCU	3412

Duplex ID	Sense Sequence	SEQ ID NO	Antisense Sequence	SEQ ID NO
AD-2139103.2	AGAGAAAUGCAGAGAAAAGCA	2863	UGCUUUUCUCUGCAUUUCUCUGC	3413
AD-2139104.2	GAGAAAUGCAGAGAAAAGCAA	2864	UUGCUUUUCUCUGCAUUUCUCUG	3414
AD-2139105.2	AGAAAUGCAGAGAAAAGCAAA	2865	UUUGCUUUUCUCUGCAUUUCUCU	3415
AD-2139106.2	GAAAUGCAGAGAAAAGCAAAA	2866	UUUUGCUUUUCUCUGCAUUUCUC	3416
AD-2139107.2	AAAUGCAGAGAAAAGCAAAAA	2867	UUUUUGCUUUUCUCUGCAUUUCU	3417
AD-2139108.2	AAUGCAGAGAAAAGCAAAACA	2868	UGUUUUGCUUUUCUCUGCAUUUC	3418
AD-2139109.2	AUGCAGAGAAAAGCAAAACUA	2869	UAGUUUUGCUUUUCUCUGCAUUU	3419
AD-2139110.2	UGCAGAGAAAAGCAAAACUGA	2870	UCAGUUUUGCUUUUCUCUGCAUU	3420
AD-2139111.2	GCAGAGAAAAGCAAAACUGCA	2871	UGCAGUUUUGCUUUUCUCUGCAU	3421
AD-2139112.2	CAGAGAAAAGCAAAACUGCAA	2872	UUGCAGUUUUGCUUUUCUCUGCA	3422
AD-2139113.2	AGAGAAAAGCAAAACUGCAAA	2873	UUUGCAGUUUUGCUUUUCUCUGC	3423
AD-2139114.2	AGAAAAGCAAAACUGCAAGUA	2874	UACUUGCAGUUUUGCUUUUCUCU	3424
AD-2139115.2	AAAAGCAAAACUGCAAGUGAA	2875	UUCACUUGCAGUUUUGCUUUUCU	3425
AD-2139116.2	AAAGCAAAACUGCAAGUGACA	2876	UGUCACUUGCAGUUUUGCUUUUC	3426
AD-2139117.2	AAGCAAAACUGCAAGUGACUA	2877	UAGUCACUUGCAGUUUUGCUUUU	3427
AD-2139118.2	AAACUGCAAGUGACUGUGAAA	2878	UUUCACAGUCACUUGCAGUUUUG	3428
AD-2139119.2	AACUGCAAGUGACUGUGAAUA	2879	UAUUCACAGUCACUUGCAGUUUU	3429
AD-2139120.2	ACUGCAAGUGACUGUGAAUAA	2880	UUAUUCACAGUCACUUGCAGUUU	3430
AD-2139121.2	CUGCAAGUGACUGUGAAUAAA	2881	UUUAUUCACAGUCACUUGCAGUU	3431
AD-2139122.2	UGCAAGUGACUGUGAAUAAAA	2882	UUUUAUUCACAGUCACUUGCAGU	3432
AD-2139123.2	GCAAGUGACUGUGAAUAAAGA	2883	UCUUUAUUCACAGUCACUUGCAG	3433
AD-2139124.2	CAAGUGACUGUGAAUAAAGGA	2884	UCCUUUAUUCACAGUCACUUGCA	3434
AD-2139125.2	GACUGUGAAUAAAGGGUGAAA	2885	UUUCACCCUUUAUUCACAGUCAC	3435
AD-2139126.2	ACUGUGAAUAAAGGGUGAAUA	2886	UAUUCACCCUUUAUUCACAGUCA	3436
AD-2139128.2	GUGAAUAAAGGGUGAAUGUAA	2887	UUACAUUCACCCUUUAUUCACAG	3437
AD-2139129.2	UGAAUAAAGGGUGAAUGUAGA	2888	UCUACAUUCACCCUUUAUUCACA	3438
AD-2139130.2	GAAUAAAGGGUGAAUGUAGUA	2889	UACUACAUUCACCCUUUAUUCAC	3439
AD-2139131.2	UAAAGGGUGAAUGUAGUCUCA	2890	UGAGACUACAUUCACCCUUUAUU	3440
AD-2139132.2	AAGGGUGAAUGUAGUCUCAAA	2891	UUUGAGACUACAUUCACCCUUUA	3441
AD-2139133.2	AGGGUGAAUGUAGUCUCAAAA	2892	UUUUGAGACUACAUUCACCCUUU	3442
AD-2139134.2	AUCCUCAAAGAGCUGUGUUUA	2893	UAAACACAGCUCUUUGAGGAUUU	3443
AD-2139135.2	UCCUCAAAGAGCUGUGUUUAA	2894	UUAAACACAGCUCUUUGAGGAUU	3444
AD-2139136.2	CCUCAAAGAGCUGUGUUUAUA	2895	UAUAAACACAGCUCUUUGAGGAU	3445
AD-2139137.2	CUCAAAGAGCUGUGUUUAUUA	2896	UAAUAAACACAGCUCUUUGAGGA	3446
AD-2139138.2	UCAAAGAGCUGUGUUUAUUUA	2897	UAAAUAAACACAGCUCUUUGAGG	3447
AD-2139139.2	CAAAGAGCUGUGUUUAUUUCA	2898	UGAAAUAAACACAGCUCUUUGAG	3448
AD-2139140.2	AAAGAGCUGUGUUUAUUUCAA	2899	UUGAAAUAAACACAGCUCUUUGA	3449
AD-2139141.2	AGCUGUGUUUAUUUCAUUGAA	2900	UUCAAUGAAAUAAACACAGCUCU	3450
AD-2139142.2	GCUGUGUUUAUUUCAUUGACA	2901	UGUCAAUGAAAUAAACACAGCUC	3451
AD-2139143.2	GUGUUUAUUUCAUUGACAAAA	2902	UUUUGUCAAUGAAAUAAACACAG	3452
AD-2139144.2	AUUUCAUUGACAAAUAGAUUA	2903	UAAUCUAUUUGUCAAUGAAAUAA	3453
AD-2139145.2	UUUCAUUGACAAAUAGAUUAA	2904	UUAAUCUAUUUGUCAAUGAAAUA	3454

Duplex ID	Sense Sequence	SEQ ID NO	Antisense Sequence	SEQ ID NO
AD-2139146.2	UUCAUUGACAAAUAGAUUAUA	2905	UAUAAUCUAUUUGUCAAUGAAAU	3455
AD-2139147.2	UCAUUGACAAAUAGAUUAUUA	2906	UAAUAAUCUAUUUGUCAAUGAAA	3456
AD-2139148.2	CAUUGACAAAUAGAUUAUUUA	2907	UAAAUAAUCUAUUUGUCAAUGAA	3457
AD-2139149.2	AUUGACAAAUAGAUUAUUUGA	2908	UCAAAUAAUCUAUUUGUCAAUGA	3458
AD-2139150.2	UUGACAAAUAGAUUAUUUGUA	2909	UACAAAUAAUCUAUUUGUCAAUG	3459
AD-2139151.2	UGACAAAUAGAUUAUUUGUAA	2910	UUACAAAUAAUCUAUUUGUCAAU	3460
AD-2139152.2	GACAAAUAGAUUAUUUGUAUA	2911	UAUACAAAUAAUCUAUUUGUCAA	3461
AD-2139153.2	ACAAAUAGAUUAUUUGUAUUA	2912	UAAUACAAAUAAUCUAUUUGUCA	3462
AD-2139154.2	CAAAUAGAUUAUUUGUAUUCA	2913	UGAAUACAAAUAAUCUAUUUGUC	3463
AD-2139155.2	AAAUAGAUUAUUUGUAUUCAA	2914	UUGAAUACAAAUAAUCUAUUUGU	3464

Table 8B. Additional Modified Sense and Antisense Strands of Human PLG dsRNA Agents

Duplex ID	Sense Sequence	SEQ ID NO	Antisense Sequence	SEQ ID NO
AD-2138040.1	ggacccAfcUfUfUfcugggcacua	3465	PuAfgugCfccagaaaGfuGfgguccca	4565
AD-2138041.1	gacccaCfuUfUfCfugggcacuga	3466	PuCfaguGfcccagaaAfgUfggguccc	4566
AD-2138042.1	acccacUfuUfCfUfgggcacugca	3467	PuGfcagUfgcccagaAfaGfugggucc	4567
AD-2138043.1	caguccCfaAfAfAfuggaacauaa	3468	PuUfaugUfuccauuuUfgGfgacuggc	4568
AD-2138044.1	agucccAfaAfAfUfggaacauaaa	3469	PuUfuauGfuuccauuUfuGfggacugg	4569
AD-2138045.1	gucccaAfaAfUfGfgaacauaaga	3470	PuCfuuaUfguuccauUfuUfgggacug	4570
AD-2138046.1	ucccaaAfaUfGfGfaacauaagga	3471	PuCfcuuAfuguuccaUfuUfugggacu	4571
AD-2138047.1	cccaaaAfuGfGfAfacauaaggaa	3472	PuUfccuUfauguuccAfuUfuugggac	4572
AD-2138048.1	ccaaaaUfgGfAfAfcauaaggaaa	3473	PuUfuccUfuauguucCfaUfuuuggga	4573
AD-2138049.1	caaaauGfgAfAfCfauaaggaaga	3474	PuCfuucCfuuauguuCfcAfuuuuggg	4574
AD-2138050.1	aaaaugGfaAfCfAfuaaggaagua	3475	PuAfcuuCfcuuauguUfcCfauuuugg	4575
AD-2138051.1	aaauggAfaCfAfUfaaggaaguga	3476	PuCfacuUfccuuaugUfuCfcauuuug	4576
AD-2138052.1	aauggaAfcAfUfAfaggaagugga	3477	PuCfcacUfuccuuauGfuUfccauuuu	4577
AD-2138053.1	auggaaCfaUfAfAfggaaguggua	3478	PuAfccaCfuuccuuaUfgUfuccauuu	4578
AD-2138054.1	uggaacAfuAfAfGfgaagugguua	3479	PuAfaccAfcuuccuuAfuGfuuccauu	4579
AD-2138055.1	ccucugGfaUfGfAfcuaugugaaa	3480	PuUfucaCfauagucaUfcCfagaggcu	4580
AD-2138056.1	uaagaaGfcAfGfCfugggagcaga	3481	PuCfugcUfcccagcuGfcUfucuuagu	4581
AD-2138057.1	agcagcUfgGfGfAfgcaggaagua	3482	PuAfcuuCfcugcuccCfaGfcugcuuc	4582
AD-2138059.1	agcuggGfaGfCfAfggaaguauaa	3483	PuUfauaCfuuccugcUfcCfcagcugc	4583
AD-2138060.1	cugggaGfcAfGfGfaaguauagaa	3484	PuUfcuaUfacuuccuGfcUfcccagcu	4584
AD-2138061.1	ugggagCfaGfGfAfaguauagaaa	3485	PuUfucuAfuacuuccUfgCfucccagc	4585
AD-2138062.1	gggagcAfgGfAfAfguauagaaga	3486	PuCfuucUfauacuucCfuGfcucccag	4586
AD-2138063.1	ggagcaGfgAfAfGfuauagaagaa	3487	PuUfcuuCfuauacuuCfcUfgcuccca	4587
AD-2138064.1	gagcagGfaAfGfUfauagaagaaa	3488	PuUfucuUfcuauacuUfcCfugcuccc	4588
AD-2138065.1	agcaggAfaGfUfAfuagaagaaua	3489	PuAfuucUfucuauacUfuCfcugcucc	4589
AD-2138066.1	gcaggaAfgUfAfUfagaagaauga	3490	PuCfauuCfuucuauaCfuUfccugcuc	4590
AD-2138067.1	caggaaGfuAfUfAfgaagaaugua	3491	PuAfcauUfcuucuauAfcUfuccugcu	4591
AD-2138068.1	aggaagUfaUfAfGfaagaauguga	3492	PuCfacaUfucuucuaUfaCfuuccugc	4592
AD-2138069.1	ggaaguAfuAfGfAfagaaugugca	3493	PuGfcacAfuucuucuAfuAfcuuccug	4593
AD-2138070.1	gaaguaUfaGfAfAfgaaugugcaa	3494	PuUfgcaCfauucuucUfaUfacuuccu	4594
AD-2138071.1	aaguauAfgAfAfGfaaugugcaga	3495	PuCfugcAfcauucuuCfuAfuacuucc	4595
AD-2138072.1	aguauaGfaAfGfAfaugugcagca	3496	PuGfcugCfacauucuUfcUfauacuuc	4596

Duplex ID	Sense Sequence	SEQ ID NO	Antisense Sequence	SEQ ID NO
AD-2138073.1	guauagAfaGfAfAfugugcagcaa	3497	PuUfgcuGfcacauucUfuCfuauacuu	4597
AD-2138074.1	uauagaAfgAfAfUfgugcagcaaa	3498	PuUfugcUfgcacauuCfuUfcuauacu	4598
AD-2138075.1	uccaauAfuCfAfCfaguaaagaga	3499	PuCfucuUfuacugugAfuAfuuggaau	4599
AD-2138076.1	ccaauaUfcAfCfAfguaaagagca	3500	PuGfcucUfuuacuguGfaUfauuggaa	4600
AD-2138077.1	caauauCfaCfAfGfuaaagagcaa	3501	PuUfgcuCfuuuacugUfgAfuauugga	4601
AD-2138078.1	aauaucAfcAfGfUfaaagagcaaa	3502	PuUfugcUfcuuuacuGfuGfauauugg	4602
AD-2138079.1	auaucaCfaGfUfAfaagagcaaca	3503	PuGfuugCfucuuuacUfgUfgauauug	4603
AD-2138080.1	uaucacAfgUfAfAfagagcaacaa	3504	PuUfguuGfcucuuuaCfuGfugauauu	4604
AD-2138081.1	aucacaGfuAfAfAfgagcaacaaa	3505	PuUfuguUfgcucuuuAfcUfgugauau	4605
AD-2138082.1	ucacagUfaAfAfGfagcaacaaua	3506	PuAfuugUfugcucuuUfaCfugugaua	4606
AD-2138083.1	cacaguAfaAfGfAfgcaacaauga	3507	PuCfauuGfuugcucuUfuAfcugugau	4607
AD-2138084.1	acaguaAfaGfAfGfcaacaaugua	3508	PuAfcauUfguugcucUfuUfacuguga	4608
AD-2138085.1	caguaaAfgAfGfCfaacaauguga	3509	PuCfacaUfuguugcuCfuUfuacugug	4609
AD-2138086.1	aguaaaGfaGfCfAfacaaugugua	3510	PuAfcacAfuuguugcUfcUfuuacugu	4610
AD-2138087.1	ggaugaGfaGfAfUfguaguuuuaa	3511	PuUfaaaAfcuacaucUfcUfcauccua	4611
AD-2138088.1	gaugagAfgAfUfGfuaguuuuaua	3512	PuAfuaaAfacuacauCfuCfucauccu	4612
AD-2138089.1	augagaGfaUfGfUfaguuuuauua	3513	PuAfauaAfaacuacaUfcUfcucaucc	4613
AD-2138090.1	ugagagAfuGfUfAfguuuuauuua	3514	PuAfaauAfaaacuacAfuCfucucauc	4614
AD-2138091.1	gagagaUfgUfAfGfuuuuauuuga	3515	PuCfaaaUfaaaacuaCfaUfcucucau	4615
AD-2138092.1	agagauGfuAfGfUfuuuauuugaa	3516	PuUfcaaAfuaaaacuAfcAfucucuca	4616
AD-2138093.1	gagaugUfaGfUfUfuuauuugaaa	3517	PuUfucaAfauaaaacUfaCfaucucuc	4617
AD-2138094.1	agauguAfgUfUfUfuauuugaaaa	3518	PuUfuucAfaauaaaaCfuAfcaucucu	4618
AD-2138095.1	gauguaGfuUfUfUfauuugaaaaa	3519	PuUfuuuCfaaauaaaAfcUfacaucuc	4619
AD-2138096.1	auguagUfuUfUfAfuuugaaaaga	3520	PuCfuuuUfcaaauaaAfaCfuacaucu	4620
AD-2138097.1	uguaguUfuUfAfUfuugaaaagaa	3521	PuUfcuuUfucaaauaAfaAfcuacauc	4621
AD-2138098.1	guaguuUfuAfUfUfugaaaagaaa	3522	PuUfucuUfuucaaauAfaAfacuacau	4622
AD-2138099.1	ugaaaaGfaAfAfGfuguaucucua	3523	PuAfgagAfuacacuuUfcUfuuucaaa	4623
AD-2138100.1	gaaaagAfaAfGfUfguaucucuca	3524	PuGfagaGfauacacuUfuCfuuuucaa	4624
AD-2138101.1	aaaagaAfaGfUfGfuaucucucaa	3525	PuUfgagAfgauacacUfuUfcuuuuca	4625
AD-2138102.1	aaagaaAfgUfGfUfaucucucaga	3526	PuCfugaGfagauacaCfuUfucuuuuc	4626
AD-2138103.1	aagaaaGfuGfUfAfucucucagaa	3527	PuUfcugAfgagauacAfcUfuucuuuu	4627
AD-2138104.1	agaaagUfgUfAfUfcucucagaga	3528	PuCfucuGfagagauaCfaCfuuucuuu	4628
AD-2138105.1	gaaaguGfuAfUfCfucucagagua	3529	PuAfcucUfgagagauAfcAfcuuucuu	4629
AD-2138106.1	aaagugUfaUfCfUfcucagaguga	3530	PuCfacuCfugagagaUfaCfacuuucu	4630
AD-2138107.1	aaguguAfuCfUfCfucagagugca	3531	PuGfcacUfcugagagAfuAfcacuuuc	4631
AD-2138108.1	aguguaUfcUfCfUfcagagugcaa	3532	PuUfgcaCfucugagaGfaUfacacuuu	4632
AD-2138109.1	guguauCfuCfUfCfagagugcaaa	3533	PuUfugcAfcucugagAfgAfuacacuu	4633
AD-2138110.1	uguaucUfcUfCfAfgagugcaaga	3534	PuCfuugCfacucugaGfaGfauacacu	4634
AD-2138111.1	guaucuCfuCfAfGfagugcaagaa	3535	PuUfcuuGfcacucugAfgAfgauacac	4635
AD-2138112.1	aucucuCfaGfAfGfugcaagacua	3536	PuAfgucUfugcacucUfgAfgagauac	4636
AD-2138113.1	acagagGfgAfCfGfauguccaaaa	3537	PuUfuugGfacaucguCfcCfucuguag	4637
AD-2138114.1	cagaggGfaCfGfAfuguccaaaaa	3538	PuUfuuuGfgacaucgUfcCfcucugua	4638
AD-2138115.1	agagggAfcGfAfUfguccaaaaca	3539	PuGfuuuUfggacaucGfuCfccucugu	4639
AD-2138116.1	gagggaCfgAfUfGfuccaaaacaa	3540	PuUfguuUfuggacauCfgUfcccucug	4640
AD-2138117.1	agggacGfaUfGfUfccaaaacaaa	3541	PuUfuguUfuuggacaUfcGfucccucu	4641
AD-2138118.1	gggacgAfuGfUfCfcaaaacaaaa	3542	PuUfuugUfuuuggacAfuCfgucccuc	4642
AD-2138119.1	ggacgaUfgUfCfCfaaaacaaaaa	3543	PuUfuuuGfuuuuggaCfaUfcgucccu	4643
AD-2138120.1	gacgauGfuCfCfAfaaacaaaaaa	3544	PuUfuuuUfguuuuggAfcAfucguccc	4644

Duplex ID	Sense Sequence	SEQ ID NO	Antisense Sequence	SEQ ID NO
AD-2138121.1	acgaugUfcCfAfAfaacaaaaaaa	3545	PuUfuuuUfuguuuugGfaCfaucgucc	4645
AD-2138122.1	cgauguCfcAfAfAfacaaaaaaua	3546	PuAfuuuUfuuguuuuGfgAfcaucguc	4646
AD-2138123.1	gaugucCfaAfAfAfcaaaaaauga	3547	PuCfauuUfuuuguuuUfgGfacaucgu	4647
AD-2138124.1	auguccAfaAfAfCfaaaaaaugga	3548	PuCfcauUfuuuuguuUfuGfgacaucg	4648
AD-2138125.1	cacagaCfcUfAfGfauucucacca	3549	PuGfgugAfgaaucuaGfgUfcuguggg	4649
AD-2138126.1	acagacCfuAfGfAfuucucaccua	3550	PuAfgguGfagaaucuAfgGfucugugg	4650
AD-2138127.1	cagaccUfaGfAfUfucucaccuga	3551	PuCfaggUfgagaaucUfaGfgucugug	4651
AD-2138128.1	gaccuaGfaUfUfCfucaccugcua	3552	PuAfgcaGfgugagaaUfcUfaggucug	4652
AD-2138129.1	accuagAfuUfCfUfcaccugcuaa	3553	PuUfagcAfggugagaAfuCfuaggucu	4653
AD-2138130.1	ccuagaUfuCfUfCfaccugcuaca	3554	PuGfuagCfaggugagAfaUfcuagguc	4654
AD-2138131.1	cucagaGfgGfAfCfuggaggagaa	3555	PuUfcucCfuccagucCfcUfcugaggg	4655
AD-2138132.1	ucagagGfgAfCfUfggaggagaaa	3556	PuUfucuCfcuccaguCfcCfucugagg	4656
AD-2138133.1	cagaggGfaCfUfGfgaggagaaca	3557	PuGfuucUfccuccagUfcCfcucugag	4657
AD-2138134.1	agagggAfcUfGfGfaggagaacua	3558	PuAfguuCfuccuccaGfuCfccucuga	4658
AD-2138135.1	gagggaCfuGfGfAfggagaacuaa	3559	PuUfaguUfcuccuccAfgUfcccucug	4659
AD-2138136.1	agggacUfgGfAfGfgagaacuaca	3560	PuGfuagUfucuccucCfaGfucccucu	4660
AD-2138137.1	gggacuGfgAfGfGfagaacuacua	3561	PuAfguaGfuucuccuCfcAfgucccuc	4661
AD-2138138.1	ggacugGfaGfGfAfgaacuacuga	3562	PuCfaguAfguucuccUfcCfagucccu	4662
AD-2138139.1	acuggaGfgAfGfAfacuacugcaa	3563	PuUfgcaGfuaguucuCfcUfccagucc	4663
AD-2138140.1	cuggagGfaGfAfAfcuacugcaga	3564	PuCfugcAfguaguucUfcCfuccaguc	4664
AD-2138141.1	uggaggAfgAfAfCfuacugcagga	3565	PuCfcugCfaguaguuCfuCfcuccagu	4665
AD-2138142.1	gaggagAfaCfUfAfcugcaggaaa	3566	PuUfuccUfgcaguagUfuCfuccucca	4666
AD-2138143.1	aauccaGfaCfAfAfcgauccgcaa	3567	PuUfgcgGfaucguugUfcUfggauucc	4667
AD-2138144.1	uccagaCfaAfCfGfauccgcagga	3568	PuCfcugCfggaucguUfgUfcuggauu	4668
AD-2138145.1	ugcuauAfcUfAfCfugauccagaa	3569	PuUfcugGfaucaguaGfuAfuagcacc	4669
AD-2138146.1	gcuauaCfuAfCfUfgauccagaaa	3570	PuUfucuGfgaucaguAfgUfauagcac	4670
AD-2138147.1	cuauacUfaCfUfGfauccagaaaa	3571	PuUfuucUfggaucagUfaGfuauagca	4671
AD-2138148.1	uauacuAfcUfGfAfuccagaaaaa	3572	PuUfuuuCfuggaucaGfuAfguauagc	4672
AD-2138149.1	auacuaCfuGfAfUfccagaaaaga	3573	PuCfuuuUfcuggaucAfgUfaguauag	4673
AD-2138150.1	uacuacUfgAfUfCfcagaaaagaa	3574	PuUfcuuUfucuggauCfaGfuaguaua	4674
AD-2138151.1	acuacuGfaUfCfCfagaaaagaga	3575	PuCfucuUfuucuggaUfcAfguaguau	4675
AD-2138152.1	cuacugAfuCfCfAfgaaaagagaa	3576	PuUfcucUfuuucuggAfuCfaguagua	4676
AD-2138153.1	uacugaUfcCfAfGfaaaagagaua	3577	PuAfucuCfuuuucugGfaUfcaguagu	4677
AD-2138154.1	acugauCfcAfGfAfaaagagauaa	3578	PuUfaucUfcuuuucuGfgAfucaguag	4678
AD-2138155.1	cugaucCfaGfAfAfaagagauaua	3579	PuAfuauCfucuuuucUfgGfaucagua	4679
AD-2138156.1	ugauccAfgAfAfAfagagauauga	3580	PuCfauaUfcucuuuuCfuGfgaucagu	4680
AD-2138157.1	gauccaGfaAfAfAfgagauaugaa	3581	PuUfcauAfucucuuuUfcUfggaucag	4681
AD-2138158.1	auccagAfaAfAfGfagauaugaca	3582	PuGfucaUfaucucuuUfuCfuggauca	4682
AD-2138159.1	uccagaAfaAfGfAfgauaugacua	3583	PuAfgucAfuaucucuUfuUfcuggauc	4683
AD-2138160.1	ccagaaAfaGfAfGfauaugacuaa	3584	PuUfaguCfauaucucUfuUfucuggau	4684
AD-2138161.1	cagaaaAfgAfGfAfuaugacuaca	3585	PuGfuagUfcauaucuCfuUfuucugga	4685
AD-2138162.1	agaaaaGfaGfAfUfaugacuacua	3586	PuAfguaGfucauaucUfcUfuuucugg	4686
AD-2138163.1	gaaaagAfgAfUfAfugacuacuga	3587	PuCfaguAfgucauauCfuCfuuuucug	4687
AD-2138164.1	aaaagaGfaUfAfUfgacuacugca	3588	PuGfcagUfagucauaUfcUfcuuuucu	4688
AD-2138165.1	uaugacUfaCfUfGfcgacauucua	3589	PuAfgaaUfgucgcagUfaGfucauauc	4689
AD-2138166.1	augacuAfcUfGfCfgacauucuua	3590	PuAfagaAfugucgcaGfuAfgucauau	4690
AD-2138167.1	ugacuaCfuGfCfGfacauucuuga	3591	PuCfaagAfaugucgcAfgUfagucaua	4691
AD-2138168.1	gacuacUfgCfGfAfcauucuugaa	3592	PuUfcaaGfaaugucgCfaGfuagucau	4692

Duplex ID	Sense Sequence	SEQ ID NO	Antisense Sequence	SEQ ID NO
AD-2138169.1	cuacugCfgAfCfAfuucuugagua	3593	PuAfcucAfagaauguCfgCfaguaguc	4693
AD-2138170.1	uacugcGfaCfAfUfucuugaguga	3594	PuCfacuCfaagaaugUfcGfcaguagu	4694
AD-2138171.1	acugcgAfcAfUfUfcuugagugua	3595	PuAfcacUfcaagaauGfuCfgcaguag	4695
AD-2138172.1	cugcgaCfaUfUfCfuugaguguga	3596	PuCfacaCfucaagaaUfgUfcgcagua	4696
AD-2138173.1	ugcgacAfuUfCfUfugagugugaa	3597	PuUfcacAfcucaagaAfuGfucgcagu	4697
AD-2138174.1	gcgacaUfuCfUfUfgagugugaaa	3598	PuUfucaCfacucaagAfaUfgucgcag	4698
AD-2138175.1	cgacauUfcUfUfGfagugugaaga	3599	PuCfuucAfcacucaaGfaAfugucgca	4699
AD-2138176.1	gacauuCfuUfGfAfgugugaagaa	3600	PuUfcuuCfacacucaAfgAfaugucgc	4700
AD-2138177.1	acauucUfuGfAfGfugugaagaga	3601	PuCfucuUfcacacucAfaGfaaugucg	4701
AD-2138178.1	auucuuGfaGfUfGfugaagaggaa	3602	PuUfccuCfuucacacUfcAfagaaugu	4702
AD-2138179.1	uucuugAfgUfGfUfgaagaggaaa	3603	PuUfuccUfcuucacaCfuCfaagaaug	4703
AD-2138180.1	ucuugaGfuGfUfGfaagaggaaua	3604	PuAfuucCfucuucacAfcUfcaagaau	4704
AD-2138181.1	cuugagUfgUfGfAfagaggaauga	3605	PuCfauuCfcucuucaCfaCfucaagaa	4705
AD-2138182.1	uugaguGfuGfAfAfgaggaaugua	3606	PuAfcauUfccucuucAfcAfcucaaga	4706
AD-2138183.1	ugagugUfgAfAfGfaggaauguaa	3607	PuUfacaUfuccucuuCfaCfacucaag	4707
AD-2138184.1	gaguguGfaAfGfAfggaauguaua	3608	PuAfuacAfuuccucuUfcAfcacucaa	4708
AD-2138185.1	agugugAfaGfAfGfgaauguauga	3609	PuCfauaCfauuccucUfuCfacacuca	4709
AD-2138186.1	gugugaAfgAfGfGfaauguaugca	3610	PuGfcauAfcauuccuCfuUfcacacuc	4710
AD-2138187.1	ugugaaGfaGfGfAfauguaugcaa	3611	PuUfgcaUfacauuccUfcUfucacacu	4711
AD-2138188.1	gugaagAfgGfAfAfuguaugcaua	3612	PuAfugcAfuacauucCfuCfuucacac	4712
AD-2138189.1	ugaagaGfgAfAfUfguaugcauua	3613	PuAfaugCfauacauuCfcUfcuucaca	4713
AD-2138190.1	gaagagGfaAfUfGfuaugcauuga	3614	PuCfaauGfcauacauUfcCfucuucac	4714
AD-2138191.1	aagaggAfaUfGfUfaugcauugca	3615	PuGfcaaUfgcauacaUfuCfcucuuca	4715
AD-2138192.1	agaggaAfuGfUfAfugcauugcaa	3616	PuUfgcaAfugcauacAfuUfccucuuc	4716
AD-2138193.1	gaggaaUfgUfAfUfgcauugcaga	3617	PuCfugcAfaugcauaCfaUfuccucuu	4717
AD-2138195.1	ggaaugUfaUfGfCfauugcaguga	3618	PuCfacuGfcaaugcaUfaCfauuccuc	4718
AD-2138196.1	gaauguAfuGfCfAfuugcagugga	3619	PuCfcacUfgcaaugcAfuAfcauuccu	4719
AD-2138197.1	aauguaUfgCfAfUfugcaguggaa	3620	PuUfccaCfugcaaugCfaUfacauucc	4720
AD-2138198.1	auguauGfcAfUfUfgcaguggaga	3621	PuCfuccAfcugcaauGfcAfuacauuc	4721
AD-2138199.1	uguaugCfaUfUfGfcaguggagaa	3622	PuUfcucCfacugcaaUfgCfauacauu	4722
AD-2138200.1	guaugcAfuUfGfCfaguggagaaa	3623	PuUfucuCfcacugcaAfuGfcauacau	4723
AD-2138201.1	uaugcaUfuGfCfAfguggagaaaa	3624	PuUfuucUfccacugcAfaUfgcauaca	4724
AD-2138202.1	augcauUfgCfAfGfuggagaaaaa	3625	PuUfuuuCfuccacugCfaAfugcauac	4725
AD-2138203.1	ugcauuGfcAfGfUfggagaaaaca	3626	PuGfuuuUfcuccacuGfcAfaugcaua	4726
AD-2138204.1	gcauugCfaGfUfGfgagaaaacua	3627	PuAfguuUfucuccacUfgCfaaugcau	4727
AD-2138205.1	cauugcAfgUfGfGfagaaaacuaa	3628	PuUfaguUfuucuccaCfuGfcaaugca	4728
AD-2138206.1	auugcaGfuGfGfAfgaaaacuaua	3629	PuAfuagUfuuucuccAfcUfgcaaugc	4729
AD-2138207.1	uugcagUfgGfAfGfaaaacuauga	3630	PuCfauaGfuuuucucCfaCfugcaaug	4730
AD-2138208.1	ugcaguGfgAfGfAfaaacuaugaa	3631	PuUfcauAfguuuucuCfcAfcugcaau	4731
AD-2138209.1	acggcaAfaAfUfUfuccaagacca	3632	PuGfgucUfuggaaauUfuUfgccguca	4732
AD-2138210.1	cggcaaAfaUfUfUfccaagaccaa	3633	PuUfgguCfuuggaaaUfuUfugccguc	4733
AD-2138211.1	ggcaaaAfuUfUfCfcaagaccaua	3634	PuAfuggUfcuuggaaAfuUfuugccgu	4734
AD-2138212.1	gcaaaaUfuUfCfCfaagaccauga	3635	PuCfaugGfucuuggaAfaUfuuugccg	4735
AD-2138213.1	caaaauUfuCfCfAfagaccaugua	3636	PuAfcauGfgucuuggAfaAfuuuugcc	4736
AD-2138214.1	aaaauuUfcCfAfAfgaccauguca	3637	PuGfacaUfggucuugGfaAfauuuugc	4737
AD-2138215.1	aaauuuCfcAfAfGfaccaugucua	3638	PuAfgacAfuggucuuGfgAfaauuuug	4738
AD-2138216.1	aauuucCfaAfGfAfccaugucuga	3639	PuCfagaCfauggucuUfgGfaaauuuu	4739
AD-2138217.1	auuuccAfaGfAfCfcaugucugga	3640	PuCfcagAfcauggucUfuGfgaaauuu	4740

Duplex ID	Sense Sequence	SEQ ID NO	Antisense Sequence	SEQ ID NO
AD-2138218.1	uuuccaAfgAfCfCfaugucuggaa	3641	PuUfccaGfacaugguCfuUfggaaauu	4741
AD-2138219.1	aaugccAfgGfCfCfugggacucua	3642	PuAfgagUfcccaggcCfuGfgcauucc	4742
AD-2138220.1	gccaggCfcUfGfGfgacucucaga	3643	PuCfugaGfagucccaGfgCfcuggcau	4743
AD-2138221.1	ccaggcCfuGfGfGfacucucagaa	3644	PuUfcugAfgagucccAfgGfccuggca	4744
AD-2138222.1	agcccaCfaCfGfCfucauggauaa	3645	PuUfaucCfaugagcgUfgUfgggcucu	4745
AD-2138223.1	ccacacGfcUfCfAfuggauacaua	3646	PuAfuguAfuccaugaGfcGfugugggc	4746
AD-2138224.1	cacacgCfuCfAfUfggauacauua	3647	PuAfaugUfauccaugAfgCfgugugg	4747
AD-2138225.1	acgcucAfuGfGfAfuacauuccua	3648	PuAfggaAfuguauccAfuGfagcgugu	4748
AD-2138226.1	cgcucaUfgGfAfUfacauuccuua	3649	PuAfaggAfauguaucCfaUfgagcgug	4749
AD-2138227.1	gcucauGfgAfUfAfcauuccuuca	3650	PuGfaagGfaauguauCfcAfugagcgu	4750
AD-2138228.1	cucaugGfaUfAfCfauuccuucca	3651	PuGfgaaGfgaauguaUfcCfaugagcg	4751
AD-2138229.1	ucauggAfuAfCfAfuuccuuccaa	3652	PuUfggaAfggaauguAfuCfcaugagc	4752
AD-2138230.1	cauggaUfaCfAfUfuccuuccaaa	3653	PuUfuggAfaggaaugUfaUfccaugag	4753
AD-2138231.1	auggauAfcAfUfUfccuuccaaaa	3654	PuUfuugGfaaggaauGfuAfuccauga	4754
AD-2138232.1	uggauaCfaUfUfCfcuuccaaaua	3655	PuAfuuuGfgaaggaaUfgUfauccaug	4755
AD-2138233.1	ggauacAfuUfCfCfuuccaaauua	3656	PuAfauuUfggaaggaAfuGfuauccau	4756
AD-2138234.1	gauacaUfuCfCfUfuccaaauuua	3657	PuAfaauUfuggaaggAfaUfguaucca	4757
AD-2138235.1	auacauUfcCfUfUfccaaauuuca	3658	PuGfaaaUfuuggaagGfaAfuguaucc	4758
AD-2138236.1	uacauuCfcUfUfCfcaaauuucca	3659	PuGfgaaAfuuuggaaGfgAfauguauc	4759
AD-2138237.1	acauucCfuUfCfCfaaauuuccaa	3660	PuUfggaAfauuuggaAfgGfaauguau	4760
AD-2138238.1	cauuccUfuCfCfAfaauuuccaaa	3661	PuUfuggAfaauuuggAfaGfgaaugua	4761
AD-2138239.1	auuccuUfcCfAfAfauuuccaaaa	3662	PuUfuugGfaaauuugGfaAfggaaugu	4762
AD-2138240.1	uuccuuCfcAfAfAfuuuccaaaca	3663	PuGfuuuGfgaaauuuGfgAfaggaaug	4763
AD-2138241.1	uccuucCfaAfAfUfuuccaaacaa	3664	PuUfguuUfggaaauuUfgGfaaggaau	4764
AD-2138242.1	ccuuccAfaAfUfUfuccaaacaaa	3665	PuUfuguUfuggaaauUfuGfgaaggaa	4765
AD-2138243.1	cuuccaAfaUfUfUfccaaacaaga	3666	PuCfuugUfuuggaaaUfuUfggaagga	4766
AD-2138244.1	uuccaaAfuUfUfCfcaaacaagaa	3667	PuUfcuuGfuuuggaaAfuUfuggaagg	4767
AD-2138245.1	uccaaaUfuUfCfCfaaacaagaaa	3668	PuUfucuUfguuuggaAfaUfuuggaag	4768
AD-2138246.1	ccaaauUfuCfCfAfaacaagaaca	3669	PuGfuucUfuguuuggAfaAfuuuggaa	4769
AD-2138247.1	caaauuUfcCfAfAfacaagaacca	3670	PuGfguuCfuuguuugGfaAfauuugga	4770
AD-2138248.1	aaauuuCfcAfAfAfcaagaaccua	3671	PuAfgguUfcuuguuuGfgAfaauuugg	4771
AD-2138249.1	aauuucCfaAfAfCfaagaaccuga	3672	PuCfaggUfucuuguuUfgGfaaauuug	4772
AD-2138250.1	auuuccAfaAfCfAfagaaccugaa	3673	PuUfcagGfuucuuguUfuGfgaaauuu	4773
AD-2138251.1	uuuccaAfaCfAfAfgaaccugaaa	3674	PuUfucaGfguucuugUfuUfggaaauu	4774
AD-2138252.1	uuccaaAfcAfAfGfaaccugaaga	3675	PuCfuucAfgguucuuGfuUfuggaaau	4775
AD-2138253.1	uccaaaCfaAfGfAfaccugaagaa	3676	PuUfcuuCfagguucuUfgUfuuggaaa	4776
AD-2138254.1	ccaaacAfaGfAfAfccugaagaaa	3677	PuUfucuUfcagguucUfuGfuuuggaa	4777
AD-2138255.1	caaacaAfgAfAfCfcugaagaaga	3678	PuCfuucUfucagguuCfuUfguuugga	4778
AD-2138256.1	aaacaaGfaAfCfCfugaagaagaa	3679	PuUfcuuCfuucagguUfcUfuguuugg	4779
AD-2138257.1	aacaagAfaCfCfUfgaagaagaaa	3680	PuUfucuUfcuucaggUfuCfuuguuug	4780
AD-2138258.1	acaagaAfcCfUfGfaagaagaaua	3681	PuAfuucUfucuucagGfuUfcuuguuu	4781
AD-2138259.1	caagaaCfcUfGfAfagaagaauua	3682	PuAfauuCfuucuucaGfgUfucuuguu	4782
AD-2138260.1	aagaacCfuGfAfAfgaagaauuaa	3683	PuUfaauUfcuucuucAfgGfuucuugu	4783
AD-2138261.1	agaaccUfgAfAfGfaagaauuaca	3684	PuGfuaaUfucuucuuCfaGfguucuug	4784
AD-2138262.1	gaaccuGfaAfGfAfagaauuacua	3685	PuAfguaAfuucuucuUfcAfgguucuu	4785
AD-2138263.1	aaccugAfaGfAfAfgaauuacuga	3686	PuCfaguAfauucuucUfuCfagguucu	4786
AD-2138264.1	accugaAfgAfAfGfaauuacugua	3687	PuAfcagUfaauucuuCfuUfcagguuc	4787
AD-2138265.1	ccugaaGfaAfGfAfauuacuguca	3688	PuGfacaGfuaauucuUfcUfucagguu	4788

Duplex ID	Sense Sequence	SEQ ID NO	Antisense Sequence	SEQ ID NO
AD-2138266.1	cugaagAfaGfAfAfuuacugucga	3689	PuCfgacAfguaauucUfuCfuucaggu	4789
AD-2138267.1	ugaagaAfgAfAfUfuacugucgua	3690	PuAfcgaCfaguaauuCfuUfcuucagg	4790
AD-2138268.1	gaagaaGfaAfUfUfacugucguaa	3691	PuUfacgAfcaguaauUfcUfucuucag	4791
AD-2138269.1	aagaagAfaUfUfAfcugucguaaa	3692	PuUfuacGfacaguaaUfuCfuucuuca	4792
AD-2138270.1	agggagCfuGfCfGfgccuugguga	3693	PuCfaccAfaggccgcAfgCfucccuau	4793
AD-2138271.1	ggagcuGfcGfGfCfcuugguguua	3694	PuAfacaCfcaaggccGfcAfgcucccu	4794
AD-2138272.1	gagcugCfgGfCfCfuugguguuua	3695	PuAfaacAfccaaggcCfgCfagcuccc	4795
AD-2138273.1	agcugcGfgCfCfUfugguguuuca	3696	PuGfaaaCfaccaaggCfcGfcagcucc	4796
AD-2138274.1	ugcggcCfuUfGfGfuguuucacca	3697	PuGfgugAfaacaccaAfgGfccgcagc	4797
AD-2138275.1	cggccuUfgGfUfGfuuucaccaca	3698	PuGfuggUfgaaacacCfaAfggccgca	4798
AD-2138276.1	ggccuuGfgUfGfUfuucaccacca	3699	PuGfgugGfugaaacaCfcAfaggccgc	4799
AD-2138277.1	gccuugGfuGfUfUfucaccaccga	3700	PuCfgguGfgugaaacAfcCfaaggccg	4800
AD-2138278.1	caacaaGfcGfCfUfgggaacuuua	3701	PuAfaagUfucccagcGfcUfuguuggg	4801
AD-2138279.1	aacaagCfgCfUfGfggaacuuuga	3702	PuCfaaaGfuucccagCfgCfuuguugg	4802
AD-2138280.1	gcugcaCfaAfCfAfccuccaccaa	3703	PuUfgguGfgagguguUfgUfgcagcgg	4803
AD-2138281.1	cugcacAfaCfAfCfcuccaccaua	3704	PuAfuggUfggaggugUfuGfugcagcg	4804
AD-2138282.1	ugcacaAfcAfCfCfuccaccauca	3705	PuGfaugGfuggagguGfuUfgugcagc	4805
AD-2138283.1	gcacaaCfaCfCfUfccaccaucua	3706	PuAfgauGfguggaggUfgUfugugcag	4806
AD-2138284.1	cacaacAfcCfUfCfcaccaucuua	3707	PuAfagaUfgguggagGfuGfuugugca	4807
AD-2138285.1	acaacaCfcUfCfCfaccaucuuca	3708	PuGfaagAfugguggaGfgUfguugugc	4808
AD-2138286.1	caacacCfuCfCfAfccaucuucua	3709	PuAfgaaGfaugguggAfgGfuguugug	4809
AD-2138287.1	caccucCfaCfCfAfucuucuggua	3710	PuAfccaGfaagauggUfgGfagguguu	4810
AD-2138288.1	accuccAfcCfAfUfcuucugguca	3711	PuGfaccAfgaagaugGfuGfgaggugu	4811
AD-2138289.1	ccuccaCfcAfUfCfuucuggucca	3712	PuGfgacCfagaagauGfgUfggaggug	4812
AD-2138290.1	cuccacCfaUfCfUfucugguccca	3713	PuGfggaCfcagaagaUfgGfuggaggu	4813
AD-2138291.1	uccaccAfuCfUfUfcuggucccaa	3714	PuUfgggAfccagaagAfuGfguggagg	4814
AD-2138292.1	ccaccaUfcUfUfCfuggucccaca	3715	PuGfuggGfaccagaaGfaUfgguggag	4815
AD-2138293.1	caccauCfuUfCfUfggucccacca	3716	PuGfgugGfgaccagaAfgAfuggugga	4816
AD-2138295.1	caucuuCfuGfGfUfcccaccuaca	3717	PuGfuagGfugggaccAfgAfagauggu	4817
AD-2138296.1	uucuggUfcCfCfAfccuaccagua	3718	PuAfcugGfuagguggGfaCfcagaaga	4818
AD-2138297.1	ucugguCfcCfAfCfcuaccaguga	3719	PuCfacuGfguaggugGfgAfccagaag	4819
AD-2138298.1	cuggucCfcAfCfCfuaccagugua	3720	PuAfcacUfgguagguGfgGfaccagaa	4820
AD-2138299.1	uggucCfaCfCfUfaccaguguca	3721	PuGfacaCfugguaggUfgGfgaccaga	4821
AD-2138300.1	cccaccUfaCfCfAfgugucugaaa	3722	PuUfucaGfacacuggUfaGfgugggac	4822
AD-2138301.1	ccaccuAfcCfAfGfugucugaaga	3723	PuCfuucAfgacacugGfuAfgguggga	4823
AD-2138302.1	accuacCfaGfUfGfucugaaggga	3724	PuCfccuUfcagacacUfgGfuaggugg	4824
AD-2138303.1	ccuaccAfgUfGfUfcugaagggaa	3725	PuUfcccUfucagacaCfuGfguaggug	4825
AD-2138304.1	cuaccaGfuGfUfCfugaagggaaa	3726	PuUfuccCfuucagacAfcUfgguaggu	4826
AD-2138305.1	uaccagUfgUfCfUfgaagggaaca	3727	PuGfuucCfcuucagaCfaCfugguagg	4827
AD-2138306.1	gugucuGfaAfGfGfgaacagguga	3728	PuCfaccUfguucccuUfcAfgacacug	4828
AD-2138307.1	gucugaAfgGfGfAfacaggugaaa	3729	PuUfucaCfcuguuccCfuUfcagacac	4829
AD-2138308.1	ucugaaGfgGfAfAfcaggugaaaa	3730	PuUfuucAfccuguucCfcUfucagaca	4830
AD-2138309.1	cugaagGfgAfAfCfaggugaaaaa	3731	PuUfuuuCfaccuguuCfcCfuucagac	4831
AD-2138310.1	ugaaggGfaAfCfAfggugaaaaca	3732	PuGfuuuUfcaccuguUfcCfcuucaga	4832
AD-2138311.1	gaagggAfaCfAfGfgugaaaacua	3733	PuAfguuUfucaccugUfuCfccuucag	4833
AD-2138312.1	aagggaAfcAfGfGfugaaaacuaa	3734	PuUfaguUfuucaccuGfuUfcccuuca	4834
AD-2138313.1	agggaaCfaGfGfUfgaaaacuaua	3735	PuAfuagUfuuucaccUfgUfucccuuc	4835
AD-2138314.1	gggaacAfgGfUfGfaaaacuauca	3736	PuGfauaGfuuuucacCfuGfuucccuu	4836

Duplex ID	Sense Sequence	SEQ ID NO	Antisense Sequence	SEQ ID NO
AD-2138315.1	ggaacaGfgUfGfAfaaacuaucga	3737	PuCfgauAfguuuucaCfcUfguucccu	4837
AD-2138316.1	gaacagGfuGfAfAfaacuaucgca	3738	PuGfcgaUfaguuuucAfcCfuguuccc	4838
AD-2138317.1	gugaaaAfcUfAfUfcgcgggaaua	3739	PuAfuucCfcgcgauaGfuUfuucaccu	4839
AD-2138318.1	gaaaacUfaUfCfGfcgggaaugua	3740	PuAfcauUfcccgcgaUfaGfuuuucac	4840
AD-2138319.1	aaaacuAfuCfGfCfgggaauguga	3741	PuCfacaUfucccgcgAfuAfguuuuca	4841
AD-2138320.1	uaucgcGfgGfAfAfuguggcugua	3742	PuAfcagCfcacauucCfcGfcgauagu	4842
AD-2138321.1	aucgcgGfgAfAfUfguggcuguua	3743	PuAfacaGfccacauuCfcCfgcgauag	4843
AD-2138322.1	ucgcggGfaAfUfGfuggcuguuaa	3744	PuUfaacAfgccacauUfcCfcgcgaua	4844
AD-2138323.1	cgcgggAfaUfGfUfggcuguuaca	3745	PuGfuaaCfagccacaUfuCfccgcgau	4845
AD-2138324.1	gggaauGfuGfGfCfuguuaccgua	3746	PuAfcggUfaacagccAfcAfuucccgc	4846
AD-2138325.1	gaauguGfgCfUfGfuuaccgugua	3747	PuAfcacGfguaacagCfcAfcauuccc	4847
AD-2138326.1	aaugugGfcUfGfUfuaccguguca	3748	PuGfacaCfgguaacaGfcCfacauucc	4848
AD-2138327.1	ccguguCfcGfGfGfcacaccugua	3749	PuAfcagGfugugcccGfgAfcacggua	4849
AD-2138328.1	uccgggCfaCfAfCfcugucagcaa	3750	PuUfgcuGfacaggugUfgCfccggaca	4850
AD-2138329.1	cgggcaCfaCfCfUfgucagcacua	3751	PuAfgugCfugacaggUfgUfgcccgga	4851
AD-2138330.1	gcacacCfuGfUfCfagcacuggaa	3752	PuUfccaGfugcugacAfgGfugugccc	4852
AD-2138331.1	cacaccUfgUfCfAfgcacuggaga	3753	PuCfuccAfgugcugaCfaGfgugugcc	4853
AD-2138332.1	acaccuGfuCfAfGfcacuggagua	3754	PuAfcucCfagugcugAfcAfggugugc	4854
AD-2138333.1	ccugucAfgCfAfCfuggagugcaa	3755	PuUfgcaCfuccagugCfuGfacaggug	4855
AD-2138334.1	ugucagCfaCfUfGfgagugcacaa	3756	PuUfgugCfacuccagUfgCfugacagg	4856
AD-2138335.1	ucagcaCfuGfGfAfgugcacagaa	3757	PuUfcugUfgcacuccAfgUfgcugaca	4857
AD-2138336.1	cagcacUfgGfAfGfugcacagaca	3758	PuGfucuGfugcacucCfaGfugcugac	4858
AD-2138337.1	agcacuGfgAfGfUfgcacagacca	3759	PuGfgucUfgugcacuCfcAfgugcuga	4859
AD-2138338.1	cucacaCfaCfAfUfaacaggacaa	3760	PuUfgucCfuguuaugUfgUfgugaggg	4860
AD-2138339.1	cacacaCfaUfAfAfcaggacacca	3761	PuGfgugUfccuguuaUfgUfgugugag	4861
AD-2138340.1	acacacAfuAfAfCfaggacaccaa	3762	PuUfgguGfuccuguuAfuGfuguguga	4862
AD-2138341.1	cacacaUfaAfCfAfggacaccaga	3763	PuCfuggUfguccuguUfaUfgugugug	4863
AD-2138342.1	acacauAfaCfAfGfgacaccagaa	3764	PuUfcugGfuguccugUfuAfugugugu	4864
AD-2138343.1	cacauaAfcAfGfGfacaccagaaa	3765	PuUfucuGfguguccuGfuUfaugugug	4865
AD-2138344.1	acauaaCfaGfGfAfcaccagaaaa	3766	PuUfuucUfgguguccUfgUfuaugugu	4866
AD-2138345.1	cauaacAfgGfAfCfaccagaaaaa	3767	PuUfuuuCfuggugucCfuGfuuaugug	4867
AD-2138346.1	auaacaGfgAfCfAfccagaaaaca	3768	PuGfuuuUfcuggugucCfcUfguuaugu	4868
AD-2138347.1	uaacagGfaCfAfCfcagaaaacua	3769	PuAfguuUfucuggugUfcCfuguuaug	4869
AD-2138348.1	aacaggAfcAfCfCfagaaaacuua	3770	PuAfaguUfuucugguGfuCfcuguuau	4870
AD-2138349.1	ccugcaAfaAfAfUfuuggaugaaa	3771	PuUfucaUfccaaauuUfuUfgcagggg	4871
AD-2138350.1	cugcaaAfaAfUfUfuggaugaaaa	3772	PuUfuucAfuccaaauUfuUfugcaggg	4872
AD-2138351.1	ugcaaaAfaUfUfUfggaugaaaaa	3773	PuUfuuuCfauccaaaUfuUfuugcagg	4873
AD-2138352.1	gcaaaaAfuUfUfGfgaugaaaaca	3774	PuGfuuuUfcauccaaAfuUfuuugcag	4874
AD-2138353.1	caaaaaUfuUfGfGfaugaaaacua	3775	PuAfguuUfucauccaAfaUfuuuugca	4875
AD-2138354.1	aaaaauUfuGfGfAfugaaaacuaa	3776	PuUfaguUfuucauccAfaAfuuuuugc	4876
AD-2138355.1	aaaauuUfgGfAfUfgaaaacuaca	3777	PuGfuagUfuuucaucCfaAfauuuuug	4877
AD-2138356.1	aaauuuGfgAfUfGfaaaacuacua	3778	PuAfguaGfuuuucauCfcAfaauuuuu	4878
AD-2138357.1	aauuugGfaUfGfAfaaacuacuga	3779	PuCfaguAfguuuucaUfcCfaaauuuu	4879
AD-2138358.1	auuuggAfuGfAfAfaacuacugca	3780	PuGfcagUfaguuuucAfuCfcaaauuu	4880
AD-2138359.1	uuuggaUfgAfAfAfacuacugcca	3781	PuGfgcaGfuaguuuuCfaUfccaaauu	4881
AD-2138360.1	uuggauGfaAfAfAfcuacugccga	3782	PuCfggcAfguaguuuUfcAfuccaaau	4882
AD-2138361.1	uggaugAfaAfAfCfuacugccgca	3783	PuGfcggCfaguaguuUfuCfauccaaa	4883
AD-2138362.1	ggaugaAfaAfCfUfacugccgcaa	3784	PuUfgcgGfcaguaguUfuUfcauccaa	4884

Duplex ID	Sense Sequence	SEQ ID NO	Antisense Sequence	SEQ ID NO
AD-2138363.1	gaugaaAfaCfUfAfcugccgcaaa	3785	PuUfugcGfgcaguagUfuUfucaucca	4885
AD-2138364.1	augaaaAfcUfAfCfugccgcaaua	3786	PuAfuugCfggcaguaGfuUfuucaucc	4886
AD-2138365.1	ugaaaaCfuAfCfUfgccgcaauca	3787	PuGfauuGfcggcaguAfgUfuuucauc	4887
AD-2138366.1	gaaaacUfaCfUfGfccgcaaucca	3788	PuGfgauUfgcggcagUfaGfuuuucau	4888
AD-2138367.1	aaaacuAfcUfGfCfcgcaauccua	3789	PuAfggaUfugcggcaGfuAfguuuuca	4889
AD-2138368.1	aaacuaCfuGfCfCfgcaauccuga	3790	PuCfaggAfuugcggcAfgUfaguuuuc	4890
AD-2138369.1	aacuacUfgCfCfGfcaauccugaa	3791	PuUfcagGfauugcggCfaGfuaguuuu	4891
AD-2138370.1	uacugcCfgCfAfAfuccugacgga	3792	PuCfcguCfaggauugCfgGfcaguagu	4892
AD-2138371.1	acugccGfcAfAfUfccugacggaa	3793	PuUfccgUfcaggauuGfcGfgcaguag	4893
AD-2138372.1	cugccgCfaAfUfCfcugacggaaa	3794	PuUfuccGfucaggauUfgCfggcagua	4894
AD-2138373.1	ugccgcAfaUfCfCfugacggaaaa	3795	PuUfuucCfgucaggaUfuGfcggcagu	4895
AD-2138374.1	gccgcaAfuCfCfUfgacggaaaaa	3796	PuUfuuuCfcgucaggAfuUfgcggcag	4896
AD-2138375.1	ccgcaaUfcCfUfGfacggaaaaaa	3797	PuUfuuuUfccgucagGfaUfugcggca	4897
AD-2138376.1	cgcaauCfcUfGfAfcggaaaaaga	3798	PuCfuuuUfuccgucaGfgAfuugcggc	4898
AD-2138377.1	gcaaucCfuGfAfCfggaaaaagga	3799	PuCfcuuUfuuccgucAfgGfauugcgg	4899
AD-2138378.1	caauccUfgAfCfGfgaaaaaggga	3800	PuCfccuUfuuuccguCfaGfgauugcg	4900
AD-2138379.1	aauccuGfaCfGfGfaaaaagggca	3801	PuGfcccUfuuuuccgUfcAfggauugc	4901
AD-2138380.1	auccugAfcGfGfAfaaaagggcca	3802	PuGfgccCfuuuuuccGfuCfaggauug	4902
AD-2138381.1	caugguGfcCfAfUfacaaccaaca	3803	PuGfuugGfuuguaugGfcAfccauggg	4903
AD-2138383.1	uggugcCfaUfAfCfaaccaacaga	3804	PuCfuguUfgguuguaUfgGfcaccaug	4904
AD-2138384.1	gugccaUfaCfAfAfccaacagcca	3805	PuGfgcuGfuugguugUfaUfggcacca	4905
AD-2138385.1	gccauaCfaAfCfCfaacagccaaa	3806	PuUfuggCfuguugguUfgUfauggcac	4906
AD-2138386.1	ccauacAfaCfCfAfacagccaaga	3807	PuCfuugGfcuguuggUfuGfuauggca	4907
AD-2138387.1	cauacaAfcCfAfAfcagccaagua	3808	PuAfcuuGfgcuguugGfuUfguauggc	4908
AD-2138388.1	auacaaCfcAfAfCfagccaaguga	3809	PuCfacuUfggcuguuGfgUfuguaugg	4909
AD-2138389.1	uacaacCfaAfCfAfgccaagugca	3810	PuGfcacUfuggcuguUfgGfuuguaug	4910
AD-2138390.1	acaaccAfaCfAfGfccaagugcga	3811	PuCfgcaCfuuggcugUfuGfguuguau	4911
AD-2138391.1	gccaagUfgCfGfGfugggaguaca	3812	PuGfuacUfcccaccgCfaCfuuggcug	4912
AD-2138392.1	aagugcGfgUfGfGfgaguacugua	3813	PuAfcagUfacucccaCfcGfcacuugg	4913
AD-2138393.1	agugcgGfuGfGfGfaguacuguaa	3814	PuUfacaGfuacucccAfcCfgcacuug	4914
AD-2138394.1	gugcggUfgGfGfAfguacuguaaa	3815	PuUfuacAfguacuccCfaCfcgcacuu	4915
AD-2138395.1	ugcgguGfgGfAfGfuacuguaaga	3816	PuCfuuaCfaguacucCfcAfccgcacu	4916
AD-2138396.1	gcggugGfgAfGfUfacuguaagaa	3817	PuUfcuuAfcaguacuCfcCfaccgcac	4917
AD-2138397.1	cgguggGfaGfUfAfcuguaagaua	3818	PuAfucuUfacaguacUfcCfcaccgca	4918
AD-2138398.1	gguggggAfgUfAfCfuguaagauaa	3819	PuUfaucUfuacaguaCfuCfccaccgc	4919
AD-2138399.1	gugggaGfuAfCfUfguaagauaca	3820	PuGfuauCfuuacaguAfcUfcccaccg	4920
AD-2138400.1	ugggagUfaCfUfGfuaagauacca	3821	PuGfguaUfcuuacagUfaCfucccacc	4921
AD-2138401.1	ggaguaCfuGfUfAfagauaccgua	3822	PuAfcggUfaucuuacAfgUfacuccca	4922
AD-2138402.1	gaguacUfgUfAfAfgauaccguca	3823	PuGfacgGfuaucuuaCfaGfuacuccc	4923
AD-2138403.1	aguacuGfuAfAfGfauaccgucca	3824	PuGfgacGfguaucuuAfcAfguacucc	4924
AD-2138405.1	acuguaAfgAfUfAfccguccugua	3825	PuAfcagGfacgguauCfuUfacaguac	4925
AD-2138406.1	cuguaaGfaUfAfCfcguccuguga	3826	PuCfacaGfgacgguaUfcUfuacagua	4926
AD-2138407.1	guaagaUfaCfCfGfuccugugaca	3827	PuGfucaCfaggacggUfaUfcuuacag	4927
AD-2138408.1	uuggcuCfcCfAfCfagcaccacca	3828	PuGfgugGfugcugugGfgAfgccaauu	4928
AD-2138409.1	ggcuccCfaCfAfGfcaccaccuga	3829	PuCfaggUfggugcugUfgGfgagccaa	4929
AD-2138410.1	gcucccAfcAfGfCfaccaccugaa	3830	PuUfcagGfuggugcuGfuGfggagcca	4930
AD-2138412.1	acagcaCfcAfCfCfugagcuaaca	3831	PuGfuuaGfcucagguGfgUfgcugugg	4931
AD-2138413.1	cagcacCfaCfCfUfgagcuaacca	3832	PuGfguuAfgcucaggUfgGfugcugug	4932

Duplex ID	Sense Sequence	SEQ ID NO	Antisense Sequence	SEQ ID NO
AD-2138414.1	caugguGfaUfGfGfacagagcuaa	3833	PuUfagcUfcuguccaUfcAfccauggu	4933
AD-2138415.1	gacagaGfcUfAfCfcgaggcacaa	3834	PuUfgugCfcucgguaGfcUfcugucca	4934
AD-2138416.1	acagagCfuAfCfCfgaggcacaua	3835	PuAfuguGfccucgguAfgCfucugucc	4935
AD-2138417.1	cagagcUfaCfCfGfaggcacauca	3836	PuGfaugUfgccucggUfaGfcucuguc	4936
AD-2138418.1	gagcuaCfcGfAfGfgcacauccua	3837	PuAfggaUfgugccucGfgUfagcucug	4937
AD-2138419.1	accgagGfcAfCfAfuccuccacca	3838	PuGfgugGfaggauguGfcCfucgguag	4938
AD-2138420.1	cgaggcAfcAfUfCfcuccaccaca	3839	PuGfuggUfggaggauGfuGfccucggu	4939
AD-2138421.1	aggcacAfuCfCfUfccaccaccaa	3840	PuUfgguGfguggaggAfuGfugccucg	4940
AD-2138422.1	gcacauCfcUfCfCfaccaccacca	3841	PuGfgugGfugguggaGfgAfugugccu	4941
AD-2138423.1	cauccuCfcAfCfCfaccaccacaa	3842	PuUfgugGfuggugguGfgAfggaugug	4942
AD-2138424.1	auccucCfaCfCfAfccaccacaga	3843	PuCfuguGfgugguggUfgGfaggaugu	4943
AD-2138425.1	uccuccAfcCfAfCfcaccacagga	3844	PuCfcugUfgguggugGfuGfgaggaug	4944
AD-2138426.1	ccuccaCfcAfCfCfaccacaggaa	3845	PuUfccuGfuggugguGfgUfggaggau	4945
AD-2138427.1	cuccacCfaCfCfAfccacaggaaa	3846	PuUfuccUfguggugguGfgGfuggagga	4946
AD-2138428.1	uccaccAfcCfAfCfcacaggaaaa	3847	PuUfuucCfuguggugGfuGfguggagg	4947
AD-2138429.1	ccaccaCfcAfCfCfacaggaaaga	3848	PuCfuuuCfcuguggugGfgUfgguggag	4948
AD-2138430.1	caccacCfaCfCfAfcaggaaagaa	3849	PuUfcuuUfccuguggUfgGfuggugga	4949
AD-2138431.1	accaccAfcCfAfCfaggaaagaaa	3850	PuUfucuUfuccugugGfuGfguggugg	4950
AD-2138432.1	ccaccaCfcAfCfAfggaaagaaga	3851	PuCfuucUfuuccuguGfgUfgguggug	4951
AD-2138433.1	caccacCfaCfAfGfgaaagaagua	3852	PuAfcuuCfuuuccugUfgGfugguggu	4952
AD-2138434.1	ccaccaCfaGfGfAfaagaagugua	3853	PuAfcacUfucuuuccUfgUfgguggug	4953
AD-2138435.1	caccacAfgGfAfAfagaaguguca	3854	PuGfacaCfuucuuucCfuGfugguggu	4954
AD-2138436.1	accacaGfgAfAfAfgaagugucaa	3855	PuUfgacAfcuucuuuCfcUfguggugg	4955
AD-2138437.1	ccacagGfaAfAfGfaagugucaga	3856	PuCfugaCfacuucuuUfcCfuguggug	4956
AD-2138438.1	cacaggAfaAfGfAfagugucagua	3857	PuAfcugAfcacuucuUfuCfcuguggu	4957
AD-2138439.1	acaggaAfaGfAfAfgugucaguca	3858	PuGfacuGfacacuucUfuUfccugugg	4958
AD-2138440.1	caggaaAfgAfAfGfugucagucua	3859	PuAfgacUfgacacuuCfuUfuccugug	4959
AD-2138441.1	aggaaaGfaAfGfUfgucagucuua	3860	PuAfagaCfugacacuUfcUfuuccugu	4960
AD-2138442.1	ggaaagAfaGfUfGfucagucuuga	3861	PuCfaagAfcugacacUfuCfuuuccug	4961
AD-2138443.1	gaaagaAfgUfGfUfcagucuugga	3862	PuCfcaaGfacugacaCfuUfcuuuccu	4962
AD-2138444.1	aaagaaGfuGfUfCfagucuuggua	3863	PuAfccaAfgacugacAfcUfucuuucc	4963
AD-2138445.1	agaaguGfuCfAfGfucuuggucaa	3864	PuUfgacCfaagacugAfcAfcuucuuu	4964
AD-2138446.1	gaagugUfcAfGfUfcuuggucaua	3865	PuAfugaCfcaagacuGfaCfacuucuu	4965
AD-2138447.1	aaguguCfaGfUfCfuuggucauca	3866	PuGfaugAfccaagacUfgAfcacuucu	4966
AD-2138448.1	agugucAfgUfCfUfuggucaucua	3867	PuAfgauGfaccaagaCfuGfacacuuc	4967
AD-2138449.1	gugucaGfuCfUfUfggucaucuaa	3868	PuUfagaUfgaccaagAfcUfgacacuu	4968
AD-2138450.1	ugucagUfcUfUfGfgucaucuaua	3869	PuAfuagAfugaccaaGfaCfugacacu	4969
AD-2138451.1	gucaguCfuUfGfGfucaucuauga	3870	PuCfauaGfaugaccaAfgAfcugacac	4970
AD-2138452.1	ucagucUfuGfGfUfcaucuaugaa	3871	PuUfcauAfgaugaccAfaGfacugaca	4971
AD-2138453.1	cagucuUfgGfUfCfaucuaugaca	3872	PuGfucaUfagaugacCfaAfgacugac	4972
AD-2138454.1	agucuuGfgUfCfAfucuaugacaa	3873	PuUfgucAfuagaugaCfcAfagacuga	4973
AD-2138455.1	ggaaucCfaGfAfUfgccgauaaaa	3874	PuUfuuaUfcggcaucUfgGfauuccug	4974
AD-2138456.1	gaauccAfgAfUfGfccgauaaaga	3875	PuCfuuuAfucggcauCfuGfgauuccu	4975
AD-2138457.1	ggugggAfgUfAfCfugcaaccuga	3876	PuCfaggUfugcaguaCfuCfccaccug	4976
AD-2138458.1	gugggaGfuAfCfUfgcaaccugaa	3877	PuUfcagGfuugcaguAfcUfcccaccu	4977
AD-2138459.1	ugggagUfaCfUfGfcaaccugaaa	3878	PuUfucaGfguugcagUfaCfucccacc	4978
AD-2138460.1	gggaguAfcUfGfCfaaccugaaaa	3879	PuUfuucAfgguugcaGfuAfcucccac	4979
AD-2138461.1	ggaguaCfuGfCfAfaccugaaaaa	3880	PuUfuuuCfagguugcAfgUfacuccca	4980

Duplex ID	Sense Sequence	SEQ ID NO	Antisense Sequence	SEQ ID NO
AD-2138462.1	gaguacUfgCfAfAfccugaaaaaa	3881	PuUfuuuUfcagguugCfaGfuacuccc	4981
AD-2138463.1	aguacuGfcAfAfCfcugaaaaaaa	3882	PuUfuuuUfucagguuGfcAfguacucc	4982
AD-2138464.1	guacugCfaAfCfCfugaaaaaaua	3883	PuAfuuuUfuucagguUfgCfaguacuc	4983
AD-2138465.1	uacugcAfaCfCfUfgaaaaaauga	3884	PuCfauuUfuuucaggUfuGfcaguacu	4984
AD-2138466.1	acugcaAfcCfUfGfaaaaaaugca	3885	PuGfcauUfuuuucagGfuUfgcaguac	4985
AD-2138467.1	cugcaaCfcUfGfAfaaaaaugcua	3886	PuAfgcaUfuuuuucaGfgUfugcagua	4986
AD-2138468.1	ugcaacCfuGfAfAfaaaaugcuca	3887	PuGfagcAfuuuuuucAfgGfuugcagu	4987
AD-2138469.1	gcaaccUfgAfAfAfaaaugcucaa	3888	PuUfgagCfauuuuuuCfaGfguugcag	4988
AD-2138470.1	caaccuGfaAfAfAfaaugcucaga	3889	PuCfugaGfcauuuuuUfcAfgguugca	4989
AD-2138471.1	aaccugAfaAfAfAfaugcucagga	3890	PuCfcugAfgcauuuuUfuCfagguugc	4990
AD-2138472.1	accugaAfaAfAfAfugcucaggaa	3891	PuUfccuGfagcauuuUfuUfcagguug	4991
AD-2138473.1	ccugaaAfaAfAfUfgcucaggaaa	3892	PuUfuccUfgagcauuUfuUfucagguu	4992
AD-2138474.1	cugaaaAfaAfUfGfcucaggaaca	3893	PuGfuucCfugagcauUfuUfuucaggu	4993
AD-2138475.1	ugaaaaAfaUfGfCfucaggaacaa	3894	PuUfguuCfcugagcaUfuUfuuucagg	4994
AD-2138476.1	gaaaaaAfuGfCfUfcaggaacaga	3895	PuCfuguUfccugagcAfuUfuuuucag	4995
AD-2138477.1	aaaaaaUfgCfUfCfaggaacagaa	3896	PuUfcugUfuccugagCfaUfuuuuuca	4996
AD-2138478.1	aaaaauGfcUfCfAfggaacagaaa	3897	PuUfucuGfuuccugaGfcAfuuuuuuc	4997
AD-2138479.1	aaaaugCfuCfAfGfgaacagaaga	3898	PuCfuucUfguuccugAfgCfauuuuuu	4998
AD-2138480.1	aaaugcUfcAfGfGfaacagaagca	3899	PuGfcuuCfuguuccuGfaGfcauuuuu	4999
AD-2138481.1	gcaccuCfcGfCfCfuguuguccua	3900	PuAfggaCfaacaggcGfgAfggugcua	5000
AD-2138482.1	caccucCfgCfCfUfguuguccuga	3901	PuCfaggAfcaacaggCfgGfaggugcu	5001
AD-2138483.1	ccuccgCfcUfGfUfuguccugcua	3902	PuAfgcaGfgacaacaGfgCfggaggug	5002
AD-2138484.1	cuccgcCfuGfUfUfguccugcuua	3903	PuAfagcAfggacaacAfgGfcggaggu	5003
AD-2138485.1	uccgccUfgUfUfGfuccugcuuca	3904	PuGfaagCfaggacaaCfaGfgcggagg	5004
AD-2138486.1	ccgccuGfuUfGfUfccugcuucca	3905	PuGfgaaGfcaggacaAfcAfggcggag	5005
AD-2138487.1	cgccugUfuGfUfCfcugcuuccaa	3906	PuUfggaAfgcaggacAfaCfaggcgga	5006
AD-2138488.1	ccgaagAfaGfAfCfuguauguuua	3907	PuAfaacAfuacagucUfuCfuucggaa	5007
AD-2138489.1	cgaagaAfgAfCfUfguauguuuga	3908	PuCfaaaCfauacaguCfuUfcuucgga	5008
AD-2138490.1	gaagaaGfaCfUfGfuauguuugga	3909	PuCfcaaAfcauacagUfcUfucuucgg	5009
AD-2138491.1	aagaagAfcUfGfUfauguuuggga	3910	PuCfccaAfacauacaGfuCfuucuucg	5010
AD-2138492.1	gcgaccAfcUfGfUfuacugggaca	3911	PuGfuccCfaguaacaGfuGfgucgccc	5011
AD-2138493.1	cugggaCfgCfCfAfugccaggaca	3912	PuGfuccUfggcauggCfgUfcccagua	5012
AD-2138494.1	ugggacGfcCfAfUfgccaggacua	3913	PuAfgucCfuggcaugGfcGfucccagu	5013
AD-2138495.1	cauagaCfaCfAfGfcauuuucaca	3914	PuGfugaAfaaugcugUfgUfcuauggg	5014
AD-2138496.1	auagacAfcAfGfCfauuuucacua	3915	PuAfgugAfaaaugcuGfuGfucuaugg	5015
AD-2138497.1	uagacaCfaGfCfAfuuuucacuca	3916	PuGfaguGfaaaaugcUfgUfgucuaug	5016
AD-2138498.1	agacacAfgCfAfUfuuucacucca	3917	PuGfgagUfgaaaaugCfuGfugucuau	5017
AD-2138499.1	gacacaGfcAfUfUfuucacuccaa	3918	PuUfggaGfugaaaauGfcUfgugucua	5018
AD-2138500.1	acacagCfaUfUfUfucacuccaga	3919	PuCfuggAfgugaaaaUfgCfugugucu	5019
AD-2138501.1	cacagcAfuUfUfUfcacuccagaa	3920	PuUfcugGfagugaaaAfuGfcuguguc	5020
AD-2138502.1	acagcaUfuUfUfCfacuccagaga	3921	PuCfucuGfgagugaaAfaUfgcugugu	5021
AD-2138503.1	cagcauUfuUfCfAfcuccagagaa	3922	PuUfcucUfggagugaAfaAfugcugug	5022
AD-2138504.1	agcauuUfuCfAfCfuccagagaca	3923	PuGfucuCfuggagugAfaAfaugcugu	5023
AD-2138505.1	gcauuuUfcAfCfUfccagagacaa	3924	PuUfgucUfcuggaguGfaAfaaugcug	5024
AD-2138506.1	cauuuuCfaCfUfCfcagagacaaa	3925	PuUfuguCfucuggagUfgAfaaaugcu	5025
AD-2138507.1	auuuucAfcUfCfCfagagacaaaa	3926	PuUfuugUfcucuggaGfuGfaaaaugc	5026
AD-2138508.1	uuuucaCfuCfCfAfgagacaaaua	3927	PuAfuuuGfucucuggAfgUfgaaaaug	5027
AD-2138509.1	uuucacUfcCfAfGfagacaaauca	3928	PuGfauuUfgucucugGfaGfugaaaau	5028

Duplex ID	Sense Sequence	SEQ ID NO	Antisense Sequence	SEQ ID NO
AD-2138510.1	uucacuCfcAfGfAfgacaaaucca	3929	PuGfgauUfugucucuGfgAfgugaaaa	5029
AD-2138511.1	ucacucCfaGfAfGfacaaauccaa	3930	PuUfggaUfuugucucUfgGfagugaaa	5030
AD-2138512.1	acgggcGfgGfUfCfuggaaaaaaa	3931	PuUfuuuUfuccagacCfcGfcccgugg	5031
AD-2138513.1	cgggcgGfgUfCfUfggaaaaaaaa	3932	PuUfuuuUfuuccagaCfcCfgcccgug	5032
AD-2138514.1	gggcggGfuCfUfGfgaaaaaaaua	3933	PuAfuuuUfuuuccagAfcCfcgcccgu	5033
AD-2138515.1	ggcgggUfcUfGfGfaaaaaauua	3934	PuAfauuUfuuuuccaGfaCfccgcccg	5034
AD-2138516.1	gcggguCfuGfGfAfaaaaaauuaa	3935	PuUfaauUfuuuuuccAfgAfcccgccc	5035
AD-2138517.1	cgggucUfgGfAfAfaaaaauuaca	3936	PuGfuaaUfuuuuuucCfaGfacccgcc	5036
AD-2138518.1	gggucuGfgAfAfAfaaaauuacua	3937	PuAfguaAfuuuuuuuCfcAfgacccgc	5037
AD-2138519.1	ggucugGfaAfAfAfaaauuacuga	3938	PuCfaguAfauuuuuuUfcCfagacccg	5038
AD-2138520.1	gucuggAfaAfAfAfaauuacugca	3939	PuGfcagUfaauuuuuUfuCfcagaccc	5039
AD-2138521.1	ucuggaAfaAfAfAfauuacugcca	3940	PuGfgcaGfuaauuuuUfuUfccagacc	5040
AD-2138522.1	cuggaaAfaAfAfAfuuacugccga	3941	PuCfggcAfguaauuuUfuUfuccagac	5041
AD-2138523.1	uggaaaAfaAfAfUfuacugccgua	3942	PuAfcggCfaguaauuUfuUfuuccaga	5042
AD-2138524.1	cguaacCfcUfGfAfuggugaugua	3943	PuAfcauCfaccaucaGfgGfuuacggc	5043
AD-2138525.1	aacccuGfaUfGfGfugauguagga	3944	PuCfcuaCfaucaccaUfcAfggguuac	5044
AD-2138526.1	cccugaUfgGfUfGfauguagguga	3945	PuCfaccUfacaucacCfaUfcaggguu	5045
AD-2138527.1	ccugauGfgUfGfAfuguaggugga	3946	PuCfcacCfuacaucaCfcAfucagggu	5046
AD-2138528.1	uaggugGfuCfCfCfuggugcuaca	3947	PuGfuagCfaccagggAfcCfaccuaca	5047
AD-2138529.1	agguggUfcCfCfUfggugcuacaa	3948	PuUfguaGfcaccaggGfaCfcaccuac	5048
AD-2138530.1	guggucCfcUfGfGfugcuacacga	3949	PuCfgugUfagcaccaGfgGfaccaccu	5049
AD-2138531.1	cuggugCfuAfCfAfcgacaaauca	3950	PuGfauuUfgucguguAfgCfaccaggg	5050
AD-2138532.1	ggugcuAfcAfCfGfacaaauccaa	3951	PuUfggaUfuugucguGfuAfgcaccag	5051
AD-2138533.1	gugcuaCfaCfGfAfcaaauccaaa	3952	PuUfuggAfuuugucgUfgUfagcacca	5052
AD-2138534.1	ugcuacAfcGfAfCfaaauccaaga	3953	PuCfuugGfauuugucGfuGfuagcacc	5053
AD-2138535.1	gcuacaCfgAfCfAfaauccaagaa	3954	PuUfcuuGfgauuuguCfgUfguagcac	5054
AD-2138536.1	cuacacGfaCfAfAfauccaagaaa	3955	PuUfucuUfggauuugUfcGfuguagca	5055
AD-2138537.1	uacacgAfcAfAfAfuccaagaaaa	3956	PuUfuucUfuggauuuGfuCfguguagc	5056
AD-2138538.1	acacgaCfaAfAfUfccaagaaaaa	3957	PuUfuuuCfuuggauuUfgUfcguguag	5057
AD-2138539.1	cacgacAfaAfUfCfcaagaaaaca	3958	PuGfuuuUfcuuggauUfuGfucgugua	5058
AD-2138540.1	acgacaAfaUfCfCfaagaaaacua	3959	PuAfguuUfucuuggaUfuUfgucgugu	5059
AD-2138541.1	cgacaaAfuCfCfAfagaaaacuua	3960	PuAfaguUfuucuuggAfuUfugucgug	5060
AD-2138542.1	gacaaaUfcCfAfAfgaaaacuuua	3961	PuAfaagUfuuucuugGfaUfuugucgu	5061
AD-2138543.1	acaaauCfcAfAfGfaaaacuuuaa	3962	PuUfaaaGfuuuucuuGfgAfuuugucg	5062
AD-2138544.1	caaaucCfaAfGfAfaaacuuuaca	3963	PuGfuaaAfguuuucuUfgGfauuuguc	5063
AD-2138545.1	aaauccAfaGfAfAfaacuuuacga	3964	PuCfguaAfaguuuucUfuGfgauuugu	5064
AD-2138546.1	aauccaAfgAfAfAfacuuuacgaa	3965	PuUfcguAfaaguuuuCfuUfggauuug	5065
AD-2138547.1	auccaaGfaAfAfAfcuuuacgaca	3966	PuGfucgUfaaaguuuUfcUfuggauuu	5066
AD-2138548.1	uccaagAfaAfAfCfuuuacgacua	3967	PuAfgucGfuaaaguuUfuCfuuggauu	5067
AD-2138549.1	ccaagaAfaAfCfUfuuacgacuaa	3968	PuUfaguCfguaaaguUfuUfcuuggau	5068
AD-2138550.1	aagaaaAfcUfUfUfacgacuacua	3969	PuAfguaGfucguaaaGfuUfuucuugg	5069
AD-2138551.1	agaaaaCfuUfUfAfcgacuacuga	3970	PuCfaguAfgucguaaAfgUfuuucuug	5070
AD-2138552.1	gaaaacUfuUfAfCfgacuacugua	3971	PuAfcagUfagucguaAfaGfuuuucuu	5071
AD-2138553.1	aaaacuUfuAfCfGfacuacuguga	3972	PuCfacaGfuagucguAfaAfguuuucu	5072
AD-2138554.1	aaacuuUfaCfGfAfcuacugugaa	3973	PuUfcacAfguagucgUfaAfaguuuuc	5073
AD-2138555.1	aacuuuAfcGfAfCfuacugugaua	3974	PuAfucaCfaguagucGfuAfaaguuuu	5074
AD-2138556.1	acuuuaCfgAfCfUfacugugauga	3975	PuCfaucAfcaguaguCfgUfaaaguuu	5075
AD-2138557.1	cuuuacGfaCfUfAfcugugaugua	3976	PuAfcauCfacaguagUfcGfuaaaguu	5076

Duplex ID	Sense Sequence	SEQ ID NO	Antisense Sequence	SEQ ID NO
AD-2138558.1	uuuacgAfcUfAfCfugugauguca	3977	PuGfacaUfcacaguaGfuCfguaaagu	5077
AD-2138559.1	gacuacUfgUfGfAfugucccucaa	3978	PuUfgagGfgacaucaCfaGfuagucgu	5078
AD-2138560.1	cugugaUfgUfCfCfcucaguguga	3979	PuCfacaCfugagggaCfaUfcacagua	5079
AD-2138561.1	auguccCfuCfAfGfugugcggcca	3980	PuGfgccGfcacacugAfgGfgacauca	5080
AD-2138562.1	aagaaaUfgUfCfCfuggaagggua	3981	PuAfcccUfuccaggaCfaUfuucuucg	5081
AD-2138563.1	gcccugGfcAfAfGfucagucuuaa	3982	PuUfaagAfcugacuuGfcCfagggcca	5082
AD-2138564.1	ccuggcAfaGfUfCfagucuuagaa	3983	PuUfcuaAfgacugacUfuGfccagggc	5083
AD-2138565.1	cuggcaAfgUfCfAfgucuuagaaa	3984	PuUfucuAfagacugaCfuUfgccaggg	5084
AD-2138566.1	uggcaaGfuCfAfGfucuuagaaca	3985	PuGfuucUfaagacugAfcUfugccagg	5085
AD-2138567.1	ggcaagUfcAfGfUfcuuagaacaa	3986	PuUfguuCfuaagacuGfaCfuugccag	5086
AD-2138568.1	gcaaguCfaGfUfCfuuagaacaaa	3987	PuUfuguUfcuaagacUfgAfcuugcca	5087
AD-2138569.1	caagucAfgUfCfUfuagaacaaga	3988	PuCfuugUfucuaagaCfuGfacuugcc	5088
AD-2138570.1	aagucaGfuCfUfUfagaacaagga	3989	PuCfcuuGfuucuaagAfcUfgacuugc	5089
AD-2138571.1	agucagUfcUfUfAfgaacaaggua	3990	PuAfccuUfguucuaaGfaCfugacuug	5090
AD-2138572.1	gucaguCfuUfAfGfaacaagguua	3991	PuAfaccUfuguucuaAfgAfcugacuu	5091
AD-2138573.1	ucagucUfuAfGfAfacaagguuua	3992	PuAfaacCfuuguucuAfaGfacugacu	5092
AD-2138574.1	cagucuUfaGfAfAfcaagguuuga	3993	PuCfaaaCfcuuguucUfaAfgacugac	5093
AD-2138575.1	agucuuAfgAfAfCfaagguuugga	3994	PuCfcaaAfccuuguuCfuAfagacuga	5094
AD-2138576.1	gucuuaGfaAfCfAfagguuuggaa	3995	PuUfccaAfaccuuguUfcUfaagacug	5095
AD-2138577.1	ucuuagAfaCfAfAfgguuuggaaa	3996	PuUfuccAfaaccuugUfuCfuaagacu	5096
AD-2138578.1	cuuagaAfcAfAfGfguuuggaaua	3997	PuAfuucCfaaaccuuGfuUfcuaagac	5097
AD-2138579.1	uuagaaCfaAfGfGfuuuggaauga	3998	PuCfauuCfcaaaccuUfgUfucuaaga	5098
AD-2138580.1	uagaacAfaGfGfUfuuggaaugca	3999	PuGfcauUfccaaaccUfuGfuucuaag	5099
AD-2138581.1	agaacaAfgGfUfUfuggaaugcaa	4000	PuUfgcaUfuccaaacCfuUfguucuaa	5100
AD-2138582.1	gaacaaGfgUfUfUfggaaugcaca	4001	PuGfugcAfuuccaaaCfcUfuguucua	5101
AD-2138583.1	aacaagGfuUfUfGfgaaugcacua	4002	PuAfgugCfauuccaaAfcCfuuguucu	5102
AD-2138584.1	acaaggUfuUfGfGfaaugcacuua	4003	PuAfaguGfcauuccaAfaCfcuuguuc	5103
AD-2138585.1	caagguUfuGfGfAfaugcacuuca	4004	PuGfaagUfgcauuccAfaAfccuuguu	5104
AD-2138586.1	aaggguuUfgGfAfAfugcacuucua	4005	PuAfgaaGfugcauucCfaAfaccuugu	5105
AD-2138587.1	agguuuGfgAfAfUfgcacuucuga	4006	PuCfagaAfgugcauuCfcAfaaccuug	5106
AD-2138588.1	gguuugGfaAfUfGfcacuucugua	4007	PuAfcagAfagugcauUfcCfaaaccuu	5107
AD-2138589.1	uuggaaUfgCfAfCfuucuguggaa	4008	PuUfccaCfagaagugCfaUfuccaaac	5108
AD-2138590.1	uggaauGfcAfCfUfucuguggaga	4009	PuCfuccAfcagaaguGfcAfuuccaaa	5109
AD-2138591.1	gaaugcAfcUfUfCfuguggaggca	4010	PuGfccuCfcacagaaGfuGfcauucca	5110
AD-2138592.1	cuguggAfgGfCfAfccuugauaua	4011	PuAfuauCfaaggugcCfuCfcacagaa	5111
AD-2138593.1	uguggaGfgCfAfCfcuugauauca	4012	PuGfauaUfcaaggugCfcUfccacaga	5112
AD-2138594.1	guggagGfcAfCfCfuugauaucca	4013	PuGfgauAfucaagguGfcCfuccacag	5113
AD-2138595.1	uugacuGfcUfGfCfccacugcuua	4014	PuAfagcAfgugggcaGfcAfgucaaca	5114
AD-2138596.1	ugacugCfuGfCfCfcacugcuuga	4015	PuCfaagCfagugggcAfgCfagucaac	5115
AD-2138597.1	acugcuGfcCfCfAfcugcuuggaa	4016	PuUfccaAfgcaguggGfcAfgcaguca	5116
AD-2138598.1	cugcugCfcCfAfCfugcuuggaga	4017	PuCfuccAfagcagugGfgCfagcaguc	5117
AD-2138599.1	ugcugcCfcAfCfUfgcuuggagaa	4018	PuUfcucCfaagcaguGfgGfcagcagu	5118
AD-2138600.1	cugcccAfcUfGfCfuuggagaaga	4019	PuCfuucUfccaagcaGfuGfggcagca	5119
AD-2138601.1	ugcccaCfuGfCfUfuggagaagua	4020	PuAfcuuCfuccaagcAfgUfgggcagc	5120
AD-2138602.1	cccacuGfcUfUfGfgagaagucca	4021	PuGfgacUfucuccaaGfcAfgugggca	5121
AD-2138603.1	gugcacAfcCfAfAfgaagugaaua	4022	PuAfuucAfcuucuugGfuGfugcaccc	5122
AD-2138604.1	gcacacCfaAfGfAfagugaaucua	4023	PuAfgauUfcacuucuUfgGfugugcac	5123
AD-2138605.1	acaccaAfgAfAfGfugaaucucga	4024	PuCfgagAfuucacuuCfuUfggugugc	5124

Duplex ID	Sense Sequence	SEQ ID NO	Antisense Sequence	SEQ ID NO
AD-2138606.1	caccaaGfaAfGfUfgaaucucgaa	4025	PuUfcgaGfauucacuUfcUfuggugug	5125
AD-2138607.1	accaagAfaGfUfGfaaucucgaaa	4026	PuUfucgAfgauucacUfuCfuuggugu	5126
AD-2138608.1	ugaaucUfcGfAfAfccgcauguua	4027	PuAfacaUfgcgguucGfaGfauucacu	5127
AD-2138609.1	aaucucGfaAfCfCfgcauguucaa	4028	PuUfgaaCfaugcgguUfcGfagauuca	5128
AD-2138610.1	cgaaccGfcAfUfGfuucaggaaaa	4029	PuUfuucCfugaacauGfcGfguucgag	5129
AD-2138611.1	gaaccgCfaUfGfUfucaggaaaua	4030	PuAfuuuCfcugaacaUfgCfgguucga	5130
AD-2138612.1	aaccgcAfuGfUfUfcaggaaauaa	4031	PuUfauuUfccugaacAfuGfcgguucg	5131
AD-2138613.1	accgcaUfgUfUfCfaggaaauaga	4032	PuCfuauUfuccugaaCfaUfgcgguuc	5132
AD-2138614.1	ccgcauGfuUfCfAfggaaauagaa	4033	PuUfcuaUfuuccugaAfcAfugcgguu	5133
AD-2138615.1	uuggagCfcCfAfCfacgaaaagaa	4034	PuUfcuuUfucgugugGfgCfuccaaga	5134
AD-2138616.1	uggagcCfcAfCfAfcgaaaagaua	4035	PuAfucuUfuucguguGfgGfcuccaag	5135
AD-2138617.1	gagcccAfcAfCfGfaaaagauaua	4036	PuAfuauCfuuuucguGfuGfggcucca	5136
AD-2138618.1	agcccaCfaCfGfAfaaagauauua	4037	PuAfauaUfcuuuucgUfgUfgggcucc	5137
AD-2138619.1	gcccacAfcGfAfAfaagauauuga	4038	PuCfaauAfucuuuucGfuGfugggcuc	5138
AD-2138620.1	cccacaCfgAfAfAfagauauugca	4039	PuGfcaaUfaucuuuuCfgUfgugggcu	5139
AD-2138621.1	ccacacGfaAfAfAfgauauugcca	4040	PuGfgcaAfuaucuuuUfcGfugugggc	5140
AD-2138622.1	cacacgAfaAfAfGfauauugccua	4041	PuAfggcAfauaucuuUfuCfguguggg	5141
AD-2138623.1	acacgaAfaAfGfAfuauugccuua	4042	PuAfaggCfaauaucuUfuUfcgugugg	5142
AD-2138624.1	cacgaaAfaGfAfUfauugccuuga	4043	PuCfaagGfcaauaucUfuUfucgugug	5143
AD-2138625.1	acgaaaAfgAfUfAfuugccuugca	4044	PuGfcaaGfgcaauauCfuUfuucgugu	5144
AD-2138626.1	cgaaaaGfaUfAfUfugccuugcua	4045	PuAfgcaAfggcaauaUfcUfuuucgug	5145
AD-2138627.1	gaaaagAfuAfUfUfgccuugcuaa	4046	PuUfagcAfaggcaauAfuCfuuuucgu	5146
AD-2138628.1	aaaagaUfaUfUfGfccuugcuaaa	4047	PuUfuagCfaaggcaaUfaUfcuuuucg	5147
AD-2138629.1	aaagauAfuUfGfCfcuugcuaaaa	4048	PuUfuuaGfcaaggcaAfuAfucuuuuc	5148
AD-2138630.1	aagauaUfuGfCfCfuugcuaaaga	4049	PuCfuuuAfgcaaggcAfaUfaucuuuu	5149
AD-2138631.1	agauauUfgCfCfUfugcuaaagca	4050	PuGfcuuUfagcaaggCfaAfuaucuuu	5150
AD-2138632.1	gauauuGfcCfUfUfgcuaaagcua	4051	PuAfgcuUfuagcaagGfcAfauaucuu	5151
AD-2138633.1	auauugCfcUfUfUfGfcuaaagcuaa	4052	PuUfagcUfuuagcaaGfgCfaauaucu	5152
AD-2138634.1	uauugcCfuUfGfCfuaaagcuaaa	4053	PuUfuagCfuuuagcaAfgGfcaauauc	5153
AD-2138635.1	ccuugcUfaAfAfGfcuaagcagua	4054	PuAfcugCfuuagcuuUfaGfcaaggca	5154
AD-2138636.1	cuugcuAfaAfGfCfuaagcaguca	4055	PuGfacuGfcuuagcuUfuAfgcaaggc	5155
AD-2138637.1	ugcuaaAfgCfUfAfagcaguccua	4056	PuAfggaCfugcuuagCfuUfuagcaag	5156
AD-2138638.1	cuaagcAfgUfCfCfugccgucaua	4057	PuAfugaCfggcaggaCfuGfcuuagcu	5157
AD-2138639.1	agcaguCfcUfGfCfcgucaucaca	4058	PuGfugaUfgacggcaGfgAfcugcuua	5158
AD-2138640.1	gcagucCfuGfCfCfgucaucacua	4059	PuAfgugAfugacggcAfgGfacugcuu	5159
AD-2138641.1	caguccUfgCfCfGfucaucacuga	4060	PuCfaguGfaugacggCfaGfgacugcu	5160
AD-2138642.1	ucaucaCfuGfAfCfaaaguaauca	4061	PuGfauuAfcuuugucAfgUfgaugacg	5161
AD-2138643.1	caucacUfgAfCfAfaaguaaucca	4062	PuGfgauUfacuuuguCfaGfugaugac	5162
AD-2138644.1	aucacuGfaCfAfAfaguaauccca	4063	PuGfggaUfuacuuugUfcAfgugauga	5163
AD-2138645.1	ucacugAfcAfAfAfguaaucccaa	4064	PuUfgggAfuuacuuuGfuCfagugaug	5164
AD-2138646.1	cacugaCfaAfAfGfuaaucccaga	4065	PuCfuggGfauuacuuUfgUfcagugau	5165
AD-2138647.1	acugacAfaAfGfUfaaucccagca	4066	PuGfcugGfgauuacuUfuGfucaguga	5166
AD-2138648.1	cugacaAfaGfUfAfaucccagcua	4067	PuAfgcuGfggauuacUfuUfgucagug	5167
AD-2138649.1	ugacaaAfgUfAfAfucccagcuua	4068	PuAfagcUfgggauuaCfuUfugucagu	5168
AD-2138650.1	gacaaaGfuAfAfUfcccagcuuga	4069	PuCfaagCfugggauuAfcUfuugucag	5169
AD-2138651.1	acaaagUfaAfUfCfccagcuugua	4070	PuAfcaaGfcugggauUfaCfuuuguca	5170
AD-2138652.1	caaaguAfaUfCfCfcagcuuguca	4071	PuGfacaAfgcugggaUfuAfcuuuguc	5171
AD-2138653.1	aaaguaAfuCfCfCfagcuugucua	4072	PuAfgacAfagcugggAfuUfacuuugu	5172

Duplex ID	Sense Sequence	SEQ ID NO	Antisense Sequence	SEQ ID NO
AD-2138654.1	uaauccCfaGfCfUfugucugccaa	4073	PuUfggcAfgacaagcUfgGfgauuacu	5173
AD-2138655.1	aucccaGfcUfUfGfucugccauca	4074	PuGfaugGfcagacaaGfcUfgggauua	5174
AD-2138656.1	cugaccGfgAfCfCfgaauguuuca	4075	PuGfaaaCfauucgguCfcGfgucagcg	5175
AD-2138657.1	gaccggAfcCfGfAfauguuucaua	4076	PuAfugaAfacauucgGfuCfcggucag	5176
AD-2138658.1	accggaCfcGfAfAfuguuucauca	4077	PuGfaugAfaacauucGfgUfccgguca	5177
AD-2138659.1	ccggacCfgAfAfUfguuucaucaa	4078	PuUfgauGfaaacauuCfgGfuccgguc	5178
AD-2138660.1	cggaccGfaAfUfGfuuucaucaca	4079	PuGfugaUfgaaacauUfcGfguccggu	5179
AD-2138661.1	ggaccgAfaUfGfUfuucaucacua	4080	PuAfgugAfugaaacaUfuCfgguccgg	5180
AD-2138662.1	gaccgaAfuGfUfUfucaucacuga	4081	PuCfaguGfaugaaacAfuUfcgguccg	5181
AD-2138663.1	cgaaugUfuUfCfAfucacuggcua	4082	PuAfgccAfgugaugaAfaCfauucggu	5182
AD-2138664.1	gagaaaCfcCfAfAfgguacuuuua	4083	PuAfaaaGfuaccuugGfgUfuucuccc	5183
AD-2138665.1	agaaacCfcAfAfGfguacuuuuga	4084	PuCfaaaAfguaccuuGfgGfuuucucc	5184
AD-2138666.1	gaaaccCfaAfGfGfuacuuuugga	4085	PuCfcaaAfaguaccuUfgGfguuucuc	5185
AD-2138667.1	aaacccAfaGfGfUfacuuuuggaa	4086	PuUfccaAfaaguaccUfuGfgguuucu	5186
AD-2138668.1	aacccaAfgGfUfAfcuuuuggaga	4087	PuCfuccAfaaaguacCfuUfggguuuc	5187
AD-2138669.1	acccaaGfgUfAfCfuuuuggagca	4088	PuGfcucCfaaaaguaCfcUfuggguuu	5188
AD-2138670.1	cccaagGfuAfCfUfuuuggagcua	4089	PuAfgcuCfcaaaaguAfcCfuuggguu	5189
AD-2138671.1	caagguAfcUfUfUfuggagcugga	4090	PuCfcagCfuccaaaaGfuAfccuuggg	5190
AD-2138672.1	acuuuuGfgAfGfCfuggccuucua	4091	PuAfgaaGfgccagcuCfcAfaaaguac	5191
AD-2138673.1	uuuggaGfcUfGfGfccuucucaaa	4092	PuUfugaGfaaggccaGfcUfccaaaag	5192
AD-2138674.1	uuggagCfuGfGfCfcuucucaaga	4093	PuCfuugAfgaaggccAfgCfuccaaaa	5193
AD-2138675.1	uggagcUfgGfCfCfuucucaagga	4094	PuCfcuuGfagaaggcCfaGfcuccaaa	5194
AD-2138676.1	ggagcuGfgCfCfUfucucaaggaa	4095	PuUfccuUfgagaaggCfcAfgcuccaa	5195
AD-2138677.1	ggaagcCfcAfGfCfucccugugaa	4096	PuUfcacAfgggagcuGfgGfcuuccuu	5196
AD-2138678.1	gaagccCfaGfCfUfcccugugaua	4097	PuAfucaCfagggagcUfgGfgcuuccu	5197
AD-2138679.1	aagcccAfgCfUfCfccugugauua	4098	PuAfaucAfcagggagCfuGfggcuucc	5198
AD-2138680.1	agcccaGfcUfCfCfcugugauuga	4099	PuCfaauCfacagggaGfcUfgggcuuc	5199
AD-2138681.1	gcccagCfuCfCfCfugugauugaa	4100	PuUfcaaUfcacagggAfgCfugggcuu	5200
AD-2138682.1	cccagcUfcCfCfUfgugauugaga	4101	PuCfucaAfucacaggGfaGfcugggcu	5201
AD-2138683.1	ccagcuCfcCfUfGfugauugagaa	4102	PuUfcucAfaucacagGfgAfgcugggc	5202
AD-2138684.1	cagcucCfcUfGfUfgauugagaaa	4103	PuUfucuCfaaucacaGfgGfagcuggg	5203
AD-2138685.1	agcuccCfuGfUfGfauugagaaua	4104	PuAfuucUfcaaucacAfgGfgagcugg	5204
AD-2138686.1	gcucccUfgUfGfAfuugagaauaa	4105	PuUfauuCfucaaucaCfaGfggagcug	5205
AD-2138687.1	cucccuGfuGfAfUfugagaauaaa	4106	PuUfuauUfcucaaucAfcAfgggagcu	5206
AD-2138688.1	ucccugUfgAfUfUfgagaauaaaa	4107	PuUfuuaUfucucaauCfaCfagggagc	5207
AD-2138689.1	cccuguGfaUfUfGfagaauaaaga	4108	PuCfuuuAfuucucaaUfcAfcagggag	5208
AD-2138690.1	ccugugAfuUfGfAfgaauaaagua	4109	PuAfcuuUfauucucaAfuCfacaggga	5209
AD-2138691.1	cugugaUfuGfAfGfaauaaaguga	4110	PuCfacuUfuauucucAfaUfcacaggg	5210
AD-2138692.1	ugugauUfgAfGfAfauaaagugua	4111	PuAfcacUfuuauucuCfaAfucacagg	5211
AD-2138693.1	gugauuGfaGfAfAfuaaaguguga	4112	PuCfacaCfuuuauucUfcAfaucacag	5212
AD-2138694.1	ugauugAfgAfAfUfaaagugugca	4113	PuGfcacAfcuuuauuCfuCfaaucaca	5213
AD-2138695.1	gauugaGfaAfUfAfaagugugcaa	4114	PuUfgcaCfacuuuauUfcUfcaaucac	5214
AD-2138696.1	auugagAfaUfAfAfagugugcaaa	4115	PuUfugcAfcacuuuaUfuCfucaauca	5215
AD-2138697.1	uugagaAfuAfAfAfgugugcaaua	4116	PuAfuugCfacacuuuAfuUfcucaauc	5216
AD-2138698.1	ugagaaUfaAfAfGfugugcaauca	4117	PuGfauuGfcacacuuUfaUfucucaau	5217
AD-2138699.1	gagaauAfaAfGfUfgugcaaucga	4118	PuCfgauUfgcacacuUfuAfuucucaa	5218
AD-2138700.1	gaauaaAfgUfGfUfgcaaucgcua	4119	PuAfgcgAfuugcacaCfuUfuauucuc	5219
AD-2138701.1	aauaaaGfuGfUfGfcaaucgcuaa	4120	PuUfagcGfauugcacAfcUfuuauucu	5220

Duplex ID	Sense Sequence	SEQ ID NO	Antisense Sequence	SEQ ID NO
AD-2138702.1	auaaagUfgUfGfCfaaucgcuaua	4121	PuAfuagCfgauugcaCfaCfuuuauuc	5221
AD-2138703.1	uaaaguGfuGfCfAfaucgcuauga	4122	PuCfauaGfcgauugcAfcAfcuuuauu	5222
AD-2138704.1	aaagugUfgCfAfAfucgcuaugaa	4123	PuUfcauAfgcgauugCfaCfacuuuau	5223
AD-2138705.1	aaguguGfcAfAfUfcgcuaugaga	4124	PuCfucaUfagcgauuGfcAfcacuuua	5224
AD-2138706.1	agugugCfaAfUfCfgcuaugagua	4125	PuAfcucAfuagcgauUfgCfacacuuu	5225
AD-2138707.1	gugugcAfaUfCfGfcuaugaguua	4126	PuAfacuCfauagcgaUfuGfcacacuu	5226
AD-2138708.1	ugugcaAfuCfGfCfuaugaguuua	4127	PuAfaacUfcauagcgAfuUfgcacacu	5227
AD-2138709.1	gugcaaUfcGfCfUfaugaguuuca	4128	PuGfaaaCfucauagcGfaUfugcacac	5228
AD-2138710.1	ugcaauCfgCfUfAfugaguuucua	4129	PuAfgaaAfcucauagCfgAfuugcaca	5229
AD-2138711.1	caaucgCfuAfUfGfaguuucugaa	4130	PuUfcagAfaacucauAfgCfgauugca	5230
AD-2138712.1	aaucgcUfaUfGfAfguuucugaaa	4131	PuUfucaGfaaacucaUfaGfcgauugc	5231
AD-2138713.1	aucgcuAfuGfAfGfuuucugaaua	4132	PuAfuucAfgaaacucAfuAfgcgauug	5232
AD-2138714.1	ucgcuaUfgAfGfUfuucugaauga	4133	PuCfauuCfagaaacuCfaUfagcgauu	5233
AD-2138715.1	cgcuauGfaGfUfUfucugaaugga	4134	PuCfcauUfcagaaacUfcAfuagcgau	5234
AD-2138716.1	gcuaugAfgUfUfUfcugaauggaa	4135	PuUfccaUfucagaaaCfuCfauagcga	5235
AD-2138717.1	cuaugaGfuUfUfCfugaauggaaa	4136	PuUfuccAfuucagaaAfcUfcauagcg	5236
AD-2138718.1	uaugagUfuUfCfUfgaauggaaga	4137	PuCfuucCfauucagaAfaCfucauagc	5237
AD-2138719.1	augaguUfuCfUfGfaauggaagaa	4138	PuUfcuuCfcauucagAfaAfcucauag	5238
AD-2138720.1	ugaguuUfcUfGfAfauggaagaga	4139	PuCfucuUfccauucaGfaAfacucaua	5239
AD-2138721.1	gaguuuCfuGfAfAfuggaagagua	4140	PuAfcucUfuccauucAfgAfaacucau	5240
AD-2138722.1	guuucuGfaAfUfGfgaagagucca	4141	PuGfgacUfcuuccauUfcAfgaaacuc	5241
AD-2138723.1	uuucugAfaUfGfGfaagaguccaa	4142	PuUfggaCfucuuccaUfuCfagaaacu	5242
AD-2138724.1	uucugaAfuGfGfAfagaguccaaa	4143	PuUfuggAfcucuuccAfuUfcagaaac	5243
AD-2138725.1	ucugaaUfgGfAfAfgaguccaaua	4144	PuAfuugGfacucuucCfaUfucagaaa	5244
AD-2138726.1	cugaauGfgAfAfGfaguccaauca	4145	PuGfauuGfgacucuuCfcAfuucagaa	5245
AD-2138727.1	gaauggAfaGfAfGfuccaauccaa	4146	PuUfggaUfuggacucUfuCfcauucag	5246
AD-2138728.1	gaacucUfgUfGfCfugggcauuua	4147	PuAfaauGfcccagcaCfaGfaguucgg	5247
AD-2138729.1	aacucuGfuGfCfUfgggcauuuga	4148	PuCfaaaUfgcccagcAfcAfgaguucg	5248
AD-2138730.1	cucuguGfcUfGfGfgcauuuggca	4149	PuGfccaAfaugcccaGfcAfcagaguu	5249
AD-2138731.1	ucugugCfuGfGfGfcauuuggcca	4150	PuGfgccAfaaugcccAfgCfacagagu	5250
AD-2138732.1	ugugcuGfgGfCfAfuuuggccgga	4151	PuCfcggCfcaaaugcCfcAfgcacaga	5251
AD-2138733.1	gugcugGfgCfAfUfuuggccggaa	4152	PuUfccgGfccaaaugCfcCfagcacag	5252
AD-2138734.1	ugcuggGfcAfUfUfuggccggaga	4153	PuCfuccGfgccaaauGfcCfcagcaca	5253
AD-2138735.1	cuucgaGfaAfGfGfacaaauacaa	4154	PuUfguaUfuuguccuUfcUfcgaagca	5254
AD-2138736.1	uucgagAfaGfGfAfcaaauacaua	4155	PuAfuguAfuuuguccUfuCfucgaagc	5255
AD-2138737.1	ucgagaAfgGfAfCfaaauacauua	4156	PuAfaugUfauuugucCfuUfcucgaag	5256
AD-2138738.1	cgagaaGfgAfCfAfaauacauuua	4157	PuAfaauGfuauuuguCfcUfucucgaa	5257
AD-2138739.1	gagaagGfaCfAfAfauacauuuua	4158	PuAfaaaUfguauuugUfcCfuucucga	5258
AD-2138740.1	agaaggAfcAfAfAfuacauuuuaa	4159	PuUfaaaAfuguauuuGfuCfcuucucg	5259
AD-2138741.1	gaaggaCfaAfAfUfacauuuuaca	4160	PuGfuaaAfauguauuUfgUfccuucuc	5260
AD-2138742.1	aaggacAfaAfUfAfcauuuuacaa	4161	PuUfguaAfaauguauUfuGfuccuucu	5261
AD-2138743.1	aggacaAfaUfAfCfauuuuacaaa	4162	PuUfuguAfaaauguaUfuUfguccuuc	5262
AD-2138744.1	ggacaaAfuAfCfAfuuuuacaaga	4163	PuCfuugUfaaaauguAfuUfuguccuu	5263
AD-2138745.1	gacaaaUfaCfAfUfuuuacaagga	4164	PuCfcuuGfuaaaaugUfaUfuuguccu	5264
AD-2138746.1	acaaauAfcAfUfUfuuacaaggaa	4165	PuUfccuUfguaaaauGfuAfuuugucc	5265
AD-2138747.1	aauaagCfcUfGfGfugucuaugua	4166	PuAfcauAfgacaccaGfgCfuuauugg	5266
AD-2138748.1	auaagcCfuGfGfUfgucuauguua	4167	PuAfacaUfagacaccAfgGfcuuauug	5267
AD-2138749.1	uaagccUfgGfUfGfucuauguuca	4168	PuGfaacAfuagacacCfaGfgcuuauu	5268

Duplex ID	Sense Sequence	SEQ ID NO	Antisense Sequence	SEQ ID NO
AD-2138750.1	agccugGfuGfUfCfuauguucgua	4169	PuAfcgaAfcauagacAfcCfaggcuua	5269
AD-2138751.1	ccugguGfuCfUfAfuguucgugua	4170	PuAfcacGfaacauagAfcAfccaggcu	5270
AD-2138752.1	cuggugUfcUfAfUfguucguguua	4171	PuAfacaCfgaacauaGfaCfaccaggc	5271
AD-2138753.1	ugguguCfuAfUfGfuucguguuua	4172	PuAfaacAfcgaacauAfgAfcaccagg	5272
AD-2138754.1	ggugucUfaUfGfUfucguguuuca	4173	PuGfaaaCfacgaacaUfaGfacaccag	5273
AD-2138755.1	gugucuAfuGfUfUfcguguuucaa	4174	PuUfgaaAfcacgaacAfuAfgacacca	5274
AD-2138756.1	ugucuaUfgUfUfCfguguuucaaa	4175	PuUfugaAfacacgaaCfaUfagacacc	5275
AD-2138757.1	gucuauGfuUfCfGfuguuucaaga	4176	PuCfuugAfaacacgaAfcAfuagacac	5276
AD-2138758.1	ucuaugUfuCfGfUfguuucaagga	4177	PuCfcuuGfaaacacgAfaCfauagaca	5277
AD-2138759.1	cuauguUfcGfUfGfuuucaaggua	4178	PuAfccuUfgaaacacGfaAfcauagac	5278
AD-2138760.1	uauguuCfgUfGfUfuucaagguua	4179	PuAfaccUfugaaacaCfgAfacauaga	5279
AD-2138761.1	auguucGfuGfUfUfucaagguuua	4180	PuAfaacCfuugaaacAfcGfaacauag	5280
AD-2138762.1	uguucgUfgUfUfUfcaagguuuga	4181	PuCfaaaCfcuugaaaCfaCfgaacaua	5281
AD-2138763.1	guucguGfuUfUfCfaagguuugua	4182	PuAfcaaAfccuugaaAfcAfcgaacau	5282
AD-2138764.1	uucgugUfuUfCfAfagguuuguua	4183	PuAfacaAfaccuugaAfaCfacgaaca	5283
AD-2138765.1	ucguguUfuCfAfAfgguuuguuaa	4184	PuUfaacAfaaccuugAfaAfcacgaac	5284
AD-2138766.1	cguguuUfcAfAfGfguuuguuaca	4185	PuGfuaaCfaaaccuuGfaAfacacgaa	5285
AD-2138767.1	guguuuCfaAfGfGfuuuguuacua	4186	PuAfguaAfcaaaccuUfgAfaacacga	5286
AD-2138768.1	uguuucAfaGfGfUfuuguuacuua	4187	PuAfaguAfacaaaccUfuGfaaacacg	5287
AD-2138769.1	guuucaAfgGfUfUfuguuacuuga	4188	PuCfaagUfaacaaacCfuUfgaaacac	5288
AD-2138770.1	uuucaaGfgUfUfUfguuacuugga	4189	PuCfcaaGfuaacaaaCfcUfugaaaca	5289
AD-2138771.1	uucaagGfuUfUfGfuuacuuggaa	4190	PuUfccaAfguaacaaAfcCfuugaaac	5290
AD-2138772.1	ucaaggUfuUfGfUfuacuuggaua	4191	PuAfuccAfaguaacaAfaCfcuugaaa	5291
AD-2138773.1	uguuacUfuGfGfAfuugagggaga	4192	PuCfuccCfucaauccAfaGfuaacaaa	5292
AD-2138774.1	guuacuUfgGfAfUfugagggagua	4193	PuAfcucCfcucaaucCfaAfguaacaa	5293
AD-2138775.1	uacuugGfaUfUfGfagggagugaa	4194	PuUfcacUfcccucaaUfcCfaaguaac	5294
AD-2138776.1	acuuggAfuUfGfAfgggagugaua	4195	PuAfucaCfucccucaAfuCfcaaguaa	5295
AD-2138777.1	cuuggaUfuGfAfGfggagugauga	4196	PuCfaucAfcucccucAfaUfccaagua	5296
AD-2138778.1	uuggauUfgAfGfGfgagugaugaa	4197	PuUfcauCfacucccuCfaAfuccaagu	5297
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AD-2138780.1	ggauugAfgGfGfAfgugaugagaa	4199	PuUfcucAfucacuccCfuCfaauccaa	5299
AD-2138781.1	gauugaGfgGfAfGfugaugagaaa	4200	PuUfucuCfaucacucCfcUfcaaucca	5300
AD-2138782.1	auugagGfgAfGfUfgaugagaaaa	4201	PuUfuucUfcaucacuCfcCfucaaucc	5301
AD-2138783.1	uugaggGfaGfUfGfaugagaaaua	4202	PuAfuuuCfucaucacUfcCfcucaauc	5302
AD-2138784.2	ugagggAfgUfGfAfugagaaauaa	4203	PuUfauuUfcucaucaCfuCfccucaau	5303
AD-2138785.2	gagggaGfuGfAfUfgagaaauaaa	4204	PuUfuauUfucucaucAfcUfcccucaa	5304
AD-2138787.2	gggaguGfaUfGfAfgaaauaauua	4205	PuAfauuAfuuucucaUfcAfcucccuc	5305
AD-2138789.2	gagugaUfgAfGfAfaauaauuaaa	4206	PuUfuaaUfuauuucuCfaUfcacuccc	5306
AD-2138790.2	agugauGfaGfAfAfauaauuaaua	4207	PuAfuuaAfuuauuucUfcAfucacucc	5307
AD-2138791.2	gugaugAfgAfAfAfuaauuaauua	4208	PuAfauuAfauuauuuCfuCfaucacuc	5308
AD-2138792.2	ugaugaGfaAfAfUfaauuaauuga	4209	PuCfaauUfaauuauuUfcUfcaucacu	5309
AD-2138793.2	gaugagAfaAfUfAfauuaauugga	4210	PuCfcaaUfuaauuauUfuCfucaucac	5310
AD-2138794.2	augagaAfaUfAfAfuuaauuggaa	4211	PuUfccaAfuuaauuaUfuUfcucauca	5311
AD-2138795.2	uggacgGfgAfGfAfcagagugaca	4212	PuGfucaCfucugucuCfcCfguccaau	5312
AD-2138796.2	ggacggGfaGfAfCfagagugacga	4213	PuCfgucAfcucugucUfcCfcguccaa	5313
AD-2138797.2	gacgggAfgAfCfAfgagugacgca	4214	PuGfcguCfacucuguCfuCfccgucca	5314
AD-2138798.2	acgggaGfaCfAfGfagugacgcaa	4215	PuUfgcgUfcacucugUfcUfcccgucc	5315
AD-2138800.2	agacagAfgUfGfAfcgcacugaca	4216	PuGfucaGfugcgucaCfuCfugucucc	5316

Duplex ID	Sense Sequence	SEQ ID NO	Antisense Sequence	SEQ ID NO
AD-2138802.2	acagagUfgAfCfGfcacugacuca	4217	PuGfaguCfagugcguCfaCfucugucu	5317
AD-2138804.2	agagugAfcGfCfAfcugacucaca	4218	PuGfugaGfucagugcGfuCfacucugu	5318
AD-2138805.2	gagugaCfgCfAfCfugacucacca	4219	PuGfgugAfgucagugCfgUfcacucug	5319
AD-2138806.2	agugacGfcAfCfUfgacucaccua	4220	PuAfgguGfagucaguGfcGfucacucu	5320
AD-2138807.2	ugacgcAfcUfGfAfcucaccuaga	4221	PuCfuagGfugagucaGfuGfcgucacu	5321
AD-2138808.2	gacgcaCfuGfAfCfucaccuagaa	4222	PuUfcuaGfgugagucAfgUfgcgucac	5322
AD-2138809.2	acgcacUfgAfCfUfcaccuagaga	4223	PuCfucuAfggugaguCfaGfugcguca	5323
AD-2138810.2	cgcacuGfaCfUfCfaccuagagga	4224	PuCfcucUfaggugagUfcAfgugcguc	5324
AD-2138811.2	gcacugAfcUfCfAfccuagaggca	4225	PuGfccuCfuaggugaGfuCfagugcgu	5325
AD-2138812.2	cacugaCfuCfAfCfcuagaggcua	4226	PuAfgccUfcuaggugAfgUfcagugcg	5326
AD-2138813.2	acugacUfcAfCfCfuagaggcuga	4227	PuCfagcCfucuagguGfaGfucagugc	5327
AD-2138814.2	gaacguGfgGfUfAfgggauuuaga	4228	PuCfuaaAfucccuacCfcAfcguucca	5328
AD-2138816.2	acguggGfuAfGfGfgauuuagcaa	4229	PuUfgcuAfaaucccuAfcCfcacguuc	5329
AD-2138819.2	uggguaGfgGfAfUfuuagcaugca	4230	PuGfcauGfcuaaaucCfcUfacccacg	5330
AD-2138820.2	ggguagGfgAfUfUfuagcaugcua	4231	PuAfgcaUfgcuaaauCfcCfuacccac	5331
AD-2138821.2	gguaggGfaUfUfUfagcaugcuga	4232	PuCfagcAfugcuaaaUfcCfcuaccca	5332
AD-2138822.2	guagggAfuUfUfAfgcaugcugga	4233	PuCfcagCfaugcuaaAfuCfccuaccc	5333
AD-2138823.2	uagggaUfuUfAfGfcaugcuggaa	4234	PuUfccaGfcaugcuaAfaUfcccuacc	5334
AD-2138824.2	uuuagcAfuGfCfUfggaaauaaca	4235	PuGfuuaUfuuccagcAfuGfcuaaauc	5335
AD-2138825.2	uuagcaUfgCfUfGfgaaauaacua	4236	PuAfguuAfuuuccagCfaUfgcuaaau	5336
AD-2138826.2	uagcauGfcUfGfGfaaauaacuga	4237	PuCfaguUfauuuccaGfcAfugcuaaa	5337
AD-2138827.2	agcaugCfuGfGfAfaauaacugga	4238	PuCfcagUfuauuuccAfgCfaugcuaa	5338
AD-2138828.2	gcaugcUfgGfAfAfauaacuggca	4239	PuGfccaGfuuauuucCfaGfcaugcua	5339
AD-2138829.2	caugcuGfgAfAfAfuaacuggcaa	4240	PuUfgccAfguuauuuCfcAfgcaugcu	5340
AD-2138830.2	augcugGfaAfAfUfaacuggcaga	4241	PuCfugcCfaguuauuUfcCfagcaugc	5341
AD-2138831.2	ugcuggAfaAfUfAfacuggcagua	4242	PuAfcugCfcaguuauUfuCfcagcaug	5342
AD-2138832.2	gcuggaAfaUfAfAfcuggcaguaa	4243	PuUfacuGfccaguuaUfuUfccagcau	5343
AD-2138833.2	cuggaaAfuAfAfCfuggcaguaaa	4244	PuUfuacUfgccaguuAfuUfuccagca	5344
AD-2138834.2	uggaaaUfaAfCfUfggcaguaaua	4245	PuAfuuaCfugccaguUfaUfuuccagc	5345
AD-2138835.2	ggaaauAfaCfUfGfgcaguaauca	4246	PuGfauuAfcugccagUfuAfuuuccag	5346
AD-2138836.2	gaaauaAfcUfGfGfcaguaaucaa	4247	PuUfgauUfacugccaGfuUfauuucca	5347
AD-2138837.2	aaauaaCfuGfGfCfaguaaucaaa	4248	PuUfugaUfuacugccAfgUfuauuucc	5348
AD-2138838.2	aauaacUfgGfCfAfguaaucaaaa	4249	PuUfuugAfuuacugcCfaGfuuauuuc	5349
AD-2138839.2	auaacuGfgCfAfGfuaaucaaaca	4250	PuGfuuuGfauuacugCfcAfguuauuu	5350
AD-2138840.2	aacuggCfaGfUfAfaucaaacgaa	4251	PuUfcguUfugauuacUfgCfcaguuau	5351
AD-2138841.2	acuggcAfgUfAfAfucaaacgaaa	4252	PuUfucgUfuugauuaCfuGfccaguua	5352
AD-2138842.2	cuggcaGfuAfAfUfcaaacgaaga	4253	PuCfuucGfuuugauuAfcUfgccaguu	5353
AD-2138843.2	uggcagUfaAfUfCfaaacgaagaa	4254	PuUfcuuCfguuugauUfaCfugccagu	5354
AD-2138844.2	ggcaguAfaUfCfAfaacgaagaca	4255	PuGfucuUfcguuugaUfuAfcugccag	5355
AD-2138845.2	gcaguaAfuCfAfAfacgaagacaa	4256	PuUfgucUfucguuugAfuUfacugcca	5356
AD-2138847.2	aguaauCfaAfAfCfgaagacacua	4257	PuAfgugUfcuucguuUfgAfuuacugc	5357
AD-2138848.2	aaucaaAfcGfAfAfgacacuguca	4258	PuGfacaGfugucuucGfuUfugauuac	5358
AD-2138849.2	aucaaaCfgAfAfGfacacugucca	4259	PuGfgacAfgugucuuCfgUfuugauua	5359
AD-2138850.2	acgccaAfaCfCfUfcggcauuuua	4260	PuAfaaaUfgccgaggUfuUfggcguag	5360
AD-2138851.2	cgccaaAfcCfUfCfggcauuuuua	4261	PuAfaaaAfugccgagGfuUfuggcgua	5361
AD-2138852.2	gccaaaCfcUfCfGfgcauuuuuua	4262	PuAfaaaAfaugccgaGfgUfuuggcgu	5362
AD-2138853.2	ccaaacCfuCfGfGfcauuuuuuga	4263	PuCfaaaAfaaugccgAfgGfuuuggcg	5363
AD-2138854.2	caaaccUfcGfGfCfauuuuuugua	4264	PuAfcaaAfaaaugccGfaGfguuuggc	5364

Duplex ID	Sense Sequence	SEQ ID NO	Antisense Sequence	SEQ ID NO
AD-2138855.2	aaaccuCfgGfCfAfuuuuuuguga	4265	PuCfacaAfaaaaugcCfgAfgguuugg	5365
AD-2138856.2	aaccucGfgCfAfUfuuuuugugua	4266	PuAfcacAfaaaaaugCfcGfagguuug	5366
AD-2138857.2	accucgGfcAfUfUfuuuuguguua	4267	PuAfacaCfaaaaaauGfcCfgagguuu	5367
AD-2138858.2	ccucggCfaUfUfUfuuuguguuaa	4268	PuUfaacAfcaaaaaaUfgCfcgagguu	5368
AD-2138859.2	cucggcAfuUfUfUfuuguguuaua	4269	PuAfuaaCfacaaaaaAfuGfccgaggu	5369
AD-2138860.2	ucggcaUfuUfUfUfuguguuauua	4270	PuAfauaAfcacaaaaAfaUfgccgagg	5370
AD-2138861.2	ggcauuUfuUfUfGfuguuauuuua	4271	PuAfaaaUfaacacaaAfaAfaugccga	5371
AD-2138862.2	gcauuuUfuUfGfUfguuauuuuca	4272	PuGfaaaAfuaacacaAfaAfaaugccg	5372
AD-2138863.2	cauuuuUfuGfUfGfuuauuuucua	4273	PuAfgaaAfauaacacAfaAfaaaugcc	5373
AD-2138864.2	uuugugUfuAfUfUfuucugacuga	4274	PuCfaguCfagaaaauAfaCfacaaaaa	5374
AD-2138865.2	uuguguUfaUfUfUfucugacugca	4275	PuGfcagUfcagaaaaUfaAfcacaaaa	5375
AD-2138866.2	uguguuAfuUfUfUfcugacugcua	4276	PuAfgcaGfucagaaaAfuAfacacaaa	5376
AD-2138867.2	guguuaUfuUfUfCfugacugcuga	4277	PuCfagcAfgucagaaAfaUfaacacaa	5377
AD-2138868.2	uguuauUfuUfCfUfgacugcugga	4278	PuCfcagCfagucagaAfaAfuaacaca	5378
AD-2138869.2	guuauuUfuCfUfGfacugcuggaa	4279	PuUfccaGfcagucagAfaAfauaacac	5379
AD-2138870.2	uuauuuUfcUfGfAfcugcuggaua	4280	PuAfuccAfgcagucaGfaAfaauaaca	5380
AD-2138871.2	uauuuuCfuGfAfCfugcuggauua	4281	PuAfaucCfagcagucAfgAfaaauaac	5381
AD-2138872.2	auuuucUfgAfCfUfgcuggauuca	4282	PuGfaauCfcagcaguCfaGfaaaauaa	5382
AD-2138873.2	ucugacUfgCfUfGfgauucuguaa	4283	PuUfacaGfaauccagCfaGfucagaaa	5383
AD-2138874.2	aguaagGfuGfAfCfauagcuauga	4284	PuCfauaGfcuaugucAfcCfuuacuac	5384
AD-2138875.2	guaaggUfgAfCfAfuagcuaugaa	4285	PuUfcauAfgcuauguCfaCfcuuacua	5385
AD-2138876.2	uaagguGfaCfAfUfagcuaugaca	4286	PuGfucaUfagcuaugUfcAfccuuacu	5386
AD-2138877.2	aaggugAfcAfUfAfgcuaugacaa	4287	PuUfgucAfuagcuauGfuCfaccuuac	5387
AD-2138878.2	aggugaCfaUfAfGfcuaugacaua	4288	PuAfuguCfauagcuaUfgUfcaccuua	5388
AD-2138879.2	ggugacAfuAfGfCfuaugacauua	4289	PuAfaugUfcauagcuAfuGfucaccuu	5389
AD-2138880.2	gugacaUfaGfCfUfaugacauuua	4290	PuAfaauGfucauagcUfaUfgucaccu	5390
AD-2138881.2	ugacauAfgCfUfAfugacauuuga	4291	PuCfaaaUfgucauagCfuAfugucacc	5391
AD-2138882.2	acauagCfuAfUfGfacauuuguua	4292	PuAfacaAfaugucauAfgCfuauguca	5392
AD-2138883.2	cauagcUfaUfGfAfcauuuguuaa	4293	PuUfaacAfaaugucaUfaGfcuauguc	5393
AD-2138884.2	auagcuAfuGfAfCfauuuguuaaa	4294	PuUfuaaCfaaaugucAfuAfgcuaugu	5394
AD-2138885.2	uagcuaUfgAfCfAfuuuguuaaaa	4295	PuUfuuaAfcaaauguCfaUfagcuaug	5395
AD-2138886.2	agcuauGfaCfAfUfuuguuaaaaa	4296	PuUfuuuAfacaaaugUfcAfuagcuau	5396
AD-2138887.2	gcuaugAfcAfUfUfuguuaaaaaa	4297	PuUfuuuUfaacaaauGfuCfauagcua	5397
AD-2138888.2	cuaugaCfaUfUfUfguuaaaaaua	4298	PuAfuuuUfuaacaaaUfgUfcauagcu	5398
AD-2138889.2	uaugacAfuUfUfGfuuaaaaauaa	4299	PuUfauuUfuuaacaaAfuGfucauagc	5399
AD-2138890.2	augacaUfuUfGfUfuaaaaauaaa	4300	PuUfuauUfuuuaacaAfaUfgucauag	5400
AD-2138891.2	ugacauUfuGfUfUfaaaaauaaaa	4301	PuUfuuaUfuuuuaacAfaAfugucaua	5401
AD-2138892.2	gacauuUfgUfUfAfaaaauaaaca	4302	PuGfuuuAfuuuuuaaCfaAfaugucau	5402
AD-2138893.2	acauuuGfuUfAfAfaaauaaacua	4303	PuAfguuUfauuuuuaAfcAfaauguca	5403
AD-2138894.2	aauaaaCfuCfUfGfuacuuaacua	4304	PuAfguuAfaguacagAfgUfuuauuuu	5404
AD-2138895.2	auaaacUfcUfGfUfacuuaacuua	4305	PuAfaguUfaaguacaGfaGfuuuauuu	5405
AD-2138896.2	uaaacuCfuGfUfAfcuuaacuuua	4306	PuAfaagUfuaaguacAfgAfguuuauu	5406
AD-2138897.2	aaacucUfgUfAfCfuuaacuuuga	4307	PuCfaaaGfuuaaguaCfaGfaguuuau	5407
AD-2138898.2	aacucuGfuAfCfUfuaacuuugaa	4308	PuUfcaaAfguuaaguAfcAfgaguuua	5408
AD-2138899.2	acucugUfaCfUfUfaacuuugaua	4309	PuAfucaAfaguuaagUfaCfagaguuu	5409
AD-2138900.2	cucuguAfcUfUfAfacuuugauua	4310	PuAfaucAfaaguuaaGfuAfcagaguu	5410
AD-2138901.2	ucuguaCfuUfAfAfcuuugauuua	4311	PuAfaauCfaaaguuaAfgUfacagagu	5411
AD-2138902.2	cuguacUfuAfAfCfuuugauuuga	4312	PuCfaaaUfcaaaguuAfaGfuacagag	5412

Duplex ID	Sense Sequence	SEQ ID NO	Antisense Sequence	SEQ ID NO
AD-2138903.2	uguacuUfaAfCfUfuugauuugaa	4313	PuUfcaaAfucaaaguUfaAfguacaga	5413
AD-2138904.2	guacuuAfaCfUfUfugauuugaga	4314	PuCfucaAfaucaaagUfuAfaguacag	5414
AD-2138905.2	uacuuaAfcUfUfUfgauuugagua	4315	PuAfcucAfaaucaaaGfuUfaaguaca	5415
AD-2138906.2	acuuaaCfuUfUfGfauuugaguaa	4316	PuUfacuCfaaaucaaAfgUfuaaguac	5416
AD-2138907.2	uugauuUfgAfGfUfaaauuuugga	4317	PuCfcaaAfauuuacuCfaAfaucaaag	5417
AD-2138908.2	ugaguaAfaUfUfUfugguuuugga	4318	PuCfcaaAfaccaaaaUfuUfacucaaa	5418
AD-2138909.2	gaguaaAfuUfUfUfgguuuuggua	4319	PuAfccaAfaaccaaaAfuUfuacucaa	5419
AD-2138910.2	aguaaaUfuUfUfGfguuuugguca	4320	PuGfaccAfaaaccaaAfaUfuuacuca	5420
AD-2138911.2	guaaauUfuUfGfGfuuuuggucua	4321	PuAfgacCfaaaaccaAfaAfuuuacuc	5421
AD-2138912.2	uaaauuUfuGfGfUfuuuggucuua	4322	PuAfagaCfcaaaaccAfaAfauuuacu	5422
AD-2138913.2	aaauuuUfgGfUfUfuuggucuuca	4323	PuGfaagAfccaaaacCfaAfaauuuac	5423
AD-2138914.2	auuuugGfuUfUfUfggucuucaaa	4324	PuUfugaAfgaccaaaAfcCfaaaauuu	5424
AD-2138915.2	uuugguUfuUfGfGfucuucaacaa	4325	PuUfguuGfaagaccaAfaAfccaaaau	5425
AD-2138916.2	uugguuUfuGfGfUfcuucaacaua	4326	PuAfuguUfgaagaccAfaAfaccaaaa	5426
AD-2138917.2	ugguuuUfgGfUfCfuucaacauua	4327	PuAfaugUfugaagacCfaAfaaccaaa	5427
AD-2138918.2	gguuuuGfgUfCfUfucaacauuua	4328	PuAfaauGfuugaagaCfcAfaaaccaa	5428
AD-2138919.2	guuuugGfuCfUfUfcaacauuuua	4329	PuAfaaaUfguugaagAfcCfaaaacca	5429
AD-2138920.2	uuuuggUfcUfUfCfaacauuuuca	4330	PuGfaaaAfuguugaaGfaCfcaaaacc	5430
AD-2138921.2	uuugguCfuUfCfAfacauuuucaa	4331	PuUfgaaAfauguugaAfgAfccaaaac	5431
AD-2138922.2	uuggucUfuCfAfAfcauuuucaua	4332	PuAfugaAfaauguugAfaGfaccaaaa	5432
AD-2138923.2	uggucuUfcAfAfCfauuuucauga	4333	PuCfaugAfaaauguuGfaAfgaccaaa	5433
AD-2138924.2	ggucuuCfaAfCfAfuuuucaugca	4334	PuGfcauGfaaaauguUfgAfagaccaa	5434
AD-2138925.2	gucuucAfaCfAfUfuuucaugcua	4335	PuAfgcaUfgaaaaugUfuGfaagacca	5435
AD-2138926.2	cuucaaCfaUfUfUfucaugcucua	4336	PuAfgagCfaugaaaaUfgUfugaagac	5436
AD-2138927.2	uucaacAfuUfUfUfcaugcucuua	4337	PuAfagaGfcaugaaaAfuGfuugaaga	5437
AD-2138928.2	ucaacaUfuUfUfCfaugcucuuua	4338	PuAfaagAfgcaugaaAfaUfguugaag	5438
AD-2138929.2	caacauUfuUfCfAfugcucuuuga	4339	PuCfaaaGfagcaugaAfaAfuguugaa	5439
AD-2138930.2	aacauuUfuCfAfUfgcucuuugua	4340	PuAfcaaAfgagcaugAfaAfauguuga	5440
AD-2138931.2	acauuuUfcAfUfGfcucuuuguua	4341	PuAfacaAfagagcauGfaAfaauguug	5441
AD-2138932.2	cauuuuCfaUfGfCfucuuuguuca	4342	PuGfaacAfaagagcaUfgAfaaauguu	5442
AD-2138933.2	auuuucAfuGfCfUfcuuuguucaa	4343	PuUfgaaCfaaagagcAfuGfaaaaugu	5443
AD-2138934.2	uuuucaUfgCfUfCfuuuguucaca	4344	PuGfugaAfcaaagagCfaUfgaaaaug	5444
AD-2138935.2	uuucauGfcUfCfUfuuguucacca	4345	PuGfgugAfacaaagaGfcAfugaaaau	5445
AD-2138936.2	gauuuaGfcUfGfCfuuuugauaaa	4346	PuUfuauCfaaaagcaGfcUfaaauccc	5446
AD-2138937.2	auuuagCfuGfCfUfuuugauaaga	4347	PuCfuuaUfcaaaagcAfgCfuaaaucc	5447
AD-2138938.2	uuagcuGfcUfUfUfugauaaggaa	4348	PuUfccuUfaucaaaaGfcAfgcuaaau	5448
AD-2138939.2	uagcugCfuUfUfUfgauaaggaaa	4349	PuUfuccUfuaucaaaAfgCfagcuaaa	5449
AD-2138940.2	agcugcUfuUfUfGfauaaggaaca	4350	PuGfuucCfuuaucaaAfaGfcagcuaa	5450
AD-2138941.2	gcugcuUfuUfGfAfuaaggaacaa	4351	PuUfguuCfcuuaucaAfaAfgcagcua	5451
AD-2138942.2	auaaggAfaCfAfGfcugcacaaaa	4352	PuUfuugUfgcagcugUfuCfcuuauca	5452
AD-2138943.2	cgcauuUfaCfCfUfcaucagcuaa	4353	PuUfagcUfgaugaggUfaAfaugcgug	5453
AD-2138944.2	gcauuuAfcCfUfCfaucagcuaaa	4354	PuUfuagCfugaugagGfuAfaaugcgu	5454
AD-2138945.2	cauuuaCfcUfCfAfucagcuaaca	4355	PuGfuuaGfcugaugaGfgUfaaaugcg	5455
AD-2138946.2	gcuugaCfaUfGfCfauuuuuacua	4356	PuAfguaAfaaaugcaUfgUfcaagccc	5456
AD-2138947.2	cuugacAfuGfCfAfuuuuuacuga	4357	PuCfaguAfaaaaugcAfuGfucaagcc	5457
AD-2138948.2	uugacaUfgCfAfUfuuuuacugua	4358	PuAfcagUfaaaaaugCfaUfgucaagc	5458
AD-2138949.2	ugacauGfcAfUfUfuuuacuguca	4359	PuGfacaGfuaaaaauGfcAfugucaag	5459
AD-2138950.2	gacaugCfaUfUfUfuuacugucua	4360	PuAfgacAfguaaaaaUfgCfaugucaa	5460

Duplex ID	Sense Sequence	SEQ ID NO	Antisense Sequence	SEQ ID NO
AD-2138951.2	acaugcAfuUfUfUfuacugucuua	4361	PuAfagaCfaguaaaaAfuGfcauguca	5461
AD-2138952.2	caugcaUfuUfUfUfacugucuuua	4362	PuAfaagAfcaguaaaAfaUfgcauguc	5462
AD-2138953.2	augcauUfuUfUfAfcugucuuuaa	4363	PuUfaaaGfacaguaaAfaAfugcaugu	5463
AD-2138954.2	ugcauuUfuUfAfCfugucuuuaua	4364	PuAfuaaAfgacaguaAfaAfaugcaug	5464
AD-2138955.2	gcauuuUfuAfCfUfgucuuuauua	4365	PuAfauaAfagacaguAfaAfaaugcau	5465
AD-2138956.2	cauuuuUfaCfUfGfucuuuauuca	4366	PuGfaauAfaagacagUfaAfaaaugca	5466
AD-2138957.2	auuuuuAfcUfGfUfcuuuauucca	4367	PuGfgaaUfaaagacaGfuAfaaaaugc	5467
AD-2138958.2	uuuuuaCfuGfUfCfuuuauuccua	4368	PuAfggaAfuaaagacAfgUfaaaaaug	5468
AD-2138959.2	uuuuacUfgUfCfUfuuauuccuga	4369	PuCfaggAfauaaagaCfaGfuaaaaau	5469
AD-2138960.2	uuuacuGfuCfUfUfuauuccugaa	4370	PuUfcagGfaauaaagAfcAfguaaaaa	5470
AD-2138961.2	uacuguCfuUfUfAfuuccugacaa	4371	PuUfgucAfggaauaaAfgAfcaguaaa	5471
AD-2138962.2	acugucUfuUfAfUfuccugacaca	4372	PuGfuguCfaggaauaAfaGfacaguaa	5472
AD-2138963.2	cugucuUfuAfUfUfccugacacua	4373	PuAfgugUfcaggaauAfaAfgacagua	5473
AD-2138964.2	gucuuuAfuUfCfCfugacacugaa	4374	PuUfcagUfgucaggaAfuAfaagacag	5474
AD-2138965.2	gacacuGfaGfAfUfgaauguuuua	4375	PuAfaaaCfauucaucUfcAfgugucag	5475
AD-2138966.2	acacugAfgAfUfGfaauguuuuca	4376	PuGfaaaAfcauucauCfuCfaguguca	5476
AD-2138967.2	cacugaGfaUfGfAfauguuuucaa	4377	PuUfgaaAfacauucaUfcUfcaguguc	5477
AD-2138968.2	acugagAfuGfAfAfuguuuucaaa	4378	PuUfugaAfaacauucAfuCfucagugu	5478
AD-2138969.2	cugagaUfgAfAfUfguuuucaaaa	4379	PuUfuugAfaaacauuCfaUfcucagug	5479
AD-2138970.2	ugagauGfaAfUfGfuuuucaaaga	4380	PuCfuuuGfaaaacauUfcAfucucagu	5480
AD-2138971.2	gagaugAfaUfGfUfuuucaaagca	4381	PuGfcuuUfgaaaacaUfuCfaucucag	5481
AD-2138972.2	agaugaAfuGfUfUfuucaaagcua	4382	PuAfgcuUfugaaaacAfuUfcaucuca	5482
AD-2138973.2	aauguuUfuCfAfAfagcugcaaca	4383	PuGfuugCfagcuuugAfaAfacauuca	5483
AD-2138974.2	auguuuUfcAfAfAfgcugcaacaa	4384	PuUfguuGfcagcuuuGfaAfaacauuc	5484
AD-2138975.2	uguuuuCfaAfAfGfcugcaacaua	4385	PuAfuguUfgcagcuuUfgAfaaacauu	5485
AD-2138976.2	guuuucAfaAfGfCfugcaacauga	4386	PuCfaugUfugcagcuUfuGfaaaacau	5486
AD-2138977.2	aaccgaUfuCfUfGfuuauugggaa	4387	PuUfcccAfauaacagAfaUfcgguuug	5487
AD-2138978.2	accgauUfcUfGfUfuauugggaaa	4388	PuUfuccCfaauaacaGfaAfucgguuu	5488
AD-2138979.2	ccgauuCfuGfUfUfauugggaaua	4389	PuAfuucCfcaauaacAfgAfaucgguu	5489
AD-2138980.2	cgauucUfgUfUfAfuugggaauga	4390	PuCfauuCfccaauaaCfaGfaaucggu	5490
AD-2138981.2	gauucuGfuUfAfUfugggaaugaa	4391	PuUfcauUfcccaauaAfcAfgaaucgg	5491
AD-2138982.2	auucugUfuAfUfUfgggaaugaaa	4392	PuUfucaUfucccaauAfaCfagaaucg	5492
AD-2138983.2	uucuguUfaUfUfGfggaaugaaaa	4393	PuUfuucAfuucccaaUfaAfcagaauc	5493
AD-2138984.2	ucuguuAfuUfGfGfgaaugaaaua	4394	PuAfuuuCfauucccaAfuAfacagaau	5494
AD-2138985.2	cuguuaUfuGfGfGfaaugaaauca	4395	PuGfauuUfcauucccAfaUfaacagaa	5495
AD-2138986.2	uguuauUfgGfGfAfaugaaaucua	4396	PuAfgauUfucauuccCfaAfuaacaga	5496
AD-2138987.2	guuauuGfgGfAfAfugaaaucuga	4397	PuCfagaUfuucauucCfcAfauaacag	5497
AD-2138988.2	uuauugGfgAfAfUfgaaaucugua	4398	PuAfcagAfuuucauuCfcCfaauaaca	5498
AD-2138989.2	auugggAfaUfGfAfaaucugucaa	4399	PuUfgacAfgauuucaUfuCfccaauaa	5499
AD-2138990.2	agagcuGfuAfUfAfugauggagua	4400	PuAfcucCfaucauauAfcAfgcucucu	5500
AD-2138991.2	gcuguaUfaUfGfAfuggagugaaa	4401	PuUfucaCfuccaucaUfaUfacagcuc	5501
AD-2138992.2	ggauguGfuAfAfCfacaagaccaa	4402	PuUfgguCfuuguguuAfcAfcauccau	5502
AD-2138993.2	gaugugUfaAfCfAfcaagaccaaa	4403	PuUfuggUfcuuguguUfaCfacaucca	5503
AD-2138994.2	guguaaCfaCfAfAfgaccaacuga	4404	PuCfaguUfggucuugUfgUfuacacau	5504
AD-2138995.2	uguaacAfcAfAfGfaccaacugaa	4405	PuUfcagUfuggucuuGfuGfuuacaca	5505
AD-2138996.2	uaacacAfaGfAfCfcaacugagaa	4406	PuUfcucAfguuggucUfuGfuguuaca	5506
AD-2138997.2	aacugaGfaGfUfCfugaauguuaa	4407	PuUfaacAfuucagacUfcUfcaguugg	5507
AD-2138998.2	acugagAfgUfCfUfgaauguuaua	4408	PuAfuaaCfauucagaCfuCfucaguug	5508

Duplex ID	Sense Sequence	SEQ ID NO	Antisense Sequence	SEQ ID NO
AD-2138999.2	cugagaGfuCfUfGfaauguuauua	4409	PuAfauaAfcauucagAfcUfcucaguu	5509
AD-2139000.2	gagaguCfuGfAfAfuguuauucua	4410	PuAfgaaUfaacauucAfgAfcucucag	5510
AD-2139001.2	gagucuGfaAfUfGfuuauucugga	4411	PuCfcagAfauaacauUfcAfgacucuc	5511
AD-2139002.2	ugccaaGfaGfCfAfuguaaaugaa	4412	PuUfcauUfuacaugcUfcUfuggcacc	5512
AD-2139003.2	gccaagAfgCfAfUfguaaaugaaa	4413	PuUfucaUfuuacaugCfuCfuuggcac	5513
AD-2139004.2	ccaagaGfcAfUfGfuaaaugaaca	4414	PuGfuucAfuuuacauGfcUfcuuggca	5514
AD-2139005.2	caagagCfaUfGfUfaaaugaacaa	4415	PuUfguuCfauuuacaUfgCfucuuggc	5515
AD-2139006.2	aagagcAfuGfUfAfaaugaacaaa	4416	PuUfuguUfcauuuacAfuGfcucuugg	5516
AD-2139007.2	agagcaUfgUfAfAfaugaacaaca	4417	PuGfuugUfucauuuaCfaUfgcucuug	5517
AD-2139008.2	gagcauGfuAfAfAfugaacaacaa	4418	PuUfguuGfuucauuuAfcAfugcucuu	5518
AD-2139009.2	agcaugUfaAfAfUfgaacaacaaa	4419	PuUfuguUfguucauuUfaCfaugcucu	5519
AD-2139010.2	gcauguAfaAfUfGfaacaacaaga	4420	PuCfuugUfuguucauUfuAfcaugcuc	5520
AD-2139011.2	cauguaAfaUfGfAfacaacaagca	4421	PuGfcuuGfuuguucaUfuUfacaugcu	5521
AD-2139012.2	auguaaAfuGfAfAfcaacaagcaa	4422	PuUfgcuUfguuguucAfuUfuacaugc	5522
AD-2139013.2	uguaaaUfgAfAfCfaacaagcaaa	4423	PuUfugcUfuguuguuCfaUfuuacaug	5523
AD-2139014.2	guaaauGfaAfCfAfacaagcaaaa	4424	PuUfuugCfuuguuguUfcAfuuuacau	5524
AD-2139015.2	uaaaugAfaCfAfAfcaagcaaaua	4425	PuAfuuuGfcuuguugUfuCfauuuaca	5525
AD-2139016.2	aaaugaAfcAfAfCfaagcaaauaa	4426	PuUfauuUfgcuuguuGfuUfcauuuac	5526
AD-2139017.2	aaugaaCfaAfCfAfagcaaauaua	4427	PuAfuauUfugcuuguUfgUfucauuua	5527
AD-2139018.2	augaacAfaCfAfAfgcaaauauua	4428	PuAfauaUfuugcuugUfuGfuucauuu	5528
AD-2139019.2	ugaacaAfcAfAfGfcaaauauuga	4429	PuCfaauAfuuugcuuGfuUfguucauu	5529
AD-2139020.2	gaacaaCfaAfGfCfaaauauugaa	4430	PuUfcaaUfauuugcuUfgUfuguucau	5530
AD-2139021.2	aacaacAfaGfCfAfaauauugaaa	4431	PuUfucaAfuauuugcUfuGfuuguuca	5531
AD-2139022.2	acaacaAfgCfAfAfauauugaaga	4432	PuCfuucAfauauuugCfuUfguuguuc	5532
AD-2139023.2	caacaaGfcAfAfAfuauugaagga	4433	PuCfcuuCfaauauuuGfcUfuguuguu	5533
AD-2139024.2	aacaagCfaAfAfUfauugaaggua	4434	PuAfccuUfcaauauuUfgCfuuguugu	5534
AD-2139025.2	acaagcAfaAfUfAfuugaagguga	4435	PuCfaccUfucaauauUfuGfcuuguug	5535
AD-2139026.2	cacuuaUfuUfCfCfcauugcuaaa	4436	PuUfuagCfaaugggaAfaUfaaguggu	5536
AD-2139027.2	acuuauUfuCfCfCfauugcuaaua	4437	PuAfuuaGfcaaugggAfaAfuaagugg	5537
AD-2139028.2	cuuauuUfcCfCfAfuugcuaauua	4438	PuAfauuAfgcaauggGfaAfauaagug	5538
AD-2139029.2	uuauuuCfcCfAfUfugcuaauuga	4439	PuCfaauUfagcaaugGfgAfaauaagu	5539
AD-2139030.2	auuuccCfaUfUfGfcuaauugcca	4440	PuGfgcaAfuuagcaaUfgGfgaaauaa	5540
AD-2139031.2	gccugcCfcGfGfUfuuugaaacaa	4441	PuUfguuUfcaaaaccGfgGfcaggcaa	5541
AD-2139032.2	uuuugaAfaCfAfGfucugcaguaa	4442	PuUfacuGfcagacugUfuUfcaaaacc	5542
AD-2139033.2	uugaaaCfaGfUfCfugcaguacaa	4443	PuUfguaCfugcagacUfgUfuucaaaa	5543
AD-2139034.2	gugggaGfaGfAfUfacauguuuaa	4444	PuUfaaaCfauguaucUfcUfcccacag	5544
AD-2139035.2	gggagaGfaUfAfCfauguuuagaa	4445	PuUfcuaAfacauguaUfcUfcucccac	5545
AD-2139036.2	ggagagAfuAfCfAfuguuuagaaa	4446	PuUfucuAfaacauguAfuCfucuccca	5546
AD-2139037.2	gagagaUfaCfAfUfguuuagaaga	4447	PuCfuucUfaaacaugUfaUfcucuccc	5547
AD-2139038.2	gagauaCfaUfGfUfuuagaaggaa	4448	PuUfccuUfcuaaacaUfgUfaucucuc	5548
AD-2139039.2	agauacAfuGfUfUfuagaaggaaa	4449	PuUfuccUfucuaaacAfuGfuaucucu	5549
AD-2139040.2	gauacaUfgUfUfUfagaaggaaga	4450	PuCfuucCfuucuaaaCfaUfguaucuc	5550
AD-2139041.2	auacauGfuUfUfAfgaaggaagaa	4451	PuUfcuuCfcuucuaaAfcAfuguaucu	5551
AD-2139042.2	cauguuUfaGfAfAfggaagagaaa	4452	PuUfucuCfuuccuucUfaAfacaugua	5552
AD-2139043.2	uguuuaGfaAfGfGfaagagaaaga	4453	PuCfuuuCfucuuccuUfcUfaaacaug	5553
AD-2139044.2	guuuagAfaGfGfAfagagaaagga	4454	PuCfcuuUfcucuuccUfuCfuaaacau	5554
AD-2139045.2	uuagaaGfgAfAfGfagaaaggaca	4455	PuGfuccUfuucucuuCfcUfucuaaac	5555
AD-2139046.2	uagaagGfaAfGfAfgaaaggacaa	4456	PuUfgucCfuuucucuUfcCfuucuaaa	5556

Duplex ID	Sense Sequence	SEQ ID NO	Antisense Sequence	SEQ ID NO
AD-2139047.2	agaaggAfaGfAfGfaaaggacaaa	4457	PuUfuguCfcuuucucUfuCfcuucuaa	5557
AD-2139048.2	gaaggaAfgAfGfAfaaggacaaaa	4458	PuUfuugUfccuuucuCfuUfccuucua	5558
AD-2139049.2	aaggcaCfaCfGfUfuuuaccauua	4459	PuAfaugGfuaaaacgUfgUfgccuuug	5559
AD-2139050.2	aggcacAfcGfUfUfuuaccauuua	4460	PuAfaauGfguaaaacGfuGfugccuuu	5560
AD-2139051.2	ggcacaCfgUfUfUfuaccauuuaa	4461	PuUfaaaUfgguaaaaCfgUfgugccuu	5561
AD-2139052.2	gcacacGfuUfUfUfaccauuuaaa	4462	PuUfuaaAfugguaaaAfcGfugugccu	5562
AD-2139053.2	cacacgUfuUfUfAfccauuuaaaa	4463	PuUfuuaAfaugguaaAfaCfgugugcc	5563
AD-2139054.2	acacguUfuUfAfCfcauuuaaaaa	4464	PuUfuuuAfaaugguaAfaAfcgugugc	5564
AD-2139055.2	cacguuUfuAfCfCfauuuaaaaua	4465	PuAfuuuUfaaaugguAfaAfacgugug	5565
AD-2139056.2	acguuuUfaCfCfAfuuuaaaauaa	4466	PuUfauuUfuaaauggUfaAfaacgugu	5566
AD-2139057.2	cguuuuAfcCfAfUfuuaaaauaua	4467	PuAfuauUfuuaaaugGfuAfaaacgug	5567
AD-2139058.2	guuuuaCfcAfUfUfuaaaauauua	4468	PuAfauaUfuuuaaauGfgUfaaaacgu	5568
AD-2139059.2	uuuuacCfaUfUfUfaaaauauuga	4469	PuCfaauAfuuuuaaaUfgGfuaaaacg	5569
AD-2139060.2	uuuaccAfuUfUfAfaaauauugua	4470	PuAfcaaUfauuuuaaAfuGfguaaaac	5570
AD-2139061.2	uuuaaaAfuAfUfUfguuaccaaaa	4471	PuUfuugGfuaacaauAfuUfuuaaaug	5571
AD-2139062.2	uuaaaaUfaUfUfGfuuaccaaaca	4472	PuGfuuuGfguaacaaUfaUfuuuaaau	5572
AD-2139063.2	uaaaauAfuUfGfUfuaccaaacaa	4473	PuUfguuUfgguaacaAfuAfuuuuaaa	5573
AD-2139064.2	aaaauaUfuGfUfUfaccaaacaaa	4474	PuUfuguUfugguaacAfaUfauuuuaa	5574
AD-2139065.2	aaauauUfgUfUfAfccaaacaaaa	4475	PuUfuugUfuugguaaCfaAfuauuuua	5575
AD-2139066.2	aauauuGfuUfAfCfcaaacaaaaa	4476	PuUfuuuGfuuugguaAfcAfauauuuu	5576
AD-2139067.2	auauugUfuAfCfCfaaacaaaaaa	4477	PuUfuuuUfguuugguAfaCfaauauuu	5577
AD-2139068.2	uauuguUfaCfCfAfaacaaaaaua	4478	PuAfuuuUfuguuuggUfaAfcaauauu	5578
AD-2139069.2	auuguuAfcCfAfAfacaaaaauaa	4479	PuUfauuUfuuguuugGfuAfacaauau	5579
AD-2139070.2	uuguuaCfcAfAfAfcaaaaauaua	4480	PuAfuauUfuuuguuuGfgUfaacaaua	5580
AD-2139071.2	uguuacCfaAfAfCfaaaaauauca	4481	PuGfauaUfuuuuguuUfgGfuaacaau	5581
AD-2139072.2	guuaccAfaAfCfAfaaaauaucca	4482	PuGfgauAfuuuuuguUfuGfguaacaa	5582
AD-2139073.2	uuaccaAfaCfAfAfaaauauccaa	4483	PuUfggaUfauuuuugUfuUfgguaaca	5583
AD-2139074.2	uaccaaAfcAfAfAfaauauccaua	4484	PuAfuggAfuauuuuuGfuUfugguaac	5584
AD-2139075.2	ccaaacAfaAfAfAfuauccauuca	4485	PuGfaauGfgauauuuUfuGfuuuggua	5585
AD-2139076.2	caaacaAfaAfAfUfauccauucaa	4486	PuUfgaaUfggauauuUfuUfguuuggu	5586
AD-2139077.2	aaacaaAfaAfUfAfuccauucaaa	4487	PuUfugaAfuggauauUfuUfuguuugg	5587
AD-2139078.2	aaaauaUfcCfAfUfucaaaauaca	4488	PuGfuauUfuugaaugGfaUfauuuuug	5588
AD-2139079.2	aaauauCfcAfUfUfcaaaauacaa	4489	PuUfguaUfuuugaauGfgAfuauuuuu	5589
AD-2139080.2	aauaucCfaUfUfCfaaaauacaaa	4490	PuUfuguAfuuuugaaUfgGfauauuuu	5590
AD-2139081.2	auauccAfuUfCfAfaaauacaaua	4491	PuAfuugUfauuuugaAfuGfgauauuu	5591
AD-2139082.2	uauccaUfuCfAfAfaauacaauua	4492	PuAfauuGfuauuuugAfaUfggauauu	5592
AD-2139083.2	auccauUfcAfAfAfauacaauuua	4493	PuAfaauUfguauuuuGfaAfuggauau	5593
AD-2139084.2	uccauuCfaAfAfAfuacaauuuaa	4494	PuUfaaaUfuguauuuUfgAfauggaua	5594
AD-2139085.2	ccauucAfaAfAfUfacaauuuaaa	4495	PuUfuaaAfuuguauuUfuGfaauggau	5595
AD-2139086.2	cauucaAfaAfUfAfcaauuuaaca	4496	PuGfuuaAfauuguauUfuUfgaaugga	5596
AD-2139087.2	auucaaAfaUfAfCfaauuuaacaa	4497	PuUfguuAfaauuguaUfuUfugaaugg	5597
AD-2139088.2	uucaaaAfuAfCfAfauuuaacaaa	4498	PuUfuguUfaaauuguAfuUfuugaaug	5598
AD-2139089.2	ucaaaaUfaCfAfAfuuuaacaaua	4499	PuAfuugUfuaaauugUfaUfuuugaau	5599
AD-2139090.2	caauuuAfaCfAfAfugcaacagua	4500	PuAfcugUfugcauugUfuAfaauugua	5600
AD-2139091.2	ucaucuUfaCfAfGfcagagaaaua	4501	PuAfuuuCfucugcugUfaAfgaugacu	5601
AD-2139092.2	caucuuAfcAfGfCfagagaaauga	4502	PuCfauuUfcucugcuGfuAfagaugac	5602
AD-2139093.2	aucuuaCfaGfCfAfgagaaaugca	4503	PuGfcauUfucucugcUfgUfaagauga	5603
AD-2139094.2	ucuuacAfgCfAfGfagaaaugcaa	4504	PuUfgcaUfuucucugCfuGfuaagaug	5604

Duplex ID	Sense Sequence	SEQ ID NO	Antisense Sequence	SEQ ID NO
AD-2139095.2	cuuacaGfcAfGfAfgaaaugcaga	4505	PuCfugcAfuuucucuGfcUfguaagau	5605
AD-2139096.2	uuacagCfaGfAfGfaaaugcagaa	4506	PuUfcugCfauuucucUfgCfuguaaga	5606
AD-2139097.2	uacagcAfgAfGfAfaaugcagaga	4507	PuCfucuGfcauuucuCfuGfcuguaag	5607
AD-2139098.2	acagcaGfaGfAfAfaugcagagaa	4508	PuUfcucUfgcauuucUfcUfgcuguaa	5608
AD-2139099.2	cagcagAfgAfAfAfugcagagaaa	4509	PuUfucuCfugcauuuCfuCfugcugua	5609
AD-2139100.2	agcagaGfaAfAfUfgcagagaaaa	4510	PuUfuucUfcugcauuUfcUfcugcugu	5610
AD-2139101.2	gcagagAfaAfUfGfcagagaaaaa	4511	PuUfuuuCfucugcauUfuCfucugcug	5611
AD-2139102.2	cagagaAfaUfGfCfagagaaaaga	4512	PuCfuuuUfcucugcaUfuUfcucugcu	5612
AD-2139103.2	agagaaAfuGfCfAfgagaaaagca	4513	PuGfcuuUfucucugcAfuUfucucugc	5613
AD-2139104.2	gagaaaUfgCfAfGfagaaaagcaa	4514	PuUfgcuUfuucucugCfaUfuucucug	5614
AD-2139105.2	agaaauGfcAfGfAfgaaaagcaaa	4515	PuUfugcUfuuucucuGfcAfuuucucu	5615
AD-2139106.2	gaaaugCfaGfAfGfaaaagcaaaa	4516	PuUfuugCfuuuucucUfgCfauuucuc	5616
AD-2139107.2	aaaugcAfgAfGfAfaaagcaaaaa	4517	PuUfuuuGfcuuuucuCfuGfcauuucu	5617
AD-2139108.2	aaugcaGfaGfAfAfaagcaaaaca	4518	PuGfuuuUfgcuuuucUfcUfgcauuuc	5618
AD-2139109.2	augcagAfgAfAfAfagcaaaacua	4519	PuAfguuUfugcuuuuCfuCfugcauuu	5619
AD-2139110.2	ugcagaGfaAfAfAfgcaaaacuga	4520	PuCfaguUfuugcuuuUfcUfcugcauu	5620
AD-2139111.2	gcagagAfaAfAfGfcaaaacugca	4521	PuGfcagUfuuugcuuUfuCfucugcau	5621
AD-2139112.2	cagagaAfaAfGfCfaaaacugcaa	4522	PuUfgcaGfuuuugcuUfuUfcucugca	5622
AD-2139113.2	agagaaAfaGfCfAfaaacugcaaa	4523	PuUfugcAfguuuugcUfuUfucucugc	5623
AD-2139114.2	agaaaaGfcAfAfAfacugcaagua	4524	PuAfcuuGfcaguuuuGfcUfuuucucu	5624
AD-2139115.2	aaaagcAfaAfAfCfugcaagugaa	4525	PuUfcacUfugcaguuUfuGfcuuuucu	5625
AD-2139116.2	aaagcaAfaAfCfUfgcaagugaca	4526	PuGfucaCfuugcaguUfuUfgcuuuuc	5626
AD-2139117.2	aagcaaAfaCfUfGfcaagugacua	4527	PuAfgucAfcuugcagUfuUfugcuuuu	5627
AD-2139118.2	aaacugCfaAfGfUfgacugugaaa	4528	PuUfucaCfagucacuUfgCfaguuuug	5628
AD-2139119.2	aacugcAfaGfUfGfacugugaaua	4529	PuAfuucAfcagucacUfuGfcaguuuu	5629
AD-2139120.2	acugcaAfgUfGfAfcugugaauaa	4530	PuUfauuCfacagucaCfuUfgcaguuu	5630
AD-2139121.2	cugcaaGfuGfAfCfugugaauaaa	4531	PuUfuauUfcacagucAfcUfugcaguu	5631
AD-2139122.2	ugcaagUfgAfCfUfgugaauaaaa	4532	PuUfuuaUfucacaguCfaCfuugcagu	5632
AD-2139123.2	gcaaguGfaCfUfGfugaauaaaga	4533	PuCfuuuAfuucacagUfcAfcuugcag	5633
AD-2139124.2	caagugAfcUfGfUfgaauaaagga	4534	PuCfcuuUfauucacaGfuCfacuugca	5634
AD-2139125.2	gacuguGfaAfUfAfaagggugaaa	4535	PuUfucaCfccuuuauUfcAfcagucac	5635
AD-2139126.2	acugugAfaUfAfAfagggugaaua	4536	PuAfuucAfcccuuuaUfuCfacaguca	5636
AD-2139128.2	gugaauAfaAfGfGfgugaauguaa	4537	PuUfacaUfucacccuUfuAfuucacag	5637
AD-2139129.2	ugaauaAfaGfGfGfugaauguaga	4538	PuCfuacAfuucacccUfuUfauucaca	5638
AD-2139130.2	gaauaaAfgGfGfUfgaauguagua	4539	PuAfcuaCfauucaccCfuUfuauucac	5639
AD-2139131.2	uaaaggGfuGfAfAfuguagucuca	4540	PuGfagaCfuacauucAfcCfcuuuauu	5640
AD-2139132.2	aaggguGfaAfUfGfuagucucaaa	4541	PuUfugaGfacuacauUfcAfcccuuua	5641
AD-2139133.2	agggugAfaUfGfUfagucucaaaa	4542	PuUfuugAfgacuacaUfuCfacccuuu	5642
AD-2139134.2	auccucAfaAfGfAfgcuguguuua	4543	PuAfaacAfcagcucuUfuGfaggauuu	5643
AD-2139135.2	uccucaAfaGfAfGfcuguguuuaa	4544	PuUfaaaCfacagcucUfuUfgaggauu	5644
AD-2139136.2	ccucaaAfgAfGfCfuguguuuaua	4545	PuAfuaaAfcacagcuCfuUfugaggau	5645
AD-2139137.2	cucaaaGfaGfCfUfguguuuauua	4546	PuAfauaAfacacagcUfcUfuugagga	5646
AD-2139138.2	ucaaagAfgCfUfGfuguuuauuua	4547	PuAfaauAfaacacagCfuCfuuugagg	5647
AD-2139139.2	caaagaGfcUfGfUfguuuauuuca	4548	PuGfaaaUfaaacacaGfcUfcuuugag	5648
AD-2139140.2	aaagagCfuGfUfGfuuuauuucaa	4549	PuUfgaaAfuaaacacAfgCfucuuuga	5649
AD-2139141.2	agcuguGfuUfUfAfuuucauugaa	4550	PuUfcaaUfgaaauaaAfcAfcagcucu	5650
AD-2139142.2	gcugugUfuUfAfUfuucauugaca	4551	PuGfucaAfugaaauaAfaCfacagcuc	5651
AD-2139143.2	guguuuAfuUfUfCfauugacaaaa	4552	PuUfuugUfcaaugaaAfuAfaacacag	5652

Duplex ID	Sense Sequence	SEQ ID NO	Antisense Sequence	SEQ ID NO
AD-2139144.2	auuucaUfuGfAfCfaaauagauua	4553	PuAfaucUfauuugucAfaUfgaaauaa	5653
AD-2139145.2	uuucauUfgAfCfAfaauagauuaa	4554	PuUfaauCfuauuuguCfaAfugaaaua	5654
AD-2139146.2	uucauuGfaCfAfAfauagauuaua	4555	PuAfuaaUfcuauuugUfcAfaugaaau	5655
AD-2139147.2	ucauugAfcAfAfAfuagauuauua	4556	PuAfauaAfucuauuuGfuCfaaugaaa	5656
AD-2139148.2	cauugaCfaAfAfUfagauuauuua	4557	PuAfaauAfaucuauuUfgUfcaaugaa	5657
AD-2139149.2	auugacAfaAfUfAfgauuauuuga	4558	PuCfaaaUfaaucuauUfuGfucaauga	5658
AD-2139150.2	uugacaAfaUfAfGfauuauuugua	4559	PuAfcaaAfuaaucuaUfuUfgucaaug	5659
AD-2139151.2	ugacaaAfuAfGfAfuuauuuguaa	4560	PuUfacaAfauaaucuAfuUfugucaau	5660
AD-2139152.2	gacaaaUfaGfAfUfuauuuguaua	4561	PuAfuacAfaauaaucUfaUfuugucaa	5661
AD-2139153.2	acaaauAfgAfUfUfauuuguauua	4562	PuAfauaCfaaauaauCfuAfuuuguca	5662
AD-2139154.2	caaauaGfaUfUfAfuuuguauuca	4563	PuGfaauAfcaaauaaUfcUfauuuguc	5663
AD-2139155.2	aaauagAfuUfAfUfuuguauucaa	4564	PuUfgaaUfacaaauaAfuCfuauuugu	5664

Example 2. *In vitro* screening of PLG siRNA

Experimental Methods

Cell culture and transfections:

Primary human hepatocytes (PHH) or primary cyno hepatocytes (PCH) were transfected by adding 4.9µl of Opti-MEM plus 0.1µl of Lipofectamine RNAiMax per well (Invitrogen, Carlsbad CA. cat # 13778-150) to 5µl of siRNA duplexes per well into a 384-well plate and incubated at room temperature for 15 minutes. 40µl of media containing 5 x10^3 cells was then added to the siRNA mixture. Cells were incubated for 24 hours prior to RNA purification. Dose response experiments were performed at various final duplex concentrations.

Free uptake:

Free uptake assay was performed similarly to the transfection assay without using Lipofectamine RNAimax and cells were incubated for 48 hours prior to the RNA purification. Dose response experiments were performed at various final duplex concentrations.

LogIC50 assay:

Free uptake assays or transfection assays of PHH or PCH cells were performed as described above, except various log concentrations of selected siRNA duplexes were used in the assays. The percent of message remaining was determined and the LogIC50 was calculated.

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, 70 µl of Lysis/Binding Buffer and 10 µl of lysis buffer containing 3 µl 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 150 µl Wash Buffer A and once with Wash Buffer B. Beads were then washed with 150 µl Elution Buffer, re-captured and supernatant removed.

Synthesis using ABI High-capacity cDNA reverse transcription kit (Applied Biosystems, Foster City, CA, Cat #4368813):

Ten µl of a master mix containing 1 µl 10X Buffer, 0.4 µl 25X dNTPs, 1 µl 10x Random primers, 0.5 µl Reverse Transcriptase, 0.5 µl RNase inhibitor and 6.6 µl 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 2 h 37°C.

Real time PCR:

Two µl of cDNA and 5µl Lightcycler 480 probe master mix (Roche Cat # 04887301001) were added to 0.5 µl of human GAPDH TaqMan Probe and 0.5 µl PLG human probe 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.

Results

An initial in vitro screen with 1110 duplexes was performed in transfected PHH cells in a multi-dose assay at 10 nM, 1 nM, or 0.1 nM final duplex concentration. The duplexes were designed to cover approximately 80% of the bases in the human NM_000301 transcript. The data were expressed as percent message remaining relative to non-targeting control. The results are provided in Table 11. FIG. 1 presents the results as percent message remaining relative to the position of the duplex on the human transcript. Many duplexes caused greater than an 85% knockdown at 10 nM and greater than 70% knockdown at 0.1 nM.

The experiments were performed at various final duplex concentrations and the data were expressed as percent message remaining relative to non-targeting control. The results of the transfection assays are provided in Tables 9 and 10 and the LogIC50 results are provided in Tables 12A, 12B, 12C, and 13.

TABLE 9. PLG Multi-Dose Screens in Primary Human Hepatocytes (PHH)

	250 nM Dose		100 nM Dose		10 nM Dose		1 nM Dose	
Duplex	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD
AD-2134523.1	7.0	1.1	8.8	0.7	25.3	5.1	56.7	10.8
AD-2222854.1	9.8	1.1	11.0	1.0	26.3	4.7	57.9	8.6
AD-2134574.1	6.4	0.5	10.5	2.3	19.1	2.5	55.5	6.8
AD-2222855.1	14.0	2.9	15.8	1.3	31.4	2.3	60.8	7.8
AD-2134577.1	21.0	3.4	24.4	3.0	48.5	5.8	80.0	7.0
AD-2134687.1	4.4	0.2	5.9	0.8	12.1	1.2	33.5	2.5
AD-2222856.1	7.1	0.9	10.8	2.0	27.3	2.2	55.1	2.9
AD-2134898.1	3.5	0.6	3.8	0.8	6.5	1.0	24.7	0.5
AD-2222857.1	5.3	0.8	4.7	1.0	15.3	1.3	39.7	6.5
AD-2134900.1	7.4	1.4	9.1	0.7	24.0	3.3	51.0	3.2
AD-2222858.1	32.7	3.3	32.9	3.5	61.1	7.4	83.8	5.5
AD-2134906.1	13.7	0.7	15.0	1.6	31.0	2.1	67.9	7.7
AD-2134907.1	8.6	1.2	9.7	0.8	23.2	1.7	58.0	3.8
AD-2135487.1	7.0	1.4	9.3	1.4	19.4	1.5	38.5	3.9
AD-2222859.1	13.8	2.0	18.3	1.1	40.3	2.1	68.9	6.5
AD-2135518.1	21.6	1.4	24.0	3.2	49.2	1.7	80.7	6.0
AD-2222860.1	57.2	9.3	65.2	5.7	89.4	5.8	102.9	5.0
AD-2135519.1	14.3	2.5	16.9	1.8	36.5	5.5	67.4	2.8
AD-2222861.1	16.5	1.9	16.1	0.8	43.9	2.5	74.6	7.3
AD-2135520.1	14.2	3.1	17.5	1.7	42.7	6.4	72.5	7.5
AD-2222862.1	40.4	2.3	37.9	3.3	79.6	4.5	93.7	4.4
AD-2135708.1	4.7	1.6	6.3	1.3	16.7	2.2	39.5	5.5
AD-2222863.1	9.9	1.4	12.5	1.7	30.2	2.5	62.6	4.1
AD-2135712.1	8.3	1.2	9.9	1.1	28.3	1.9	56.0	2.2
AD-2135713.1	7.9	0.7	8.3	1.6	24.4	3.3	54.6	7.4
AD-2135716.1	6.5	0.4	6.8	0.5	19.3	3.3	44.7	5.6
AD-2222864.1	9.1	0.8	8.3	0.8	23.4	5.2	46.9	3.2
AD-2135717.1	9.5	2.0	12.4	1.6	29.3	0.6	58.2	2.1
AD-2222865.1	40.9	7.5	49.2	3.9	73.4	4.8	96.1	3.8
AD-2135718.1	8.0	0.9	10.2	1.1	26.1	2.8	58.9	6.8
AD-2135719.1	9.9	0.7	12.7	1.4	33.6	3.9	69.5	11.0
AD-2222866.1	40.5	7.3	42.2	5.7	62.9	7.9	88.3	14.4
AD-2135721.1	9.8	0.7	10.6	1.5	32.9	3.2	64.0	3.9
AD-2222867.1	16.0	1.1	15.7	0.9	39.2	3.6	65.4	4.4
AD-2135730.1	19.4	1.8	21.9	2.7	49.7	5.1	85.6	5.6
AD-2135731.1	6.2	1.5	7.8	0.6	17.9	3.4	51.9	5.1

	250 nM Dose		100 nM Dose		10 nM Dose		1 nM Dose	
Duplex	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD
AD-2222868.1	5.9	1.2	5.7	1.0	17.4	1.6	46.7	0.6
AD-2135732.1	16.0	3.0	17.5	1.2	43.2	5.8	75.6	13.6
AD-2222869.1	8.5	1.2	10.7	0.4	30.8	3.0	61.9	4.6
AD-2135734.1	12.1	0.9	13.2	3.5	31.3	6.2	59.6	3.9
AD-2222870.1	37.6	3.6	36.1	7.3	72.8	8.9	97.9	6.1
AD-2135736.1	11.4	1.3	10.9	0.8	30.1	3.6	64.4	5.7
AD-2135737.1	9.3	1.6	8.6	1.3	24.7	3.7	51.6	4.9
AD-2135738.1	8.9	1.2	9.4	2.0	26.2	3.4	55.9	5.5
AD-2135786.1	8.4	0.4	13.0	1.8	33.9	2.4	67.8	5.8
AD-2135788.1	74.9	8.0	68.9	7.3	75.4	8.8	88.7	13.9
AD-2222871.1	77.6	7.8	67.2	7.9	78.4	6.9	88.4	6.0
AD-2135789.1	24.7	3.4	25.8	4.8	48.0	13.4	74.9	6.5
AD-2222872.1	13.6	1.0	18.0	1.9	41.3	3.5	62.3	4.0
AD-2135821.1	17.9	3.6	19.8	0.9	39.3	4.2	79.2	3.9
AD-2222873.1	43.5	1.8	44.7	3.1	71.7	5.3	92.4	6.3
AD-2135896.1	13.7	0.9	16.0	2.2	36.8	5.9	76.7	2.4
AD-2135897.1	86.5	4.5	87.7	6.5	99.4	10.3	105.3	8.7
AD-2222874.1	9.4	1.9	10.2	2.4	27.0	3.0	53.9	0.7
AD-2222875.1	4.7	0.5	4.9	0.5	11.1	1.2	35.4	3.9
AD-2135900.1	6.4	1.5	5.9	0.3	14.1	1.8	45.2	1.6
AD-2222876.1	10.4	1.3	10.9	0.5	26.8	4.3	57.0	5.6
AD-2135901.1	11.3	1.6	11.2	2.0	34.7	2.7	68.1	5.5
AD-2222877.1	36.2	2.7	34.1	5.2	67.7	3.8	86.3	5.5
AD-2135904.1	4.6	1.1	5.1	0.7	13.1	0.9	35.0	2.5
AD-2135907.1	14.9	1.2	18.0	2.0	40.3	3.2	67.3	2.9
AD-2135962.1	8.6	2.0	8.4	0.6	27.3	2.8	59.3	4.5
AD-2135964.1	26.1	2.7	23.8	2.9	50.9	5.6	83.8	6.7
AD-2222878.1	47.2	2.3	42.1	4.2	70.2	4.6	81.3	8.0
AD-2135965.1	6.8	1.1	8.3	1.6	21.9	4.5	54.4	7.0
AD-2222879.1	15.7	1.3	15.3	2.5	46.5	1.6	77.6	6.6
AD-2135967.1	17.7	0.9	25.1	2.7	61.1	2.0	92.1	4.2
AD-2135973.1	7.2	1.2	7.7	0.6	27.0	2.8	58.9	4.8
AD-2136060.1	46.4	5.5	45.8	6.3	68.2	5.9	93.5	2.3
AD-2222880.1	42.0	10.8	38.8	5.4	65.1	9.7	84.7	6.1
AD-2136066.1	28.7	4.5	29.3	4.2	58.4	3.7	84.6	3.2
AD-2222881.1	65.5	3.1	55.8	4.6	84.5	5.7	96.8	3.4
AD-2136068.1	17.0	1.8	20.0	1.5	45.5	6.7	73.3	7.5
AD-2136069.1	21.5	1.3	23.1	2.3	51.0	9.2	76.6	6.8

	250 nM Dose		100 nM Dose		10 nM Dose		1 nM Dose	
Duplex	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD
AD-2222882.1	47.9	5.1	51.9	2.6	89.4	5.1	112.1	3.7
AD-2136072.1	12.6	2.1	14.1	1.2	35.3	4.6	61.7	10.8
AD-2222883.1	30.2	3.4	34.7	3.4	58.4	13.5	83.6	12.7
AD-2136073.1	4.7	1.1	6.4	0.8	18.9	4.5	40.2	0.8
AD-2136074.1	42.0	1.2	44.9	1.3	83.0	8.0	98.6	3.0
AD-2136075.1	34.7	4.9	44.1	3.8	76.4	6.7	87.6	7.3
AD-2136077.1	6.7	1.2	7.0	1.5	22.6	1.6	48.8	3.7
AD-2136079.1	4.8	0.6	5.8	1.5	14.6	1.2	38.6	6.2
AD-2222884.1	5.7	2.0	6.5	1.0	23.5	2.7	56.6	4.8
AD-2136080.1	5.1	0.8	6.2	0.2	22.4	2.0	46.3	5.2
AD-2222885.1	12.4	1.0	16.4	1.6	41.0	8.4	60.5	1.3
AD-2136083.1	5.4	1.2	5.3	2.2	25.9	2.5	49.3	5.1
AD-2136164.1	29.5	4.1	28.7	3.1	51.9	10.2	81.1	5.3
AD-2136166.1	10.4	1.3	11.7	1.6	34.8	1.2	63.3	7.4
AD-2222886.1	6.9	1.1	10.1	0.7	30.0	5.0	53.9	4.8
AD-2136168.1	17.0	4.3	18.3	1.7	35.9	3.3	76.8	5.4
AD-2222887.1	42.4	6.0	40.2	2.3	73.3	3.7	106.1	7.5
AD-2136171.1	10.0	1.3	13.4	2.2	30.6	5.9	59.8	2.6
AD-2136172.1	13.9	2.3	17.2	2.2	36.0	6.9	68.4	8.8
AD-2136179.1	25.7	2.9	32.8	6.9	52.0	3.9	82.4	1.4
AD-2222888.1	36.8	4.2	46.3	7.5	69.0	3.9	85.5	5.6
AD-2136183.1	33.0	4.6	38.2	5.6	48.9	4.5	83.8	8.1
AD-2136263.1	55.4	1.0	51.7	3.6	80.7	11.4	97.7	12.4
AD-2136347.1	12.8	0.7	13.7	2.7	33.9	5.2	66.6	10.7
AD-2222889.1	11.8	2.6	13.8	3.4	24.4	2.6	45.6	6.8
AD-2136348.1	9.8	1.2	13.7	1.1	26.2	2.8	54.7	3.9
AD-2222890.1	20.2	1.7	23.9	1.8	45.0	8.1	80.7	2.9
AD-2136349.1	35.1	4.6	50.2	7.7	68.4	9.8	78.6	14.2
AD-2222891.1	35.8	1.6	40.5	4.5	60.5	9.2	91.5	6.9
AD-2136355.1	9.3	0.9	12.4	1.2	31.5	5.6	57.0	9.4
AD-2136421.1	6.0	0.4	7.4	0.2	23.4	3.4	45.7	7.4
AD-2222892.1	14.3	1.7	19.4	2.4	46.2	5.5	72.3	5.0
AD-2136431.1	10.2	0.7	13.8	3.9	31.1	2.9	71.2	7.3
AD-2222893.1	10.6	0.8	14.5	3.8	24.4	3.7	56.9	7.4
AD-2136433.1	57.3	2.8	67.4	8.8	82.9	4.4	107.7	4.5
AD-2136434.1	10.5	1.0	11.6	2.5	23.7	2.4	73.4	7.8
AD-2222894.1	28.5	5.4	34.5	3.4	68.1	8.8	97.7	9.5
AD-2136437.1	7.0	1.2	9.3	1.9	24.5	3.0	44.6	4.4

	250 nM Dose		100 nM Dose		10 nM Dose		1 nM Dose	
Duplex	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD
AD-2222895.1	9.0	0.7	13.6	2.6	21.4	2.8	67.4	12.0
AD-2136438.1	13.7	1.7	16.3	2.8	40.3	3.0	69.5	2.8
AD-2222896.1	47.8	5.9	48.0	9.6	66.3	7.5	91.4	4.2
AD-2136439.1	10.0	1.0	10.9	1.4	28.2	3.1	57.0	2.3
AD-2222897.1	31.0	2.7	34.5	3.6	61.3	11.3	91.0	6.1
AD-2136440.1	9.9	0.7	9.9	0.9	19.9	3.3	58.2	4.1
AD-2222898.1	8.5	0.8	9.5	1.4	23.6	4.6	54.5	5.9
AD-2136442.1	6.8	1.6	8.2	1.9	15.8	3.2	34.4	2.2
AD-2136443.1	14.1	1.0	12.3	2.6	30.6	2.4	66.2	6.7
AD-2222899.1	39.3	6.1	44.3	3.0	69.7	6.3	81.0	3.2
AD-2136465.1	16.2	1.6	21.6	2.8	43.4	6.7	83.0	4.1
AD-2222900.1	11.6	1.0	16.7	5.2	26.9	5.9	67.6	7.9
AD-2136470.1	10.4	0.9	12.2	1.1	34.6	2.3	61.2	4.2
AD-2136571.1	12.3	1.0	15.7	3.3	43.3	4.8	65.8	5.0
AD-2222901.1	14.7	1.7	24.9	2.2	48.7	8.2	85.4	7.2
AD-2136606.1	40.1	1.2	44.6	3.7	70.3	12.1	95.3	5.7
AD-2222902.1	63.5	7.1	76.8	7.3	101.6	9.6	100.3	19.7
AD-2136716.1	6.6	1.1	6.9	0.6	16.1	1.9	35.0	2.7
AD-2222903.1	11.6	0.6	15.7	2.2	37.4	1.4	71.4	5.2
AD-2136717.1	7.6	1.0	8.2	1.5	15.4	2.1	41.5	3.0
AD-2136718.3	7.6	0.2	9.2	1.3	14.0	1.7	34.9	4.5
AD-2136721.1	8.0	0.6	9.8	2.2	16.9	3.0	41.0	5.3
AD-2136726.1	12.5	1.3	15.2	2.4	27.0	1.0	67.2	5.3
AD-2222905.1	39.8	8.4	36.4	7.8	55.0	6.0	77.0	5.3
AD-2136729.1	24.5	1.8	28.9	0.3	61.1	7.7	81.1	3.6
AD-2222906.1	37.3	4.6	39.4	1.5	53.4	6.7	81.4	4.1
AD-2136753.1	19.8	3.0	25.9	2.7	51.6	9.0	78.3	5.5
AD-2136754.1	17.4	1.4	18.5	1.6	34.9	5.0	78.9	8.0
AD-2136755.1	9.2	1.2	11.8	0.2	20.9	4.4	55.3	2.2
AD-2136756.1	20.6	1.4	28.5	5.1	49.2	6.5	76.0	7.9
AD-2222907.1	79.9	1.1	79.6	7.6	107.1	8.6	103.9	14.7
AD-2136757.1	7.2	0.5	9.4	1.6	20.4	2.4	54.7	2.9
AD-2222908.1	12.5	1.7	16.0	2.0	43.4	3.5	68.0	7.2
AD-2136758.1	48.7	3.5	52.1	3.9	87.2	13.8	96.1	7.8
AD-2222909.1	28.6	1.3	33.9	2.2	66.7	4.4	101.6	2.4
AD-2136760.1	11.7	1.8	16.7	1.7	32.7	0.8	67.3	2.4
AD-2222910.1	9.9	0.6	13.0	1.6	25.1	3.4	55.0	1.5
AD-2136761.1	14.7	1.5	18.6	1.1	35.1	3.4	61.5	4.6

	250 nM Dose		100 nM Dose		10 nM Dose		1 nM Dose	
Duplex	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD
AD-2136762.1	11.0	2.5	15.5	3.8	30.7	5.0	54.6	4.3
AD-2222911.1	11.6	1.1	15.5	2.3	31.2	4.9	59.8	8.9
AD-2136763.1	7.9	0.5	8.4	0.9	18.1	1.3	44.0	0.9
AD-2136764.1	9.7	1.7	13.8	1.6	34.4	7.6	66.7	4.0
AD-2136787.1	8.5	1.5	10.3	1.3	24.7	3.3	45.7	4.4
AD-2222912.1	23.4	0.9	31.6	2.7	59.2	3.8	86.6	8.8
AD-2136790.1	9.9	1.3	12.2	2.7	36.2	7.1	61.8	5.2
AD-2136791.1	26.2	3.4	29.7	4.9	60.0	9.8	78.1	11.9
AD-2222913.1	34.7	4.9	37.9	3.8	59.7	8.3	78.2	8.5
AD-2136792.1	5.9	0.7	6.4	0.8	15.8	1.9	36.1	2.4
AD-2222914.1	10.0	2.0	12.2	1.7	33.8	5.4	59.3	4.8
AD-2136793.1	9.6	1.5	12.3	2.6	31.0	5.6	66.0	4.0
AD-2222915.1	29.9	3.8	37.4	4.1	65.1	5.4	84.7	10.2
AD-2136794.1	10.1	2.5	9.8	0.7	34.1	5.4	49.5	10.4
AD-2222916.1	31.6	2.7	40.0	6.3	72.9	9.4	87.1	8.4
AD-2136797.1	14.0	1.7	22.2	1.3	39.2	4.2	67.2	2.8
AD-2222917.1	12.1	0.8	15.7	1.6	37.7	2.6	69.3	2.4
AD-2136851.1	6.6	1.2	7.8	1.4	16.4	1.5	42.4	1.9
AD-2136852.1	6.6	1.3	8.7	0.6	25.9	3.7	48.9	8.7
AD-2136853.1	4.1	0.8	5.6	1.2	8.7	3.4	23.8	5.8
AD-2136854.1	17.1	5.3	22.1	3.8	45.1	3.6	82.7	0.6
AD-2136855.1	6.1	0.8	6.8	1.0	17.2	3.5	28.2	0.2
AD-2222918.1	37.4	6.6	42.0	4.0	72.2	3.4	84.9	6.0
AD-2136857.1	6.8	0.4	7.7	0.8	18.8	2.0	45.9	2.1
AD-2222919.1	25.6	2.4	31.1	1.4	54.7	7.0	69.8	5.0
AD-2136859.1	8.3	0.9	11.0	1.6	25.1	1.8	47.1	3.3
AD-2222920.1	23.9	4.8	29.8	2.4	52.3	4.1	73.5	5.9
AD-2136861.1	8.3	1.7	10.9	3.3	27.5	4.5	43.8	5.1
AD-2136862.1	10.0	2.7	9.6	1.7	26.5	2.2	51.2	5.3
AD-2136864.1	6.7	0.1	10.4	1.0	22.8	1.6	55.9	3.0
AD-2136865.1	12.6	3.3	12.5	1.1	27.5	4.8	53.3	1.7
AD-2222921.1	9.2	0.9	11.7	1.0	23.6	2.9	56.1	3.2
AD-2136866.1	26.1	4.0	31.7	1.6	48.8	2.3	88.6	6.7
AD-2136867.1	17.2	1.7	22.7	1.2	44.7	5.6	73.6	4.7
AD-2136868.1	7.9	1.0	8.0	1.2	15.1	1.7	43.4	3.7
AD-2222922.1	12.6	0.8	14.2	4.4	30.4	3.2	70.9	7.9
AD-2136869.1	8.2	1.8	14.1	1.2	29.3	3.7	54.9	3.0
AD-2222923.1	27.0	5.4	31.0	1.5	64.3	2.8	81.7	4.9

	250 nM Dose		100 nM Dose		10 nM Dose		1 nM Dose	
Duplex	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD
AD-2136870.1	17.9	1.4	22.5	2.6	45.2	0.9	67.4	5.9
AD-2222924.1	66.3	4.2	80.0	4.6	99.7	2.9	111.5	3.3
AD-2136871.1	8.9	1.2	11.6	1.2	15.6	2.9	39.0	2.3
AD-2136873.1	10.5	1.3	12.3	1.9	26.9	1.4	60.2	8.6
AD-2136874.1	10.7	0.9	14.2	1.9	26.1	3.2	63.2	4.1
AD-2222925.1	31.9	4.3	44.0	3.2	67.7	3.9	100.3	8.7
AD-2136875.1	8.6	1.7	8.7	1.5	19.2	2.2	45.4	5.4
AD-2222926.1	10.1	0.6	11.2	1.4	22.1	4.3	47.7	4.0
AD-2136876.1	10.8	1.3	12.7	1.2	22.7	3.0	50.2	1.5
AD-2222927.1	23.7	4.0	29.3	2.8	54.2	3.7	88.8	5.2
AD-2136877.1	10.0	0.9	9.8	1.3	18.0	2.9	47.6	2.6
AD-2136878.1	11.5	1.5	14.2	0.6	29.2	3.5	63.9	4.5
AD-2136879.1	10.1	0.4	10.1	0.9	18.0	1.5	45.3	3.6
AD-2222928.1	11.5	1.8	14.3	2.3	24.9	2.0	60.6	6.2
AD-2136880.1	14.2	1.6	17.2	1.5	41.9	1.6	70.1	3.8
AD-2222929.1	14.5	3.5	18.3	1.3	40.2	1.6	68.3	6.9
AD-2136882.1	33.0	3.4	42.6	3.3	72.0	7.8	91.7	9.9
AD-2136883.1	9.8	0.8	9.2	0.4	20.2	1.5	47.7	1.8
AD-2222930.1	16.2	1.3	16.3	2.5	36.1	4.1	62.4	6.1
AD-2136992.1	13.8	0.5	13.1	3.4	25.8	1.8	68.9	5.5
AD-2136993.1	8.6	2.0	8.0	1.4	15.7	3.1	39.8	5.3
AD-2136994.1	28.0	2.7	32.1	1.8	57.8	3.1	87.1	2.5
AD-2222931.1	62.9	1.3	67.6	7.5	85.6	8.8	102.6	4.4
AD-2136995.1	15.1	0.8	16.7	2.1	30.4	2.2	62.2	3.1
AD-2222932.1	49.9	4.8	53.6	2.3	71.6	2.6	95.3	2.2
AD-2136996.1	8.6	1.4	7.2	0.8	14.1	1.0	32.9	4.9
AD-2136997.1	8.0	1.4	7.6	0.5	15.2	1.9	36.7	3.6
AD-2136998.1	13.5	1.6	11.6	1.5	24.6	2.8	45.0	4.1
AD-2136999.1	6.5	1.6	8.3	1.1	13.0	0.9	28.9	2.8
AD-2137000.1	13.6	1.2	15.7	1.5	36.8	4.8	64.2	9.8
AD-2137001.1	18.8	2.2	23.4	0.5	45.8	2.5	83.9	7.9
AD-2137002.1	15.1	2.7	15.5	1.1	31.1	2.6	54.6	3.9
AD-2222933.1	44.9	2.6	44.1	3.3	74.6	9.8	87.3	2.8
AD-2137016.3	12.8	3.0	13.3	1.5	29.1	1.8	57.7	7.3
AD-2137017.3	5.9	1.7	6.8	1.3	10.4	2.4	33.3	3.2
AD-2137018.5	5.5	2.3	5.6	1.1	9.4	0.5	17.6	3.1
AD-2222934.1	14.4	2.1	18.6	1.7	30.6	4.2	65.1	4.3
AD-2137019.1	12.0	2.2	12.7	1.3	29.1	3.6	54.1	3.5

	250 nM Dose		100 nM Dose		10 nM Dose		1 nM Dose	
Duplex	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD
AD-2137020.1	13.9	0.7	17.3	1.4	35.4	2.9	56.5	3.8
AD-2137021.1	13.0	2.3	10.6	1.8	25.6	3.8	46.9	1.2
AD-2137022.1	14.1	1.3	15.0	1.6	41.2	5.2	58.4	6.4
AD-2137023.1	43.1	5.1	51.4	3.5	81.5	2.4	101.3	1.9
AD-2137024.1	9.5	1.4	9.5	0.8	14.9	1.7	44.2	3.1
AD-2137025.1	9.3	1.9	8.4	1.5	10.8	1.3	22.3	3.8
AD-2137026.1	20.9	4.0	25.1	4.2	54.9	6.3	77.5	7.0
AD-2137027.1	11.9	2.2	12.3	1.3	24.4	3.1	49.4	4.4
AD-2137055.1	18.1	1.9	15.5	1.4	33.0	3.3	68.1	4.3
AD-2222935.1	21.6	3.1	28.3	4.9	53.7	4.4	72.9	3.1
AD-2137056.1	13.5	1.2	12.4	3.0	20.4	2.8	45.8	5.1
AD-2222936.1	15.4	1.4	14.3	1.3	31.4	4.7	63.6	6.7
AD-2137057.1	22.5	3.3	22.8	5.0	33.3	3.6	66.3	6.2
AD-2222937.1	32.0	3.6	31.9	4.3	55.2	1.1	90.6	8.5
AD-2137059.1	5.5	2.5	7.7	1.5	13.0	1.0	21.8	2.6
AD-2137061.1	10.7	0.7	12.9	1.6	23.3	4.8	37.0	1.0
AD-2222939.1	11.3	3.4	10.0	2.3	14.1	2.3	27.4	4.2
AD-2222940.1	16.9	2.8	15.9	1.9	26.4	3.0	50.1	3.7
AD-2137062.1	31.6	5.5	40.1	3.1	64.0	5.9	90.2	8.0
AD-2137063.1	17.2	2.7	17.7	1.4	23.4	2.3	45.1	7.3
AD-2137101.1	45.3	6.5	48.2	2.8	71.7	3.8	87.1	7.0
AD-2137128.1	21.4	3.6	26.2	4.4	57.4	2.9	82.3	7.4
AD-2137130.1	16.7	1.9	17.9	3.4	41.5	3.0	69.4	6.0
AD-2137138.1	25.8	3.4	31.5	2.9	57.5	6.6	99.6	9.2
AD-2137196.1	10.5	1.2	12.5	2.8	25.4	2.8	44.6	3.7
AD-2222942.1	21.1	3.8	32.5	3.0	50.6	4.5	82.8	12.6
AD-2137197.1	9.6	0.9	14.1	1.7	24.7	4.3	45.9	6.4
AD-2222943.1	16.6	0.4	19.6	3.8	39.3	1.7	59.3	6.5
AD-2137198.1	12.0	2.2	12.0	0.8	24.6	4.0	52.1	4.2
AD-2222944.1	9.5	2.1	12.4	1.9	22.8	2.9	40.5	5.0
AD-2137199.1	7.4	0.5	5.9	0.6	12.0	2.1	28.7	2.3
AD-2222945.1	12.6	1.5	12.1	1.7	19.3	6.3	34.8	2.1
AD-2137200.1	9.4	1.6	11.5	2.8	23.4	0.8	46.4	7.7
AD-2222946.1	15.3	0.9	16.4	1.6	32.5	2.8	58.0	4.5
AD-2137204.1	6.3	1.4	5.7	0.7	11.7	0.4	23.5	2.1
AD-2137223.1	5.9	1.6	5.5	1.1	10.5	0.6	20.4	1.3
AD-2137224.1	16.8	3.6	18.0	3.4	25.9	3.6	54.5	2.7
AD-2222947.1	11.2	2.7	8.9	3.3	20.4	3.0	37.4	3.5

	250 nM Dose		100 nM Dose		10 nM Dose		1 nM Dose	
Duplex	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD
AD-2137225.1	6.3	1.0	6.3	1.1	7.5	2.1	18.4	1.6
AD-2222949.1	11.7	2.5	10.2	2.6	17.0	2.8	33.1	4.1

TABLE 10. PLG Multi-Dose Screens in Primary Cyno Hepatocytes (PCH)

	250 nM Dose		100 nM Dose		10 nM Dose		1 nM Dose	
Duplex	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD
AD-2134523.1	3.8	0.5	3.1	0.3	6.6	1.2	20.7	3.5
AD-2222854.1	5.1	0.9	3.5	0.6	7.6	1.6	23.7	4.0
AD-2134574.1	3.2	0.4	2.7	0.4	7.0	0.7	16.8	5.0
AD-2222855.1	8.2	0.8	6.8	1.0	15.4	1.2	29.2	6.1
AD-2134577.1	6.1	0.2	4.9	0.2	11.2	3.0	28.2	2.4
AD-2134687.1	1.4	0.2	0.9	0.2	2.3	0.4	6.3	0.3
AD-2222856.1	3.5	0.4	2.9	0.3	7.3	0.8	21.1	1.5
AD-2134898.1	1.9	0.3	1.7	0.2	3.8	0.4	8.2	0.7
AD-2222857.1	3.2	0.4	3.1	0.7	6.8	0.6	14.0	2.5
AD-2134900.1	8.8	1.4	7.7	0.8	17.4	1.8	26.3	3.8
AD-2222858.1	22.7	2.4	24.6	3.1	34.1	6.0	35.8	5.2
AD-2134906.1	7.4	0.9	7.1	0.2	13.3	0.8	28.4	2.8
AD-2134907.1	4.9	0.7	4.7	1.0	8.8	1.2	20.0	0.8
AD-2135487.1	2.0	0.3	1.8	0.3	5.0	0.6	9.6	0.7
AD-2222859.1	6.3	1.0	5.9	0.5	15.5	0.8	26.9	3.0
AD-2135518.1	9.1	0.8	9.2	1.0	19.4	3.6	40.4	4.9
AD-2222860.1	27.4	9.2	33.1	8.5	60.8	3.4	51.4	4.6
AD-2135519.1	6.7	1.1	6.1	0.6	12.9	1.4	26.2	5.5
AD-2222861.1	6.0	0.8	6.0	0.5	13.5	1.6	26.3	3.9
AD-2135520.1	7.7	0.7	7.3	0.5	14.4	0.9	27.2	2.6
AD-2222862.1	16.2	0.9	15.3	1.2	27.3	6.2	42.3	3.5
AD-2135708.1	1.4	0.3	1.3	0.3	4.0	0.7	10.7	1.7
AD-2222863.1	2.1	0.2	2.4	0.4	6.5	1.9	17.3	0.9
AD-2135712.1	2.9	0.2	3.1	0.3	8.6	2.0	22.2	3.5
AD-2135713.1	3.3	0.4	3.6	0.1	8.1	1.1	22.7	1.8
AD-2135716.1	2.2	0.2	2.3	0.2	6.6	0.2	16.2	3.3
AD-2222864.1	2.6	0.2	2.3	0.4	7.3	0.9	16.8	4.2
AD-2135717.1	3.1	0.3	3.2	0.1	8.3	1.0	16.0	1.8
AD-2222865.1	19.6	2.7	19.4	2.5	33.2	3.5	48.9	7.0

	250 nM Dose		100 nM Dose		10 nM Dose		1 nM Dose	
Duplex	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD
AD-2135718.1	3.0	0.7	3.2	0.8	8.0	1.6	19.0	3.4
AD-2135719.1	6.1	0.8	5.0	0.8	12.3	1.7	25.6	6.2
AD-2222866.1	18.8	2.1	18.4	2.7	32.8	4.9	55.6	8.0
AD-2135721.1	4.8	0.5	4.1	0.7	10.6	2.3	23.4	4.4
AD-2222867.1	10.9	2.1	8.8	0.6	19.0	2.8	35.7	3.8
AD-2135730.1	11.2	0.8	10.0	1.3	19.3	2.6	37.1	4.3
AD-2135731.1	3.1	0.5	2.7	0.1	6.0	0.9	13.5	1.4
AD-2222868.1	3.4	0.5	3.0	0.3	6.3	0.7	13.3	1.0
AD-2135732.1	14.6	3.3	13.2	2.0	22.2	2.1	36.5	3.8
AD-2222869.1	7.3	0.7	6.2	1.6	12.6	2.3	21.7	1.8
AD-2135734.1	9.5	1.3	8.5	1.2	13.7	1.1	31.1	2.4
AD-2222870.1	25.5	2.9	21.2	2.3	34.0	6.2	49.5	9.3
AD-2135736.1	7.2	0.9	5.1	0.6	10.5	1.2	18.7	1.9
AD-2135737.1	4.0	0.5	2.8	0.5	6.8	0.6	17.4	1.5
AD-2135738.1	4.2	0.2	3.7	0.5	6.9	0.8	15.4	0.8
AD-2135786.1	4.8	0.3	4.4	0.3	10.9	0.8	19.9	0.9
AD-2135788.1	59.5	8.3	54.4	6.8	64.8	8.4	96.7	5.0
AD-2222871.1	65.2	9.5	57.6	7.1	87.1	12.2	103.4	14.6
AD-2135789.1	14.7	1.2	11.9	1.3	24.4	4.0	42.8	3.3
AD-2222872.1	11.9	1.2	11.6	1.9	25.6	1.5	56.2	7.6
AD-2135821.1	12.1	1.9	9.1	0.6	16.6	3.7	34.2	2.9
AD-2222873.1	27.8	4.5	20.3	0.5	40.0	6.7	70.1	13.5
AD-2135896.1	7.9	1.1	6.7	0.5	13.2	1.6	24.7	0.6
AD-2135897.1	39.5	9.4	35.2	7.1	55.1	3.0	60.2	5.1
AD-2222874.1	6.6	0.4	5.0	0.5	15.2	1.8	41.4	6.1
AD-2222875.1	2.4	0.2	2.4	0.4	5.1	0.5	14.9	0.8
AD-2135900.1	2.6	0.3	2.7	0.1	5.6	0.9	15.6	1.9
AD-2222876.1	7.8	1.1	8.3	0.9	16.2	0.9	42.9	6.2
AD-2135901.1	7.0	0.7	5.8	1.2	12.2	1.3	24.4	2.3
AD-2222877.1	18.4	2.6	15.0	2.9	26.6	1.5	49.3	1.9
AD-2135904.1	1.7	0.1	1.6	0.1	3.4	0.1	7.6	0.6
AD-2135907.1	7.8	2.8	7.4	2.3	11.4	2.3	26.0	2.3
AD-2135962.1	6.3	0.4	6.4	0.5	15.7	2.7	41.6	2.5
AD-2135964.1	14.1	2.0	12.7	1.7	22.6	1.9	50.9	6.1
AD-2222878.1	32.1	4.0	27.1	1.3	45.4	4.3	74.2	7.6
AD-2135965.1	5.2	0.6	5.2	1.1	9.4	0.9	23.9	1.3
AD-2222879.1	9.5	0.7	9.5	1.6	15.6	0.7	31.1	2.1

	250 nM Dose		100 nM Dose		10 nM Dose		1 nM Dose	
Duplex	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD
AD-2135967.1	7.9	1.1	8.4	1.0	19.1	2.2	32.9	2.8
AD-2135973.1	4.9	1.3	4.3	0.9	9.7	2.0	21.7	2.8
AD-2136060.1	43.0	6.8	38.0	2.7	59.7	9.1	82.7	9.8
AD-2222880.1	31.5	4.0	32.4	3.6	43.6	3.9	71.9	2.9
AD-2136066.1	19.3	1.9	16.5	2.9	23.6	2.5	51.7	7.6
AD-2222881.1	37.9	3.1	33.1	5.1	43.3	6.9	86.6	5.2
AD-2136068.1	12.2	0.5	12.4	1.3	18.4	1.5	37.5	3.2
AD-2136069.1	11.9	3.0	9.7	2.0	22.8	4.1	36.9	7.4
AD-2222882.1	20.8	2.6	20.9	1.7	38.2	1.1	58.8	2.6
AD-2136072.1	7.8	0.7	8.6	1.5	16.3	1.3	42.8	2.3
AD-2222883.1	22.7	1.9	23.4	1.9	31.1	10.2	84.2	10.2
AD-2136073.1	4.5	0.5	4.8	1.1	12.4	2.4	35.6	5.1
AD-2136074.1	25.7	2.9	25.1	3.3	27.3	4.5	75.4	9.2
AD-2136075.1	21.0	1.9	20.0	4.5	32.4	3.7	67.0	3.1
AD-2136077.1	6.2	1.2	6.2	0.9	10.7	1.3	28.9	1.1
AD-2136079.1	2.8	0.5	3.1	0.3	5.2	0.9	14.9	2.5
AD-2222884.1	4.4	1.0	4.6	0.4	10.7	2.9	23.8	3.9
AD-2136080.1	3.6	0.5	4.6	0.9	11.6	2.4	31.5	5.5
AD-2222885.1	7.9	0.4	10.3	2.2	18.1	4.3	48.0	9.8
AD-2136083.1	5.9	1.2	7.3	0.6	17.0	3.6	47.8	12.8
AD-2136164.1	21.9	4.1	21.2	1.7	40.4	3.2	75.1	5.4
AD-2136166.1	9.3	1.8	8.2	1.7	16.8	2.7	43.3	6.1
AD-2222886.1	8.7	1.2	9.1	1.9	18.7	1.6	46.1	10.3
AD-2136168.1	5.3	1.4	7.6	1.4	16.7	0.9	29.6	6.0
AD-2222887.1	24.9	3.0	26.5	2.1	38.3	3.7	64.8	8.7
AD-2136171.1	4.8	0.9	8.9	1.2	14.0	2.0	28.6	4.4
AD-2136172.1	10.3	1.4	16.1	2.3	20.9	1.7	44.3	9.5
AD-2136179.1	11.9	0.6	14.3	0.5	20.6	4.5	44.8	4.3
AD-2222888.1	11.8	0.6	16.3	1.4	26.3	3.6	43.9	10.5
AD-2136183.1	20.2	8.9	15.6	2.9	28.0	5.6	40.9	3.1
AD-2136263.1	23.7	5.7	27.8	3.4	39.3	6.7	68.9	1.2
AD-2136347.1	4.6	0.5	5.9	1.3	14.1	2.0	28.9	4.0
AD-2222889.1	4.2	0.8	6.3	1.0	3.6	2.9	24.3	4.0
AD-2136348.1	6.1	0.4	8.4	2.0	15.8	1.4	26.5	4.0
AD-2222890.1	14.9	0.8	21.4	4.3	25.9	4.3	39.2	8.2
AD-2136349.1	26.3	2.7	31.1	1.3	49.0	3.9	54.1	11.2
AD-2222891.1	22.4	3.6	35.6	3.8	57.6	11.2	80.3	15.8

	250 nM Dose		100 nM Dose		10 nM Dose		1 nM Dose	
Duplex	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD
AD-2136355.1	7.3	2.8	8.9	0.3	16.7	2.1	28.8	9.9
AD-2136421.1	2.6	0.5	3.9	0.6	6.1	1.9	24.8	1.6
AD-2222892.1	6.4	0.9	9.2	0.7	19.3	1.3	40.2	5.3
AD-2136431.1	4.3	0.4	5.7	0.4	12.4	0.8	27.0	3.0
AD-2222893.1	4.4	0.7	6.0	0.8	10.9	1.0	28.8	1.7
AD-2136433.1	22.1	1.3	27.8	1.3	43.7	5.1	70.8	10.6
AD-2136434.1	6.0	0.2	7.6	0.9	13.5	1.3	29.8	3.3
AD-2222894.1	17.6	1.8	17.5	1.8	31.1	4.1	50.1	5.8
AD-2136437.1	3.5	0.6	4.4	0.5	6.0	1.2	19.8	0.5
AD-2222895.1	2.7	0.2	3.2	0.5	5.7	0.8	17.5	1.1
AD-2136438.1	8.3	1.0	10.0	1.5	17.4	2.2	38.9	3.0
AD-2222896.1	24.9	5.0	26.2	6.7	36.1	8.2	68.3	4.8
AD-2136439.1	8.2	3.2	7.6	0.7	15.6	1.8	32.3	3.7
AD-2222897.1	21.5	2.5	23.9	3.7	37.1	3.4	71.2	5.2
AD-2136440.1	3.9	0.1	4.1	0.5	8.0	0.8	18.6	1.8
AD-2222898.1	4.5	0.2	6.6	0.3	11.7	1.7	24.1	3.0
AD-2136442.1	3.6	2.2	3.1	0.2	6.5	1.3	16.3	1.9
AD-2136443.1	5.7	0.3	6.5	1.1	13.9	1.4	29.3	1.4
AD-2222899.1	23.6	5.9	24.4	3.9	30.1	10.2	62.2	6.6
AD-2136465.1	7.4	1.3	8.9	1.5	17.2	2.0	41.2	4.6
AD-2222900.1	5.4	0.3	6.6	0.5	14.5	3.2	32.8	2.6
AD-2136470.1	3.8	0.4	4.8	0.6	12.2	1.6	28.1	1.5
AD-2136571.1	5.0	0.4	6.7	0.7	14.5	0.9	28.0	2.9
AD-2222901.1	10.9	0.7	13.9	0.9	26.6	1.2	42.7	4.4
AD-2136606.1	22.8	6.2	24.4	1.4	37.2	3.7	51.9	6.4
AD-2222902.1	31.3	3.8	53.2	9.6	63.8	12.3	72.0	5.1
AD-2136716.1	14.4	0.9	16.6	2.4	27.2	2.5	48.8	3.4
AD-2222903.1	55.9	5.8	71.4	7.4	75.9	2.9	80.0	3.2
AD-2136717.1	4.3	0.5	4.5	0.4	10.0	1.2	21.3	1.4
AD-2136718.3	3.3	0.3	4.6	0.6	8.3	0.3	19.5	3.3
AD-2136721.1	2.9	0.3	3.7	0.5	7.2	0.4	17.0	1.3
AD-2136726.1	8.7	0.5	9.6	1.7	16.9	1.9	39.1	2.0
AD-2222905.1	31.0	2.3	34.3	5.3	54.9	4.4	78.7	9.4
AD-2136729.1	13.3	0.9	15.6	2.2	23.7	2.5	53.5	4.2
AD-2222906.1	34.1	6.0	38.2	6.6	60.2	3.4	94.5	9.2
AD-2136753.1	19.2	2.2	26.7	5.0	38.6	5.4	61.8	4.7
AD-2136754.1	7.1	0.6	8.7	1.7	16.6	1.6	35.5	2.5

	250 nM Dose		100 nM Dose		10 nM Dose		1 nM Dose	
Duplex	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD
AD-2136755.1	3.4	0.5	4.2	0.5	7.7	0.8	20.6	1.8
AD-2136756.1	13.4	2.4	15.7	1.7	34.6	4.0	64.3	5.2
AD-2222907.1	26.6	7.3	46.0	4.0	54.9	9.2	61.1	12.4
AD-2136757.1	4.8	0.5	6.1	0.9	15.7	1.9	34.5	2.9
AD-2222908.1	6.9	0.6	8.7	2.0	21.3	0.6	49.7	2.2
AD-2136758.1	23.0	2.8	29.3	1.8	45.3	3.3	65.7	10.1
AD-2222909.1	15.9	1.5	18.9	1.7	32.6	3.8	56.9	7.7
AD-2136760.1	5.3	2.4	6.3	1.0	12.9	0.7	29.8	1.7
AD-2222910.1	3.4	0.2	4.8	0.7	11.7	1.2	28.2	2.3
AD-2136761.1	3.3	1.8	6.5	1.2	12.1	1.5	27.4	4.5
AD-2136762.1	6.3	0.3	7.6	1.2	15.8	2.4	37.1	11.8
AD-2222911.1	5.9	0.5	8.1	0.7	14.7	1.9	41.9	7.9
AD-2136763.1	3.4	0.1	3.5	0.5	8.6	1.1	19.4	2.2
AD-2136764.1	5.7	0.4	7.1	1.4	16.0	1.4	31.9	4.4
AD-2136787.1	3.1	0.3	4.0	0.8	8.9	0.6	20.7	3.2
AD-2222912.1	12.8	2.1	16.9	1.8	33.5	4.9	56.4	10.0
AD-2136790.1	4.5	1.0	6.9	0.6	12.7	2.7	32.2	3.7
AD-2136791.1	14.1	1.5	16.9	2.7	33.3	2.7	62.4	5.2
AD-2222913.1	25.4	8.7	27.9	2.8	47.0	5.6	66.5	8.6
AD-2136792.1	3.6	1.6	3.6	0.7	8.3	1.0	20.2	0.2
AD-2222914.1	6.0	0.2	8.0	1.0	18.4	0.8	35.9	1.7
AD-2136793.1	3.8	0.4	5.7	0.2	13.9	1.4	33.5	4.4
AD-2222915.1	18.6	0.9	23.1	0.8	43.5	2.6	61.3	2.2
AD-2136794.1	9.4	1.6	10.6	1.0	21.7	4.4	56.1	7.9
AD-2222916.1	17.9	2.4	22.9	5.1	32.7	5.1	68.0	20.7
AD-2136797.1	11.6	1.9	13.9	2.1	29.2	0.9	64.2	3.4
AD-2222917.1	8.2	0.8	10.5	0.2	22.8	2.4	52.9	5.3
AD-2136851.1	3.4	1.5	4.7	0.5	10.5	0.8	27.2	4.2
AD-2136852.1	3.8	0.9	5.6	0.9	14.1	0.8	36.0	5.3
AD-2136853.1	1.5	0.0	1.7	0.2	5.3	0.2	14.2	0.8
AD-2136854.1	8.6	1.5	11.1	1.6	22.1	1.9	50.9	10.4
AD-2136855.1	3.1	1.4	4.6	1.3	19.2	5.5	40.3	5.0
AD-2222918.1	13.5	6.1	22.1	2.7	33.2	4.4	64.7	5.4
AD-2136857.1	5.7	1.8	7.2	1.3	16.6	0.6	44.0	2.6
AD-2222919.1	19.5	4.0	26.4	4.4	43.4	3.7	95.9	13.4
AD-2136859.1	6.3	0.9	9.6	2.0	15.9	3.6	34.1	1.8
AD-2222920.1	18.6	6.0	22.9	3.6	36.2	6.7	75.8	14.1

	250 nM Dose		100 nM Dose		10 nM Dose		1 nM Dose	
Duplex	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD
AD-2136861.1	4.7	1.0	7.0	0.9	15.0	1.7	32.2	4.4
AD-2136862.1	4.3	1.0	6.0	1.5	13.4	3.7	28.3	4.6
AD-2136864.1	5.7	1.1	3.5	1.0	16.6	1.5	22.6	2.3
AD-2136865.1	6.4	0.2	6.8	0.5	20.1	2.7	25.5	0.7
AD-2222921.1	3.7	0.2	4.3	0.3	13.4	1.7	21.3	4.3
AD-2136866.1	11.2	3.1	11.0	1.2	31.3	2.1	40.9	6.8
AD-2136867.1	10.1	1.4	10.4	0.5	28.1	2.5	33.4	3.9
AD-2136868.1	2.2	0.2	2.5	0.4	8.7	1.9	15.5	0.9
AD-2222922.1	5.4	0.4	7.3	0.8	22.7	1.4	25.2	2.4
AD-2136869.1	5.3	0.3	6.2	0.9	17.9	1.3	23.2	0.9
AD-2222923.1	24.2	2.9	26.4	3.4	46.3	3.6	35.0	6.5
AD-2136870.1	15.2	1.1	14.9	2.1	30.8	1.2	39.4	5.1
AD-2222924.1	46.7	4.0	45.6	1.8	66.6	3.9	58.4	5.5
AD-2136871.1	3.0	0.5	2.9	0.7	10.7	2.1	16.9	1.3
AD-2136873.1	6.3	0.7	5.5	0.1	14.2	1.4	23.6	2.0
AD-2136874.1	8.4	1.2	7.8	1.3	21.8	2.8	25.0	2.4
AD-2222925.1	31.3	6.3	29.3	2.6	56.8	7.0	52.1	5.9
AD-2136875.1	5.2	0.6	5.2	0.7	14.6	1.8	22.1	1.5
AD-2222926.1	4.9	0.4	7.3	1.4	15.9	1.3	19.7	4.3
AD-2136876.1	5.5	0.8	5.0	0.9	14.1	1.3	20.7	1.6
AD-2222927.1	13.1	1.9	14.8	0.8	34.3	3.7	37.2	3.7
AD-2136877.1	3.4	0.7	3.7	0.3	9.9	0.9	16.0	3.4
AD-2136878.1	5.7	0.3	5.2	0.9	15.3	0.8	22.9	2.3
AD-2136879.1	2.4	0.4	2.6	0.4	9.5	0.8	12.7	2.1
AD-2222928.1	4.6	1.2	4.0	0.5	13.3	1.1	21.3	1.6
AD-2136880.1	8.5	1.0	9.1	0.9	22.0	0.9	32.4	2.3
AD-2222929.1	6.8	1.4	7.8	1.7	26.4	3.7	32.1	3.3
AD-2136882.1	17.6	1.7	19.0	1.6	45.0	5.2	46.7	4.5
AD-2136883.1	2.7	0.6	3.3	0.8	8.9	0.6	16.2	2.1
AD-2222930.1	5.0	0.5	5.8	0.4	16.7	0.8	26.8	4.0
AD-2136992.1	4.5	0.3	4.0	1.1	8.9	1.1	16.8	1.2
AD-2136993.1	3.3	0.6	2.9	0.7	11.7	0.5	15.8	1.5
AD-2136994.1	17.0	1.2	17.8	1.1	34.8	1.9	43.1	4.3
AD-2222931.1	40.4	2.2	47.1	7.8	75.0	5.2	65.6	7.7
AD-2136995.1	8.2	0.5	8.2	1.4	22.5	1.6	27.4	1.7
AD-2222932.1	40.9	3.0	40.1	4.9	75.6	3.5	72.7	9.2
AD-2136996.1	2.7	0.5	2.7	0.2	10.5	0.4	13.9	0.7

	250 nM Dose		100 nM Dose		10 nM Dose		1 nM Dose	
Duplex	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD
AD-2136997.1	3.2	0.2	3.0	0.8	7.8	1.1	12.9	1.3
AD-2136998.1	4.2	0.1	4.8	1.3	13.1	1.6	15.7	1.7
AD-2136999.1	2.8	0.7	4.0	0.9	6.5	0.3	10.1	0.7
AD-2137000.1	10.1	1.1	12.2	1.4	30.2	4.7	31.1	2.0
AD-2137001.1	9.2	1.0	10.0	1.5	24.9	2.2	32.1	3.0
AD-2137002.1	5.5	0.4	5.3	0.7	13.5	1.2	18.5	2.5
AD-2222933.1	31.9	2.9	26.5	4.8	50.2	4.1	59.0	4.8
AD-2137016.3	6.5	0.5	7.9	0.7	23.2	0.3	31.7	0.8
AD-2137017.3	3.7	1.7	2.8	0.8	5.7	1.2	10.8	0.6
AD-2137018.5	1.7	0.5	1.2	0.2	4.4	0.5	7.3	0.9
AD-2222934.1	4.9	0.7	5.7	0.7	16.2	0.9	22.6	1.8
AD-2137019.1	6.2	0.6	9.9	3.0	22.7	1.2	36.1	3.1
AD-2137020.1	10.8	1.4	12.0	0.2	30.4	1.7	49.9	2.6
AD-2137021.1	3.1	0.6	3.0	0.9	11.9	1.1	22.3	1.8
AD-2137022.1	7.5	0.8	7.7	1.0	25.2	4.8	43.1	5.4
AD-2137023.1	24.7	1.2	27.2	4.0	57.2	4.8	66.0	7.4
AD-2137024.1	3.4	1.7	3.1	0.7	7.4	0.5	15.6	2.0
AD-2137025.1	2.0	0.7	3.4	1.3	5.4	1.3	8.4	1.6
AD-2137026.1	18.8	1.1	28.0	4.4	66.4	5.4	66.0	12.9
AD-2137027.1	4.3	0.7	6.5	0.7	20.1	1.2	37.1	5.5
AD-2137055.1	7.9	1.1	9.7	1.3	20.7	1.5	40.4	2.2
AD-2222935.1	23.2	1.6	27.6	2.2	57.4	6.5	91.7	12.0
AD-2137056.1	4.6	0.4	5.5	0.3	18.2	2.1	24.1	3.2
AD-2222936.1	8.0	0.5	10.3	1.8	22.5	2.8	37.0	2.4
AD-2137057.1	10.2	1.6	11.6	4.0	19.7	3.5	29.7	1.0
AD-2222937.1	18.5	1.7	22.4	2.6	43.5	1.5	51.6	3.7
AD-2137059.1	2.2	0.3	4.0	0.9	7.4	0.6	14.7	1.2
AD-2137061.1	5.9	1.2	6.0	1.1	12.8	2.0	26.5	2.5
AD-2222939.1	2.5	0.2	2.2	0.3	6.5	1.4	13.2	1.3
AD-2222940.1	4.8	0.2	5.3	0.9	15.7	1.3	22.4	1.3
AD-2137062.1	16.8	2.2	17.0	1.0	40.0	2.7	40.2	2.8
AD-2137063.1	3.7	0.7	4.6	1.1	11.4	1.6	17.1	1.9
AD-2137101.1	41.6	6.8	45.6	3.5	63.7	8.9	95.7	15.1
AD-2137128.1	5.0	0.7	6.6	0.3	19.1	1.6	37.6	5.1
AD-2137130.1	2.5	0.5	3.2	0.4	9.0	0.6	18.5	1.8
AD-2137138.1	5.0	1.6	5.7	0.3	15.2	2.0	25.1	0.8
AD-2137196.1	2.0	0.2	3.4	0.8	7.2	2.8	13.5	2.4

	250 nM Dose		100 nM Dose		10 nM Dose		1 nM Dose	
Duplex	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD	Avg % PLG mRNA Remaining	SD
AD-2222942.1	47.0	2.7	51.4	5.2	77.6	4.3	56.0	4.9
AD-2137197.1	5.6	0.5	5.9	0.5	21.7	2.5	35.2	4.4
AD-2222943.1	67.5	6.4	73.8	13.8	100.4	10.8	83.2	15.6
AD-2137198.1	4.4	0.7	6.5	1.3	15.5	1.5	29.1	2.4
AD-2222944.1	5.2	0.4	7.3	1.4	20.6	2.4	34.9	4.6
AD-2137199.1	2.0	0.4	2.1	0.5	5.9	1.5	11.6	1.4
AD-2222945.1	2.5	0.4	3.0	0.3	10.0	1.7	20.7	1.4
AD-2137200.1	1.9	0.3	2.6	0.5	7.0	1.3	13.2	1.9
AD-2222946.1	2.4	0.1	3.1	0.5	9.5	1.4	20.7	2.5
AD-2137204.1	1.1	0.5	1.6	0.3	4.0	1.5	9.7	0.9
AD-2137223.1	1.7	0.1	2.0	0.3	4.9	0.4	9.1	1.6
AD-2137224.1	9.1	1.7	8.4	2.6	13.9	1.6	30.6	1.1
AD-2222947.1	4.3	1.1	6.5	0.4	13.2	0.3	27.5	6.2
AD-2137225.1	2.3	0.5	1.8	0.4	3.8	0.3	8.6	0.6
AD-2222949.1	4.2	0.5	5.2	1.4	13.7	2.0	28.9	5.7

Table 11. Initial *in vitro* screening assay in PHH cells

	10 nM Dose		1 nM Dose		0.1 nM Dose			10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**	**Duplex**	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**
AD-2138754.1	6	1	7	1	12	2	AD-2138688.1	20	2	25	1	40	3
AD-2138631.1	5	0	7	1	12	2	AD-2138805.2	18	1	25	4	40	7
AD-2138874.2	7	1	8	1	16	2	AD-2138525.1	15	1	25	1	40	7
AD-2138256.1	8	2	8	3	13	4	AD-2138083.1	15	2	25	1	41	2
AD-2138876.2	6	1	8	1	14	1	AD-2138074.1	19	1	25	2	43	6
AD-2138644.1	9	2	9	2	16	3	AD-2138360.1	18	1	25	3	48	11
AD-2138630.1	6	1	9	1	16	2	AD-2138121.1	16	1	25	2	39	1
AD-2138752.1	7	0	9	1	17	4	AD-2138364.1	23	4	25	3	32	2
AD-2138695.1	6	1	9	0	17	3	AD-2138728.1	19	1	25	2	38	9
AD-2138753.1	7	2	9	2	17	3	AD-2138235.1	21	5	25	1	39	2
AD-2138757.1	6	0	9	3	17	3	AD-2138782.1	21	2	25	3	51	3
AD-2138660.1	7	1	9	2	16	3	AD-2138195.1	21	3	25	1	43	3
AD-2138755.1	8	2	9	1	17	1	AD-2138230.1	19	1	25	2	50	6
AD-2138721.1	8	1	10	1	18	3	AD-2138368.1	19	2	25	4	51	2
AD-2138736.1	6	1	10	3	14	1	AD-2138109.1	18	4	25	3	39	4
AD-2138536.1	7	1	10	1	22	5	AD-2138222.1	18	2	25	2	50	4
AD-2138629.1	9	1	10	1	14	1	AD-2138167.1	19	3	25	3	72	7
AD-2138873.2	9	1	10	2	21	1	AD-2138082.1	14	1	26	2	36	2
AD-2138739.1	8	1	10	1	13	2	AD-2138224.1	18	2	26	2	40	7
AD-2138537.1	7	0	10	0	21	1	AD-2138066.1	22	2	26	3	41	6
AD-2138893.2	8	0	10	1	23	2	AD-2138101.1	15	1	26	2	45	2
AD-2138693.1	7	1	10	0	15	3	AD-2138310.1	18	4	26	1	47	7
AD-2138692.1	8	1	10	1	17	3	AD-2138177.1	21	2	26	1	37	1
AD-2138694.1	8	0	11	1	22	3	AD-2138050.1	16	2	26	2	37	5

	10 nM Dose		1 nM Dose		0.1 nM Dose			10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**	**Duplex**	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**
AD-2138461.1	10	1	11	3	22	2	AD-2138356.1	18	3	26	5	45	8
AD-2138661.1	16	7	11	2	22	6	AD-2138097.1	16	2	26	1	40	7
AD-2138539.1	8	1	11	2	23	7	AD-2138292.1	25	3	26	1	44	1
AD-2138709.1	11	1	11	2	22	4	AD-2138277.1	22	3	26	1	35	3
AD-2138738.1	10	1	11	2	23	3	AD-2138188.1	16	1	26	2	38	8
AD-2138241.1	13	1	11	3	28	1	AD-2138120.1	19	1	26	4	38	3
AD-2138707.1	8	1	11	1	18	3	AD-2138209.1	18	2	26	3	42	2
AD-2138662.1	8	1	11	2	28	6	AD-2138200.1	19	1	26	2	48	4
AD-2138646.1	8	0	11	2	18	2	AD-2138598.1	19	3	26	4	34	4
AD-2138735.1	8	1	11	2	21	1	AD-2138450.1	18	1	26	5	43	5
AD-2138737.1	15	2	11	1	26	6	AD-2138417.1	22	3	26	2	38	9
AD-2138761.1	9	1	12	2	19	3	AD-2138670.1	20	1	26	1	42	4
AD-2138763.1	11	1	12	1	21	2	AD-2138572.1	16	3	26	3	56	9
AD-2138706.1	9	1	12	2	24	8	AD-2138596.1	22	1	26	2	42	6
AD-2138697.1	8	2	12	2	26	4	AD-2138325.1	16	1	26	3	46	4
AD-2138760.1	10	1	12	3	21	3	AD-2138333.1	17	2	26	2	31	2
AD-2138740.1	10	1	12	2	26	9	AD-2138131.1	23	4	26	2	36	3
AD-2138758.1	10	1	12	1	26	5	AD-2138281.1	21	4	26	1	38	4
AD-2138875.2	8	1	12	0	19	2	AD-2138052.1	20	1	26	4	47	7
AD-2138708.1	11	2	12	1	30	3	AD-2138590.1	17	2	26	7	47	3
AD-2138538.1	10	2	12	1	29	5	AD-2138449.1	20	2	26	4	58	1
AD-2138872.2	11	1	13	0	21	2	AD-2138189.1	21	5	27	2	44	8
AD-2138541.1	8	1	13	2	25	5	AD-2138138.1	20	2	27	2	45	3
AD-2138703.1	9	1	13	1	22	4	AD-2138065.1	17	1	27	1	33	6
AD-2138720.1	11	1	13	4	26	5	AD-2138455.1	22	1	27	5	50	5
AD-2138871.2	9	1	13	1	22	3	AD-2138731.1	26	2	27	4	41	1

	10 nM Dose		1 nM Dose		0.1 nM Dose			10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % mRNA Remaining	SD	Avg % mRNA Remaining	SD	Avg % mRNA Remaining	SD	Duplex	Avg % mRNA Remaining	SD	Avg % mRNA Remaining	SD	Avg % mRNA Remaining	SD
AD-2138791.2	9	2	13	1	25	2	AD-2138094.1	17	1	27	1	43	3
AD-2138511.1	11	1	13	1	23	6	AD-2138326.1	18	2	27	3	46	5
AD-2138504.1	9	1	13	1	21	5	AD-2138345.1	18	3	27	2	48	4
AD-2138503.1	11	1	14	3	24	4	AD-2138286.1	17	2	27	1	46	3
AD-2138445.1	8	0	14	1	21	5	AD-2138436.1	15	1	27	4	39	7
AD-2138691.1	11	0	14	2	23	1	AD-2138311.1	20	3	27	4	41	6
AD-2138653.1	12	1	14	2	24	6	AD-2138081.1	19	2	27	2	41	4
AD-2138659.1	15	1	14	1	24	2	AD-2138264.1	15	2	27	1	46	3
AD-2138533.1	10	2	14	2	24	4	AD-2138064.1	17	3	27	3	46	6
AD-2138741.1	8	1	14	2	16	3	AD-2138078.1	16	0	27	6	37	3
AD-2138756.1	9	2	14	1	29	2	AD-2138140.1	21	1	27	1	41	1
AD-2138645.1	11	0	14	1	19	3	AD-2138122.1	16	1	27	3	38	2
AD-2138892.2	11	1	14	1	29	3	AD-2138152.1	14	1	27	4	38	2
AD-2138699.1	11	2	14	1	26	6	AD-2138308.1	23	3	27	3	45	3
AD-2138505.1	11	1	14	1	26	3	AD-2138146.1	21	2	27	3	60	7
AD-2138652.1	10	1	14	2	19	4	AD-2138096.1	15	2	28	3	38	4
AD-2138350.1	11	3	14	3	25	2	AD-2138595.1	22	3	28	2	41	4
AD-2138759.1	12	1	14	1	27	3	AD-2138452.1	19	2	28	3	46	3
AD-2138869.2	11	1	14	2	26	1	AD-2138100.1	19	2	28	4	44	5
AD-2138787.2	13	1	15	2	26	2	AD-2138453.1	21	1	28	3	57	7
AD-2138790.2	11	1	15	2	22	2	AD-2138092.1	19	2	28	2	38	4
AD-2138743.1	10	2	15	3	29	3	AD-2138615.1	24	4	28	2	51	2
AD-2138464.1	12	2	15	3	31	6	AD-2138300.1	20	0	28	2	44	5
AD-2138647.1	12	1	15	1	29	4	AD-2138312.1	19	3	28	2	38	3
AD-2138244.1	10	3	15	1	21	2	AD-2138153.1	18	2	28	0	39	6
AD-2138349.1	9	2	15	1	22	2	AD-2138137.1	22	1	28	5	44	6

	10 nM Dose		1 nM Dose		0.1 nM Dose			10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**	**Duplex**	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**
AD-2138532.1	15	2	15	1	26	2	AD-2138095.1	20	3	28	3	44	2
AD-2138868.2	9	1	15	2	23	3	AD-2138377.1	19	2	28	2	51	4
AD-2138658.1	11	1	15	2	22	3	AD-2138108.1	18	1	28	2	38	4
AD-2138713.1	10	1	15	2	24	4	AD-2138299.1	24	3	28	4	43	4
AD-2138745.1	12	2	15	4	25	4	AD-2138341.1	19	2	28	2	45	2
AD-2138351.1	13	1	15	1	26	1	AD-2138318.1	22	2	29	2	49	2
AD-2138663.1	12	1	15	1	28	8	AD-2138067.1	15	2	29	7	42	3
AD-2138649.1	12	0	15	0	29	4	AD-2138746.1	21	1	29	6	66	6
AD-2138651.1	11	1	15	0	30	6	AD-2138075.1	18	3	29	5	39	4
AD-2138399.1	12	3	15	2	27	2	AD-2138046.1	17	1	29	3	41	3
AD-2138710.1	14	1	15	3	20	3	AD-2138427.1	16	2	29	2	50	8
AD-2138635.1	11	1	15	2	23	5	AD-2138571.1	17	1	29	3	55	10
AD-2138643.1	12	1	15	2	20	3	AD-2138362.1	20	1	29	1	51	4
AD-2138634.1	10	1	15	3	26	4	AD-2138201.1	20	6	29	1	56	10
AD-2138531.1	12	0	16	3	25	3	AD-2138076.1	16	1	29	3	60	3
AD-2138700.1	9	1	16	3	29	6	AD-2138302.1	22	1	29	1	40	1
AD-2138711.1	11	1	16	2	27	8	AD-2138216.1	22	2	29	3	43	1
AD-2138257.1	12	3	16	2	25	4	AD-2138112.1	20	3	29	2	44	5
AD-2138601.1	14	1	16	1	28	4	AD-2138084.1	19	3	29	1	50	7
AD-2138717.1	12	1	16	3	24	2	AD-2138478.1	16	2	29	5	63	5
AD-2138715.1	11	1	16	1	26	2	AD-2138203.1	24	4	29	5	39	3
AD-2138077.1	10	2	16	3	30	4	AD-2138186.1	18	3	30	2	50	5
AD-2138259.1	10	2	16	3	22	4	AD-2138248.1	25	7	30	4	50	7
AD-2138476.1	10	1	16	2	26	5	AD-2138056.1	25	2	30	4	34	3
AD-2138400.1	11	3	16	3	29	1	AD-2138135.1	28	2	30	1	36	3
AD-2138870.2	12	2	16	1	30	1	AD-2138143.1	15	4	30	4	35	3

	10 nM Dose		1 nM Dose		0.1 nM Dose			10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % mRNA Remaining	SD	Avg % mRNA Remaining	SD	Avg % mRNA Remaining	SD	Duplex	Avg % mRNA Remaining	SD	Avg % mRNA Remaining	SD	Avg % mRNA Remaining	SD
AD-2138442.1	11	2	16	2	22	3	AD-2138303.1	23	3	30	1	42	1
AD-2138704.1	12	2	16	2	25	4	AD-2138370.1	25	6	30	2	75	0
AD-2138792.2	14	2	16	2	34	1	AD-2138393.1	28	2	30	4	43	5
AD-2138637.1	13	1	16	1	22	6	AD-2138139.1	21	4	30	4	43	8
AD-2138542.1	12	2	17	1	30	3	AD-2138463.1	27	3	30	3	63	2
AD-2138785.2	16	0	17	3	24	2	AD-2138198.1	23	2	30	3	67	11
AD-2138642.1	15	3	17	1	25	4	AD-2138283.1	19	2	30	2	50	7
AD-2138444.1	17	6	17	1	29	5	AD-2138051.1	21	2	30	3	44	7
AD-2138354.1	14	2	17	1	29	0	AD-2138515.1	53	9	30	3	45	4
AD-2138243.1	14	1	17	2	23	2	AD-2138315.1	25	5	31	2	60	1
AD-2138448.1	12	1	17	5	25	4	AD-2138174.1	17	1	31	5	44	7
AD-2138701.1	12	2	17	1	26	3	AD-2138379.1	21	3	31	1	51	5
AD-2138742.1	9	1	17	2	27	8	AD-2138482.1	21	1	31	7	48	3
AD-2138430.1	11	1	17	1	30	6	AD-2138307.1	22	2	31	3	50	5
AD-2138197.1	14	1	17	1	24	2	AD-2138306.1	27	3	31	0	49	4
AD-2138560.1	13	2	17	0	23	3	AD-2138389.1	26	3	31	1	46	2
AD-2138656.1	13	1	17	0	25	3	AD-2138617.1	28	3	31	2	61	8
AD-2138443.1	11	2	17	2	37	6	AD-2138344.1	22	2	31	5	49	4
AD-2138528.1	12	1	18	1	26	4	AD-2138102.1	29	5	31	4	63	7
AD-2138744.1	11	0	18	3	28	3	AD-2138091.1	24	4	32	7	42	4
AD-2138813.2	15	2	18	1	29	2	AD-2138190.1	20	3	32	3	47	5
AD-2138718.1	14	2	18	1	30	5	AD-2138372.1	24	3	32	3	43	1
AD-2138789.2	11	1	18	6	34	3	AD-2138185.1	22	2	32	3	51	7
AD-2138043.1	13	1	18	2	28	8	AD-2138280.1	18	8	32	2	54	6
AD-2138794.2	15	1	18	1	38	1	AD-2138061.1	19	2	32	1	34	4
AD-2138210.1	14	0	18	5	29	2	AD-2138433.1	19	1	32	5	57	2

	10 nM Dose		1 nM Dose		0.1 nM Dose			10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**	**Duplex**	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**
AD-2138438.1	13	3	18	4	30	1	AD-2138288.1	24	3	32	4	44	2
AD-2138242.1	14	2	18	1	24	4	AD-2138285.1	21	3	32	1	45	3
AD-2138287.1	16	3	18	1	29	5	AD-2138484.1	23	2	32	2	47	4
AD-2138491.1	13	1	18	3	30	4	AD-2138154.1	19	2	32	2	56	3
AD-2138823.2	13	1	18	2	28	1	AD-2138098.1	20	1	33	3	40	5
AD-2138714.1	11	1	19	1	25	3	AD-2138214.1	22	4	33	3	57	4
AD-2138472.1	13	0	19	1	28	3	AD-2138141.1	24	5	33	3	47	2
AD-2138246.1	14	3	19	2	29	2	AD-2138512.1	35	2	33	2	51	5
AD-2138650.1	13	1	19	2	30	4	AD-2138396.1	28	5	33	4	46	4
AD-2138826.2	15	2	19	3	33	3	AD-2138060.1	28	3	33	1	49	0
AD-2138233.1	19	4	19	1	28	5	AD-2138179.1	26	3	33	2	50	8
AD-2138783.1	17	2	19	2	29	5	AD-2138678.1	31	3	33	3	57	2
AD-2138290.1	16	3	19	1	29	0	AD-2138251.1	22	4	33	2	60	6
AD-2138559.1	13	2	19	2	29	3	AD-2138063.1	20	2	33	2	40	3
AD-2138784.2	14	3	19	5	22	3	AD-2138301.1	22	3	33	4	43	5
AD-2138212.1	14	2	19	2	26	4	AD-2138392.1	24	1	33	2	46	3
AD-2138262.1	13	2	19	0	30	3	AD-2138376.1	21	2	34	2	44	5
AD-2138457.1	17	4	19	3	31	4	AD-2138114.1	21	2	34	5	49	2
AD-2138347.1	11	2	19	3	28	2	AD-2138087.1	29	5	35	4	37	2
AD-2138237.1	15	4	19	1	29	1	AD-2138339.1	24	3	35	7	50	5
AD-2138044.1	17	1	19	1	30	3	AD-2138215.1	22	3	35	3	59	4
AD-2138261.1	13	2	19	2	29	3	AD-2138403.1	29	4	35	1	63	0
AD-2138211.1	17	4	19	1	26	2	AD-2138111.1	21	2	35	3	47	6
AD-2138263.1	15	2	20	1	28	1	AD-2138125.1	26	4	35	1	41	5
AD-2138716.1	15	2	20	3	28	2	AD-2138439.1	29	2	35	7	53	7
AD-2138589.1	13	2	20	2	28	1	AD-2138591.1	26	3	35	4	53	10

	10 nM Dose		1 nM Dose		0.1 nM Dose			10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % mRNA Remaining	SD	Avg % mRNA Remaining	SD	Avg % mRNA Remaining	SD	Duplex	Avg % mRNA Remaining	SD	Avg % mRNA Remaining	SD	Avg % mRNA Remaining	SD
AD-2138086.1	11	1	20	4	30	7	AD-2138175.1	21	2	35	3	60	8
AD-2138793.2	13	2	20	3	33	6	AD-2138090.1	25	2	35	3	44	9
AD-2138055.1	14	2	20	2	24	1	AD-2138562.1	20	3	35	4	61	1
AD-2138459.1	14	1	20	3	29	5	AD-2138419.1	23	1	35	1	42	6
AD-2138712.1	14	2	20	1	27	5	AD-2138305.1	34	4	35	3	43	1
AD-2138085.1	13	3	20	1	35	2	AD-2138513.1	63	6	35	1	49	4
AD-2138762.1	16	2	20	2	38	3	AD-2138136.1	28	5	35	3	51	10
AD-2138441.1	17	3	20	1	25	2	AD-2138602.1	34	2	35	2	70	6
AD-2138309.1	18	2	20	2	30	3	AD-2138328.1	32	4	36	2	53	10
AD-2138401.1	14	3	20	1	29	4	AD-2138113.1	28	4	36	6	70	7
AD-2138357.1	13	1	20	2	31	1	AD-2138282.1	27	3	36	1	54	4
AD-2138238.1	17	2	20	2	34	3	AD-2138059.1	31	1	36	2	43	2
AD-2138047.1	15	1	21	3	29	3	AD-2138415.1	33	1	36	3	59	5
AD-2138465.1	12	1	21	1	37	4	AD-2138144.1	25	2	36	1	51	5
AD-2138821.2	17	3	21	1	29	4	AD-2138124.1	25	1	36	2	64	7
AD-2138397.1	18	1	21	2	30	2	AD-2138278.1	26	2	36	2	73	10
AD-2138705.1	14	2	21	1	31	2	AD-2138273.1	40	10	36	5	58	8
AD-2138447.1	14	3	22	1	26	4	AD-2138730.1	33	3	36	1	66	10
AD-2138437.1	15	1	22	3	29	5	AD-2138674.1	31	2	37	2	58	7
AD-2138406.1	16	2	23	4	30	2	AD-2138337.1	39	2	37	3	53	2
AD-2138348.1	23	6	23	1	26	1	AD-2138391.1	34	3	37	3	47	7
AD-2138289.1	19	1	24	2	30	3	AD-2138479.1	30	2	37	6	82	5
AD-2138451.1	16	1	24	0	27	2	AD-2138298.1	29	3	37	6	56	3
AD-2138255.1	17	1	25	1	30	3	AD-2138681.1	33	3	37	0	59	3
AD-2138435.1	15	2	27	5	30	2	AD-2138480.1	28	3	38	5	62	4
AD-2138079.1	13	0	27	0	29	3	AD-2138142.1	26	3	38	3	56	4

	10 nM Dose		1 nM Dose		0.1 nM Dose			10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % mRNA Remaining	SD	Avg % mRNA Remaining	SD	Avg % mRNA Remaining	SD	Duplex	Avg % mRNA Remaining	SD	Avg % mRNA Remaining	SD	Avg % mRNA Remaining	SD
AD-2138771.1	6	1	8	1	16	3	AD-2138507.1	41	6	38	2	72	5
AD-2138889.2	5	0	8	1	24	2	AD-2138608.1	28	0	38	1	77	3
AD-2138548.1	6	1	8	2	18	3	AD-2138575.1	33	4	39	3	69	2
AD-2138768.1	7	0	9	1	15	3	AD-2138374.1	30	1	40	4	55	4
AD-2138765.1	9	2	10	1	18	3	AD-2138432.1	32	3	40	3	59	9
AD-2138626.1	7	1	10	0	16	3	AD-2138217.1	32	6	40	2	59	3
AD-2138883.2	7	1	10	0	22	2	AD-2138057.1	44	5	40	3	55	4
AD-2138553.1	8	0	10	1	29	4	AD-2138612.1	44	2	40	1	80	6
AD-2138547.1	7	2	10	3	23	5	AD-2138365.1	41	6	41	3	57	6
AD-2138878.2	7	1	10	1	19	1	AD-2138835.2	28	2	41	6	79	12
AD-2138552.1	7	0	10	2	23	3	AD-2138901.2	31	3	41	1	60	2
AD-2138550.1	8	1	10	5	25	6	AD-2138291.1	37	4	41	2	51	3
AD-2138585.1	10	1	10	2	26	3	AD-2138335.1	35	4	41	4	54	1
AD-2138412.1	8	1	10	2	15	2	AD-2138665.1	38	2	41	6	66	18
AD-2138802.2	8	2	11	1	23	3	AD-2138338.1	30	1	42	5	57	3
AD-2138723.1	8	2	11	1	16	2	AD-2138180.1	35	1	42	1	49	10
AD-2138767.1	7	1	11	1	18	4	AD-2138062.1	30	3	42	3	44	7
AD-2138856.2	9	1	11	1	17	3	AD-2138363.1	34	5	42	8	66	9
AD-2138551.1	8	1	11	1	20	2	AD-2138729.1	40	1	42	3	63	8
AD-2138894.2	6	1	11	0	30	3	AD-2138314.1	37	3	43	4	62	1
AD-2138549.1	7	1	11	2	22	4	AD-2138319.1	31	3	43	2	60	2
AD-2138888.2	7	1	11	1	22	3	AD-2138166.1	38	4	43	1	73	5
AD-2138566.1	12	2	11	2	16	3	AD-2138042.1	46	5	44	4	46	3
AD-2138877.2	8	0	11	2	20	6	AD-2138685.1	30	7	44	1	57	5
AD-2138879.2	9	1	12	1	24	2	AD-2138272.1	45	6	44	9	63	8
AD-2138770.1	9	1	12	1	21	3	AD-2138239.1	39	3	44	4	72	2

	10 nM Dose		1 nM Dose		0.1 nM Dose			10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % mRNA Remaining	SD	Avg % mRNA Remaining	SD	Avg % mRNA Remaining	SD	Duplex	Avg % mRNA Remaining	SD	Avg % mRNA Remaining	SD	Avg % mRNA Remaining	SD
AD-2138544.1	7	1	12	3	20	2	AD-2138655.1	40	2	46	3	72	3
AD-2138520.1	7	0	12	1	25	5	AD-2138526.1	36	2	46	3	63	4
AD-2138890.2	7	1	12	0	25	1	AD-2138252.1	37	5	47	2	65	4
AD-2138839.2	9	1	12	2	21	1	AD-2138340.1	44	5	47	5	67	7
AD-2138764.1	9	1	12	2	24	4	AD-2138219.1	36	4	47	2	68	9
AD-2138584.1	9	1	12	0	27	6	AD-2138275.1	36	8	47	4	49	6
AD-2138751.1	11	2	12	1	23	5	AD-2138041.1	47	2	47	7	50	4
AD-2138885.2	8	1	12	1	23	3	AD-2138387.1	40	0	48	6	62	4
AD-2138540.1	7	1	12	1	34	6	AD-2138367.1	54	5	48	7	56	4
AD-2138521.1	9	1	12	1	36	6	AD-2138902.2	41	1	48	3	73	9
AD-2138880.2	10	1	12	0	23	5	AD-2138529.1	45	2	49	2	70	6
AD-2138886.2	8	1	12	1	22	2	AD-2138134.1	52	3	50	3	78	11
AD-2138881.2	10	1	12	2	27	3	AD-2138683.1	47	3	50	3	76	7
AD-2138518.1	10	1	13	4	24	4	AD-2138429.1	50	2	51	6	65	6
AD-2138557.1	9	2	13	1	24	2	AD-2138231.1	72	10	51	3	67	7
AD-2138623.1	10	1	13	1	25	5	AD-2138424.1	47	5	52	6	89	8
AD-2138545.1	8	0	13	2	19	4	AD-2138680.1	54	5	52	3	73	3
AD-2138858.2	13	1	13	1	28	1	AD-2138395.1	49	8	53	6	56	2
AD-2138490.1	11	1	13	1	21	3	AD-2138421.1	45	1	54	1	83	6
AD-2138724.1	9	0	13	1	25	3	AD-2138774.1	46	6	54	2	65	7
AD-2138866.2	9	2	13	0	27	1	AD-2138040.1	49	3	54	4	50	2
AD-2138586.1	10	1	13	1	33	7	AD-2138466.1	49	4	55	7	76	4
AD-2138614.1	11	3	13	2	19	2	AD-2138133.1	65	10	55	5	63	7
AD-2138625.1	11	1	13	1	25	2	AD-2138343.1	31	2	55	5	68	3
AD-2138229.1	8	1	13	2	22	2	AD-2138330.1	42	6	55	5	74	11
AD-2138841.2	10	0	13	1	26	1	AD-2138481.1	48	6	56	5	68	5

	10 nM Dose		1 nM Dose		0.1 nM Dose			10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % mRNA Remaining	SD	Avg % mRNA Remaining	SD	Avg % mRNA Remaining	SD	Duplex	Avg % mRNA Remaining	SD	Avg % mRNA Remaining	SD	Avg % mRNA Remaining	SD
AD-2138840.2	9	1	13	2	23	2	AD-2138733.1	56	4	57	3	71	7
AD-2138621.1	8	1	13	2	23	3	AD-2138380.1	77	3	57	6	70	4
AD-2138882.2	11	2	13	1	25	1	AD-2138119.1	53	11	58	4	65	7
AD-2138568.1	10	1	13	2	22	4	AD-2138334.1	72	9	58	8	73	5
AD-2138804.2	10	1	13	1	24	1	AD-2138329.1	48	2	58	2	71	6
AD-2138519.1	11	0	13	3	27	6	AD-2138342.1	54	1	59	6	80	7
AD-2138567.1	15	1	13	3	22	4	AD-2139124.2	60	11	59	4	68	3
AD-2138749.1	12	4	13	3	23	0	AD-2138675.1	57	12	60	5	75	4
AD-2138769.1	10	1	13	1	24	2	AD-2138676.1	55	5	60	6	76	3
AD-2138772.1	9	1	13	1	25	5	AD-2138597.1	56	7	60	5	83	7
AD-2138628.1	11	0	14	3	15	7	AD-2138297.1	53	8	60	6	69	5
AD-2138580.1	9	1	14	1	20	3	AD-2138331.1	48	2	60	2	73	2
AD-2138798.2	11	2	14	0	21	2	AD-2138593.1	55	5	60	3	79	7
AD-2138523.1	8	0	14	0	28	5	AD-2138667.1	59	3	61	7	86	4
AD-2138825.2	10	0	14	2	35	1	AD-2138909.2	64	4	61	4	70	4
AD-2138534.1	11	1	14	7	32	4	AD-2138600.1	63	2	61	10	71	4
AD-2138162.1	7	1	14	1	24	5	AD-2138483.1	56	3	62	5	74	6
AD-2138842.2	10	1	14	2	28	5	AD-2138409.1	59	4	62	4	78	7
AD-2138797.2	11	1	14	2	22	2	AD-2138295.1	67	6	62	4	74	4
AD-2138891.2	10	1	14	2	25	1	AD-2138684.1	56	5	63	2	101	18
AD-2138859.2	13	1	14	2	22	2	AD-2138276.1	64	10	63	6	71	7
AD-2138620.1	11	2	14	1	25	3	AD-2138493.1	66	6	63	2	83	6
AD-2138863.2	10	1	14	0	31	7	AD-2138908.2	63	6	63	8	64	7
AD-2138488.1	11	2	14	3	18	2	AD-2138336.1	73	6	63	17	70	7
AD-2138857.2	11	2	14	2	25	1	AD-2138332.1	65	2	63	17	75	3
AD-2138816.2	10	2	14	1	25	2	AD-2139018.2	72	6	64	4	76	1

	10 nM Dose		1 nM Dose		0.1 nM Dose			10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % mRNA Remaining	SD	Avg % mRNA Remaining	SD	Avg % mRNA Remaining	SD	Duplex	Avg % mRNA Remaining	SD	Avg % mRNA Remaining	SD	Avg % mRNA Remaining	SD
AD-2138747.1	9	1	14	1	23	4	AD-2139003.2	65	2	65	5	68	6
AD-2138638.1	12	2	14	0	26	7	AD-2139016.2	78	14	65	19	87	5
AD-2138867.2	10	0	14	1	29	2	AD-2138973.2	75	9	65	1	79	10
AD-2138228.1	13	3	15	1	19	2	AD-2138456.1	67	7	65	6	83	3
AD-2138616.1	12	1	15	1	25	3	AD-2139078.2	61	10	65	10	83	10
AD-2138164.1	9	1	15	2	25	2	AD-2139143.2	72	8	66	8	61	9
AD-2138696.1	10	1	15	2	31	5	AD-2138221.1	74	11	66	2	91	9
AD-2138475.1	12	1	15	4	38	8	AD-2139144.2	88	12	67	23	93	7
AD-2138414.1	12	0	15	1	26	6	AD-2139126.2	76	8	67	7	61	6
AD-2138838.2	10	0	15	1	27	1	AD-2138284.1	71	6	67	4	89	4
AD-2138640.1	14	2	15	3	29	6	AD-2138431.1	63	3	68	8	106	15
AD-2138887.2	12	1	15	1	22	4	AD-2138171.1	52	9	68	3	80	4
AD-2138773.1	14	2	15	1	25	4	AD-2138988.2	72	7	68	5	74	3
AD-2138440.1	10	2	15	2	39	16	AD-2138317.1	46	2	68	6	85	4
AD-2138897.2	11	0	15	2	30	2	AD-2138972.2	76	7	69	5	66	6
AD-2138486.1	10	1	15	3	22	3	AD-2139080.2	73	6	69	6	77	4
AD-2138855.2	12	2	15	2	23	3	AD-2138679.1	70	8	69	3	73	3
AD-2138833.2	9	1	15	2	28	4	AD-2139095.2	78	4	70	8	74	7
AD-2138884.2	11	0	15	1	29	2	AD-2138115.1	64	9	70	3	87	1
AD-2138822.2	14	2	15	1	32	3	AD-2138677.1	69	2	70	7	74	15
AD-2138497.1	11	1	15	2	27	8	AD-2139129.2	78	2	71	8	74	5
AD-2138569.1	12	1	15	1	26	3	AD-2139051.2	69	5	71	3	75	7
AD-2138165.1	11	2	15	1	29	1	AD-2139145.2	72	27	71	4	95	7
AD-2138072.1	10	0	15	2	22	4	AD-2139067.2	60	14	71	5	72	4
AD-2138487.1	12	2	15	3	26	8	AD-2138987.2	71	5	72	2	65	11
AD-2138836.2	10	1	15	3	27	5	AD-2138954.2	49	16	72	24	101	10

	10 nM Dose		1 nM Dose		0.1 nM Dose			10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % mRNA Remaining	SD	Avg % mRNA Remaining	SD	Avg % mRNA Remaining	SD	Duplex	Avg % mRNA Remaining	SD	Avg % mRNA Remaining	SD	Avg % mRNA Remaining	SD
AD-2138689.1	14	2	15	1	28	2	AD-2139035.2	64	8	72	5	73	7
AD-2138864.2	11	1	15	1	27	1	AD-2139094.2	71	5	72	4	77	10
AD-2138227.1	14	2	16	1	25	2	AD-2139111.2	73	4	72	5	72	2
AD-2138624.1	11	1	16	2	25	3	AD-2139019.2	77	5	72	10	78	3
AD-2138633.1	11	1	16	1	31	4	AD-2139034.2	63	4	73	7	71	11
AD-2138808.2	12	2	16	2	24	2	AD-2139032.2	77	6	73	2	74	7
AD-2138898.2	13	1	16	1	30	2	AD-2139128.2	56	16	73	1	76	8
AD-2138196.1	13	1	16	0	32	2	AD-2138956.2	78	11	73	6	79	6
AD-2138605.1	12	1	16	5	24	5	AD-2139140.2	81	9	73	8	53	13
AD-2138896.2	15	2	16	1	31	3	AD-2138390.1	75	7	73	1	77	4
AD-2138664.1	13	1	16	1	35	10	AD-2139081.2	76	10	73	9	75	9
AD-2138462.1	15	1	16	2	41	4	AD-2138599.1	65	7	73	1	78	1
AD-2138641.1	10	2	16	2	21	1	AD-2138941.2	52	12	73	2	79	1
AD-2138558.1	11	1	16	1	28	7	AD-2139079.2	86	3	73	13	85	8
AD-2138766.1	15	2	16	2	25	2	AD-2139113.2	91	3	73	6	88	2
AD-2138781.1	12	2	16	2	34	4	AD-2138913.2	71	5	74	11	72	6
AD-2138844.2	11	2	16	2	24	2	AD-2139064.2	72	7	74	9	79	5
AD-2138320.1	16	5	16	1	30	3	AD-2138903.2	76	6	75	6	83	1
AD-2138727.1	13	3	16	2	22	5	AD-2139092.2	80	14	75	5	72	6
AD-2138860.2	15	2	16	1	27	2	AD-2138971.2	74	13	75	10	85	13
AD-2138606.1	12	1	16	2	30	5	AD-2139110.2	66	5	75	7	78	6
AD-2138583.1	11	0	16	3	33	4	AD-2138957.2	82	4	76	2	79	7
AD-2138827.2	14	1	16	3	33	3	AD-2138905.2	67	6	76	9	85	8
AD-2138848.2	12	1	16	2	34	4	AD-2139142.2	61	6	76	8	65	7
AD-2138073.1	12	1	17	3	30	8	AD-2138906.2	70	3	76	3	73	11
AD-2138748.1	13	1	17	2	27	4	AD-2138911.2	74	6	76	4	80	3

	10 nM Dose		1 nM Dose		0.1 nM Dose			10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**	**Duplex**	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**
AD-2138581.1	13	1	17	1	32	4	AD-2138986.2	85	8	77	13	83	4
AD-2138556.1	11	2	17	3	33	6	AD-2139108.2	93	15	77	10	93	10
AD-2138622.1	12	2	17	1	21	1	AD-2139125.2	73	5	77	9	63	1
AD-2138795.2	14	2	17	3	26	2	AD-2139002.2	73	11	77	14	73	10
AD-2138811.2	15	1	17	3	29	2	AD-2139066.2	65	4	77	2	75	17
AD-2138579.1	12	1	17	2	30	5	AD-2139052.2	79	3	78	5	87	8
AD-2138496.1	14	1	17	2	27	4	AD-2138732.1	88	2	78	4	89	5
AD-2138582.1	12	2	17	4	29	4	AD-2138940.2	79	11	78	9	85	1
AD-2138546.1	10	1	17	3	32	5	AD-2139131.2	73	14	78	8	77	4
AD-2138607.1	14	2	17	2	33	11	AD-2139096.2	79	14	78	9	84	2
AD-2138070.1	13	1	17	4	21	1	AD-2139001.2	76	7	78	5	78	11
AD-2138627.1	14	1	17	0	25	5	AD-2138924.2	72	7	78	7	76	7
AD-2138809.2	15	2	17	1	26	4	AD-2138394.1	82	5	78	6	89	7
AD-2138385.1	13	1	17	1	28	5	AD-2138925.2	81	4	78	7	87	5
AD-2138722.1	11	1	17	3	30	5	AD-2138907.2	77	9	79	14	71	12
AD-2138845.2	11	1	17	4	28	2	AD-2139133.2	83	0	79	8	72	6
AD-2138383.1	15	3	17	2	29	3	AD-2139036.2	78	3	79	7	85	0
AD-2138498.1	14	1	17	2	29	2	AD-2138970.2	77	6	79	14	77	21
AD-2138865.2	10	1	17	3	31	3	AD-2139065.2	75	5	79	5	84	9
AD-2138824.2	11	0	17	1	39	5	AD-2138494.1	79	5	80	10	91	2
AD-2138725.1	15	1	17	3	27	5	AD-2138426.1	79	2	80	8	103	12
AD-2138524.1	12	1	17	2	31	3	AD-2139097.2	84	4	80	4	82	5
AD-2138508.1	13	1	17	1	36	4	AD-2139000.2	73	10	80	6	86	11
AD-2138495.1	10	1	17	2	23	3	AD-2138904.2	78	11	80	5	85	9
AD-2138750.1	17	4	17	2	24	6	AD-2139121.2	78	11	80	14	92	3
AD-2138690.1	12	2	17	3	26	2	AD-2139109.2	60	0	81	10	75	3

	10 nM Dose		1 nM Dose		0.1 nM Dose			10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % mRNA Remaining	SD	Avg % mRNA Remaining	SD	Avg % mRNA Remaining	SD	Duplex	Avg % mRNA Remaining	SD	Avg % mRNA Remaining	SD	Avg % mRNA Remaining	SD
AD-2138632.1	11	2	17	1	40	4	AD-2139146.2	87	1	81	2	90	3
AD-2138500.1	12	1	17	1	25	3	AD-2138327.1	83	7	81	6	86	15
AD-2138810.2	16	3	17	2	29	1	AD-2138974.2	74	3	81	8	86	4
AD-2138517.1	15	2	17	1	32	3	AD-2139050.2	70	8	81	9	81	6
AD-2138208.1	12	2	17	1	33	5	AD-2139053.2	84	2	81	5	86	4
AD-2138321.1	11	1	18	2	24	3	AD-2138371.1	79	4	81	8	83	4
AD-2138687.1	16	3	18	1	24	3	AD-2139141.2	84	9	81	12	74	12
AD-2138854.2	16	1	18	1	32	2	AD-2138926.2	92	2	82	5	94	8
AD-2138265.1	12	4	18	2	34	1	AD-2138989.2	84	11	82	3	94	8
AD-2138726.1	15	2	18	2	42	1	AD-2139130.2	78	7	82	9	81	5
AD-2138828.2	14	1	18	1	28	4	AD-2138428.1	91	11	82	19	95	5
AD-2138832.2	13	1	18	1	35	3	AD-2138375.1	75	13	82	8	84	7
AD-2138554.1	9	1	18	2	45	4	AD-2139099.2	84	0	83	8	84	4
AD-2138837.2	13	0	18	3	31	2	AD-2139049.2	83	11	83	4	76	7
AD-2138274.1	14	1	18	1	33	4	AD-2138975.2	84	6	83	5	76	5
AD-2138535.1	13	1	18	5	48	5	AD-2139101.2	85	1	83	8	79	12
AD-2138555.1	12	2	18	2	27	2	AD-2139147.2	66	18	83	9	86	3
AD-2138609.1	17	1	18	1	29	4	AD-2138915.2	83	6	83	5	96	7
AD-2138477.1	9	6	18	3	36	2	AD-2138977.2	90	3	83	3	94	2
AD-2138104.1	13	0	18	1	28	5	AD-2139103.2	87	3	84	4	90	3
AD-2138543.1	11	2	18	2	31	6	AD-2138293.1	60	1	84	27	76	2
AD-2138130.1	13	1	18	3	28	2	AD-2139135.2	84	9	84	5	88	4
AD-2138148.1	14	1	18	2	29	2	AD-2139017.2	82	5	84	5	88	4
AD-2138777.1	19	2	18	1	30	1	AD-2139098.2	86	6	84	3	92	9
AD-2138267.1	13	1	18	3	31	5	AD-2138938.2	63	25	84	11	68	20
AD-2138187.1	13	2	18	3	33	4	AD-2138985.2	95	2	84	4	85	12

	10 nM Dose		1 nM Dose		0.1 nM Dose			10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**	**Duplex**	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**
AD-2138163.1	11	2	19	2	25	4	AD-2139083.2	80	9	84	9	99	3
AD-2138161.1	9	3	19	1	33	4	AD-2138514.1	100	11	85	10	90	7
AD-2138796.2	15	1	19	3	30	2	AD-2139048.2	72	14	85	9	81	10
AD-2138654.1	15	2	19	0	32	4	AD-2139055.2	88	10	85	7	97	9
AD-2138266.1	12	1	19	3	36	4	AD-2139004.2	83	11	85	7	100	6
AD-2138407.1	11	0	19	3	28	2	AD-2138492.1	80	10	85	1	91	4
AD-2138807.2	13	1	19	2	28	3	AD-2138943.2	82	6	86	5	98	4
AD-2138226.1	16	3	19	1	29	11	AD-2139134.2	93	16	86	9	92	2
AD-2138577.1	16	1	19	0	36	6	AD-2138945.2	94	8	86	4	98	3
AD-2138843.2	12	1	19	1	37	3	AD-2139054.2	93	14	86	11	103	2
AD-2138588.1	12	2	19	2	43	7	AD-2138910.2	68	5	86	7	81	8
AD-2138323.1	15	2	19	1	27	2	AD-2139075.2	90	10	86	7	83	1
AD-2138830.2	14	1	19	2	27	6	AD-2138682.1	72	3	86	10	85	19
AD-2138576.1	14	1	19	2	30	5	AD-2139037.2	80	5	86	5	88	7
AD-2138895.2	13	2	19	1	39	3	AD-2139112.2	83	7	86	7	88	7
AD-2138454.1	15	1	19	2	40	6	AD-2138271.1	90	2	86	11	95	4
AD-2138474.1	11	1	19	3	42	3	AD-2139005.2	78	7	88	9	85	10
AD-2138618.1	15	1	19	2	30	5	AD-2139033.2	80	13	88	5	74	7
AD-2138206.1	11	0	19	1	30	5	AD-2138402.1	94	27	88	4	92	3
AD-2138522.1	11	0	19	2	50	7	AD-2138578.1	89	9	88	6	100	8
AD-2138812.2	13	1	19	3	29	1	AD-2138668.1	94	10	88	2	94	3
AD-2138506.1	11	1	19	2	40	7	AD-2139093.2	82	7	88	9	71	7
AD-2138862.2	15	1	19	1	29	2	AD-2139117.2	81	7	88	9	90	3
AD-2138145.1	10	0	19	3	30	2	AD-2139139.2	85	11	88	3	95	5
AD-2138468.1	14	3	19	4	33	5	AD-2138734.1	80	3	88	3	91	4
AD-2138183.1	17	3	19	3	35	7	AD-2138914.2	79	6	89	3	98	5

	10 nM Dose		1 nM Dose		0.1 nM Dose			10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**	**Duplex**	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**
AD-2138322.1	13	2	19	4	23	2	AD-2139089.2	93	6	89	13	89	10
AD-2138806.2	13	2	19	1	30	3	AD-2139118.2	93	4	89	11	108	7
AD-2138260.1	12	2	19	1	32	4	AD-2139115.2	87	1	89	3	73	11
AD-2138613.1	14	3	19	5	32	4	AD-2138933.2	110	5	89	9	110	9
AD-2138205.1	13	3	19	2	32	4	AD-2138922.2	94	9	89	22	84	17
AD-2138168.1	13	3	19	1	34	9	AD-2138270.1	80	3	89	7	91	9
AD-2138849.2	15	1	19	1	40	3	AD-2139105.2	88	11	89	5	91	11
AD-2138489.1	19	2	19	4	41	5	AD-2138420.1	89	6	89	11	93	16
AD-2138118.1	20	2	20	3	26	2	AD-2139155.2	77	21	89	13	94	11
AD-2138160.1	10	2	20	2	28	1	AD-2139132.2	90	12	90	7	85	13
AD-2138636.1	15	1	20	3	42	6	AD-2139123.2	77	10	90	11	98	14
AD-2138565.1	15	1	20	2	25	2	AD-2139061.2	81	13	90	17	96	4
AD-2138460.1	16	2	20	4	31	3	AD-2139008.2	95	6	90	9	108	6
AD-2138155.1	13	3	20	1	32	2	AD-2138912.2	82	7	90	4	79	3
AD-2138502.1	15	1	20	5	34	7	AD-2138927.2	93	0	91	6	97	7
AD-2138202.1	13	3	20	1	39	4	AD-2138955.2	82	9	91	10	86	4
AD-2138853.2	15	1	20	1	27	3	AD-2139020.2	85	3	91	5	86	6
AD-2138469.1	15	1	20	3	33	5	AD-2138949.2	103	6	91	5	104	2
AD-2138775.1	6	0	20	2	33	3	AD-2139013.2	93	1	91	6	107	6
AD-2138834.2	14	1	20	1	35	2	AD-2139137.2	86	6	91	7	102	6
AD-2138779.1	13	2	20	2	26	1	AD-2138920.2	88	12	91	10	99	8
AD-2138172.1	12	1	20	2	34	5	AD-2139069.2	81	15	91	2	90	9
AD-2138132.1	20	4	20	1	34	5	AD-2139063.2	86	8	91	4	101	3
AD-2138355.1	14	1	20	1	36	3	AD-2139149.2	85	20	91	10	87	6
AD-2138129.1	11	2	20	3	37	9	AD-2139006.2	101	11	91	9	91	8
AD-2138361.1	12	4	20	1	31	1	AD-2139044.2	103	12	92	14	109	4

	10 nM Dose		1 nM Dose		0.1 nM Dose			10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**	**Duplex**	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**
AD-2138666.1	17	3	20	2	35	7	AD-2138944.2	94	10	92	9	91	3
AD-2138471.1	15	2	20	3	39	2	AD-2138921.2	94	15	92	2	104	1
AD-2138088.1	17	1	20	2	29	2	AD-2139151.2	95	17	92	9	102	4
AD-2138304.1	18	2	20	1	31	1	AD-2138423.1	79	3	92	3	93	9
AD-2138253.1	13	1	20	1	31	2	AD-2138218.1	88	9	92	5	95	10
AD-2138850.2	16	2	20	0	34	3	AD-2139021.2	86	4	93	5	89	5
AD-2138245.1	15	1	20	0	38	1	AD-2138978.2	97	7	93	6	106	7
AD-2138225.1	14	3	20	2	28	1	AD-2139119.2	84	11	93	9	87	7
AD-2138369.1	16	4	20	4	33	2	AD-2138963.2	84	4	93	6	105	5
AD-2138470.1	17	1	20	6	33	4	AD-2138918.2	95	15	93	10	112	1
AD-2138509.1	16	2	20	3	52	2	AD-2138990.2	82	5	93	8	94	3
AD-2138563.1	17	3	20	1	29	6	AD-2138923.2	95	12	93	11	98	5
AD-2138117.1	19	3	20	4	31	7	AD-2139007.2	90	13	93	7	94	19
AD-2138831.2	16	3	20	3	39	4	AD-2139087.2	91	14	93	5	100	6
AD-2138847.2	15	1	20	1	69	2	AD-2139116.2	99	8	93	17	104	12
AD-2138178.1	17	1	21	2	25	5	AD-2138939.2	94	7	94	2	92	4
AD-2138587.1	15	2	21	2	31	5	AD-2138673.1	89	3	94	1	95	10
AD-2138089.1	18	5	21	1	35	4	AD-2139068.2	85	2	94	6	96	6
AD-2138080.1	14	2	21	3	37	3	AD-2138917.2	92	6	94	8	90	2
AD-2138501.1	14	5	21	8	22	0	AD-2138388.1	109	14	94	1	91	10
AD-2138353.1	13	3	21	4	31	2	AD-2138220.1	90	8	94	6	101	13
AD-2138169.1	13	2	21	2	40	3	AD-2138953.2	90	4	94	11	100	3
AD-2138485.1	14	2	21	1	35	7	AD-2139038.2	85	3	94	4	94	8
AD-2138254.1	12	4	21	3	31	5	AD-2139023.2	94	5	94	5	95	3
AD-2138467.1	15	2	21	5	34	3	AD-2138919.2	94	4	94	13	98	4
AD-2138458.1	15	1	21	4	41	10	AD-2138947.2	88	10	94	6	92	5

	10 nM Dose		1 nM Dose		0.1 nM Dose			10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**	**Duplex**	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**
AD-2138570.1	16	2	21	1	51	12	AD-2139100.2	87	4	94	7	96	7
AD-2138181.1	15	1	21	2	25	3	AD-2138952.2	98	5	94	4	97	9
AD-2138434.1	15	1	21	2	33	4	AD-2139045.2	91	3	95	5	90	6
AD-2138851.2	18	2	21	1	34	2	AD-2139082.2	97	13	95	2	99	3
AD-2138213.1	14	1	21	3	38	5	AD-2139057.2	95	3	95	7	100	2
AD-2138199.1	14	3	21	2	39	6	AD-2139062.2	86	12	95	2	102	8
AD-2138279.1	16	2	21	2	42	2	AD-2139030.2	96	8	95	5	102	7
AD-2138105.1	14	1	21	4	24	4	AD-2138378.1	88	7	95	6	101	10
AD-2138240.1	17	0	21	1	37	3	AD-2139047.2	92	7	95	4	103	4
AD-2138604.1	15	1	21	2	55	5	AD-2138969.2	92	9	96	3	97	4
AD-2138103.1	18	2	21	2	34	6	AD-2138929.2	95	3	96	4	97	7
AD-2138530.1	18	3	21	3	38	9	AD-2138592.1	99	3	96	3	112	3
AD-2138236.1	16	3	21	1	39	7	AD-2138916.2	98	11	96	5	104	5
AD-2138776.1	16	2	21	2	29	5	AD-2139027.2	97	5	96	12	107	3
AD-2138686.1	18	1	21	0	31	6	AD-2139114.2	93	7	96	5	97	6
AD-2138151.1	13	2	21	2	32	3	AD-2138979.2	85	6	96	10	116	16
AD-2138116.1	17	1	22	4	28	2	AD-2139104.2	92	9	97	4	99	12
AD-2138852.2	18	1	22	2	32	2	AD-2138561.1	95	6	97	3	99	3
AD-2138672.1	21	3	22	2	41	6	AD-2138408.1	100	8	97	9	95	2
AD-2138829.2	14	1	22	3	42	3	AD-2138935.2	91	8	97	16	94	8
AD-2138127.1	13	2	22	2	32	8	AD-2139148.2	95	14	97	7	97	5
AD-2138698.1	19	3	22	4	59	5	AD-2139106.2	89	13	97	3	99	4
AD-2138150.1	17	2	22	1	34	8	AD-2139076.2	93	12	97	4	102	3
AD-2138234.1	19	3	22	1	36	5	AD-2138422.1	79	8	97	7	100	2
AD-2138800.2	17	1	22	3	36	3	AD-2139071.2	82	10	97	5	104	3
AD-2138184.1	18	1	22	2	37	5	AD-2138418.1	101	11	98	9	86	13

	10 nM Dose		1 nM Dose		0.1 nM Dose			10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**	**Duplex**	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**
AD-2138373.1	11	1	22	4	26	2	AD-2138994.2	98	7	98	4	97	15
AD-2138110.1	15	1	22	2	34	4	AD-2139039.2	83	11	98	3	97	3
AD-2138416.1	18	3	22	2	37	4	AD-2138992.2	95	6	98	5	107	4
AD-2138611.1	18	2	22	2	25	6	AD-2138958.2	92	9	98	2	96	6
AD-2138446.1	15	2	22	2	32	3	AD-2138942.2	87	2	98	12	99	7
AD-2138173.1	14	2	22	1	35	8	AD-2139107.2	92	7	98	11	93	6
AD-2138123.1	14	2	22	3	37	8	AD-2138964.2	106	9	98	9	108	11
AD-2138499.1	16	3	22	6	39	5	AD-2139091.2	80	2	98	8	86	5
AD-2138619.1	17	2	22	1	59	13	AD-2138931.2	98	5	99	5	101	3
AD-2138249.1	16	3	22	3	43	3	AD-2138976.2	95	7	99	1	99	8
AD-2138268.1	13	1	22	1	44	4	AD-2139070.2	96	8	99	10	99	8
AD-2138639.1	17	2	22	3	29	3	AD-2138410.1	109	1	99	1	106	10
AD-2138223.1	17	3	22	4	29	1	AD-2138962.2	95	9	99	8	116	4
AD-2138702.1	12	1	22	5	39	6	AD-2139056.2	96	10	99	12	109	7
AD-2138516.1	17	2	22	3	29	2	AD-2138998.2	107	4	99	3	103	9
AD-2138398.1	24	5	22	3	32	4	AD-2138948.2	96	7	100	2	103	11
AD-2138204.1	15	2	22	2	35	3	AD-2139059.2	95	8	100	13	99	6
AD-2138510.1	16	2	22	3	38	5	AD-2139090.2	95	16	100	8	108	11
AD-2138648.1	17	1	22	2	42	3	AD-2138961.2	98	11	100	3	92	12
AD-2138814.2	17	2	22	3	33	5	AD-2138937.2	100	10	100	3	100	4
AD-2138250.1	14	3	22	2	38	3	AD-2139138.2	99	11	100	10	119	11
AD-2138358.1	18	3	22	4	44	10	AD-2139041.2	89	19	100	6	94	3
AD-2138232.1	18	4	23	1	40	4	AD-2139012.2	99	2	101	4	103	4
AD-2138128.1	12	2	23	1	29	0	AD-2138928.2	92	12	101	10	109	3
AD-2138527.1	15	2	23	3	43	7	AD-2139043.2	96	5	101	8	98	5
AD-2138258.1	17	2	23	2	44	8	AD-2138984.2	101	4	101	5	106	4

	10 nM Dose		1 nM Dose		0.1 nM Dose			10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % mRNA Remaining	SD	Avg % mRNA Remaining	SD	Avg % mRNA Remaining	SD	Duplex	Avg % mRNA Remaining	SD	Avg % mRNA Remaining	SD	Avg % mRNA Remaining	SD
AD-2138068.1	16	3	23	3	29	3	AD-2139022.2	102	9	101	3	110	4
AD-2138564.1	22	4	23	1	32	3	AD-2139136.2	96	10	101	9	100	4
AD-2138149.1	19	2	23	1	37	2	AD-2139029.2	90	5	101	2	94	7
AD-2138106.1	14	1	23	4	40	7	AD-2139077.2	93	16	101	3	107	2
AD-2138669.1	19	4	23	0	40	9	AD-2138965.2	95	5	101	4	102	10
AD-2138346.1	14	3	23	2	41	2	AD-2138932.2	111	9	101	2	108	10
AD-2138719.1	17	4	23	2	43	4	AD-2138967.2	100	7	102	9	102	1
AD-2138193.1	15	2	23	2	46	7	AD-2138950.2	92	23	102	11	114	3
AD-2138099.1	14	1	23	2	33	5	AD-2138996.2	95	1	102	0	98	12
AD-2138313.1	18	3	23	1	34	5	AD-2138982.2	94	7	102	7	101	3
AD-2138159.1	14	2	23	2	47	6	AD-2139015.2	99	4	102	4	101	9
AD-2138671.1	20	3	23	1	35	6	AD-2138930.2	99	14	102	2	108	6
AD-2138366.1	21	3	23	3	41	2	AD-2138951.2	99	10	102	7	97	7
AD-2138156.1	16	1	23	2	41	7	AD-2138966.2	91	8	102	12	112	6
AD-2138780.1	18	2	23	2	49	5	AD-2139073.2	88	4	103	5	97	8
AD-2138053.1	14	1	23	3	34	4	AD-2139028.2	102	10	103	5	111	2
AD-2138324.1	17	3	23	4	34	1	AD-2139014.2	96	6	103	11	97	2
AD-2138381.1	17	3	23	2	36	6	AD-2138999.2	106	4	103	7	112	2
AD-2138071.1	20	3	23	3	29	3	AD-2139060.2	98	13	103	10	103	5
AD-2138610.1	17	1	23	3	43	3	AD-2139074.2	101	12	103	6	109	4
AD-2138158.1	12	2	24	3	32	3	AD-2139084.2	98	9	103	6	113	4
AD-2138054.1	15	1	24	3	43	8	AD-2139009.2	94	9	103	8	105	8
AD-2138819.2	17	1	24	1	48	3	AD-2138425.1	113	8	104	8	106	16
AD-2138473.1	18	1	24	2	53	1	AD-2139150.2	103	4	104	3	108	4
AD-2138386.1	16	2	24	3	34	2	AD-2139120.2	100	14	104	1	109	10
AD-2138269.1	14	2	24	2	35	3	AD-2139085.2	100	10	104	5	96	5

	10 nM Dose		1 nM Dose		0.1 nM Dose			10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**	**Duplex**	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**
AD-2138820.2	17	1	24	1	39	5	AD-2139040.2	87	12	104	5	99	3
AD-2138405.1	17	1	24	2	43	1	AD-2139122.2	102	18	104	10	100	7
AD-2138899.2	18	1	24	3	43	2	AD-2139025.2	102	10	104	6	104	6
AD-2138352.1	17	3	24	3	43	6	AD-2139102.2	91	8	104	6	102	7
AD-2138603.1	18	1	24	3	51	2	AD-2139153.2	101	14	105	6	108	4
AD-2138247.1	18	3	24	2	52	8	AD-2138991.2	97	11	105	8	111	4
AD-2138069.1	16	2	24	3	29	2	AD-2138296.1	113	20	105	7	107	7
AD-2138048.1	14	2	24	4	34	3	AD-2138981.2	105	4	105	2	100	15
AD-2138126.1	15	1	24	5	35	2	AD-2138983.2	92	8	106	4	104	9
AD-2138147.1	16	1	24	4	41	5	AD-2139024.2	100	4	106	4	105	12
AD-2138778.1	14	1	24	2	48	4	AD-2139058.2	108	8	106	3	113	4
AD-2138191.1	20	5	24	2	35	2	AD-2139026.2	105	14	106	6	107	7
AD-2138574.1	18	3	24	4	36	10	AD-2138934.2	100	12	106	6	92	4
AD-2138900.2	21	1	24	0	49	8	AD-2138968.2	102	11	106	9	103	8
AD-2138107.1	16	6	24	4	35	6	AD-2139042.2	95	4	106	13	104	11
AD-2138316.1	16	3	24	1	39	6	AD-2139072.2	94	11	106	11	107	11
AD-2138207.1	19	4	24	2	43	1	AD-2138959.2	98	10	107	5	99	2
AD-2138573.1	13	2	24	2	39	4	AD-2138936.2	97	5	107	6	102	10
AD-2138045.1	20	1	24	3	34	2	AD-2139046.2	99	4	107	6	103	2
AD-2138413.1	22	3	24	1	35	7	AD-2138997.2	97	5	108	9	99	11
AD-2138192.1	13	2	25	1	30	4	AD-2138993.2	99	4	108	6	106	8
AD-2138176.1	16	2	25	2	35	4	AD-2139011.2	96	3	108	5	91	5
AD-2138861.2	20	2	25	1	70	4	AD-2138946.2	89	7	108	10	95	2
AD-2138157.1	16	2	25	2	30	2	AD-2138960.2	98	5	108	6	111	2
AD-2138049.1	16	2	25	4	34	2	AD-2138995.2	104	7	108	8	111	8
AD-2138170.1	14	2	25	5	37	5	AD-2139152.2	116	15	110	15	104	11

	10 nM Dose		1 nM Dose		0.1 nM Dose			10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**	**Duplex**	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**	**Avg % mRNA Remaining**	**SD**
AD-2138359.1	13	1	25	1	39	4	AD-2138980.2	101	18	110	7	97	9
AD-2138182.1	18	2	25	1	43	4	AD-2139031.2	103	4	115	3	105	4
AD-2138594.1	16	1	25	2	44	2	AD-2139154.2	109	25	116	2	111	7
AD-2138093.1	18	4	25	4	34	5	AD-2139088.2	101	2	116	14	113	3
AD-2138657.1	23	4	25	1	36	0	AD-2139086.2	94	16	117	18	108	7
AD-2138384.1	21	4	25	2	38	3	AD-2139010.2	101	8	126	35	96	8

TABLE 12A. PCH Free Uptake Log Concentration

		AD-2315874.2		AD-2315875.2		AD-2315876.2		AD-2315877.2		AD-2315878.2		AD-2315879.2		AD-2315880.2	
siRNA Conc.(nM)	Log Conc.	%Message Remaining	SD	%Message Remaining	SD	% Message Remaining	SD	%Message Remaining	SD	% Message Remaining	SD	% Message Remaining	SD	% Message Remaining	SD
250	2	11	1	19	2	11	2	19	2	16	1	40	4	27	3
25	1	18	3	25	3	16	1	31	4	26	4	52	8	39	1
2.5	0	44	5	45	2	41	2	51	0	49	4	72	12	68	3
0.25	-1	76	5	79	6	75	6	83	11	77	6	87	12	90	6
0.025	-2	91	8	90	8	92	8	83	12	87	10	96	6	87	8
0.0025	-3	90	8	84	4	88	4	71	7	68	1	84	12	92	9
0.00025	-4	98	8	93	4	93	5	74	5	77	8	87	11	98	10
0.000025	-5	98	8	101	7	99	7	94	2	88	12	96	9	102	14
0.0000025	-6	99	1	102	10	99	13	95	9	95	11	101	8	91	7
0.00000025	-7	104	5	98	10	107	6	97	6	95	5	98	4	102	3
		AD-2315881.2		AD-2315882.2		AD-2315883.2		AD-2315884.2		AD-2315885.2		AD-2315886.2		AD-2315887.2	
siRNA Conc.(nM)	Log Conc.	% Message Remaining	SD	% Message Remaining	SD	% Message Remaining	SD	% Message Remaining	SD	% Message Remaining	SD	% Message Remaining	SD	% Message Remaining	SD
250	2	49	2	30	3	36	5	28	4	18	1	29	0?	37	5
25	1	55	5	39	2	44	5	35	6	25	2	42	5	46	6
2.5	0	65	15	62	7	68	10	56	7	44	6	64	12	68	2
0.25	-1	84	13	78	2	80	3	73	9	69	9	81	12	82	8
0.025	-2	83	11	86	9	87	7	71	10	82	4	84	4	83	9
0.0025	-3	79	3	77	11	77	11	64	2	64	0	73	7	81	9
0.00025	-4	85	9	84	6	86	16	67	3	70	6	82	7	91	7
0.000025	-5	87	7	84	4	90	8	85	5	83	6	88	9	85	8
0.0000025	-6	95	4	96	5	97	8	90	10	97	14	95	17	94	15
0.00000025	-7	95	7	89	2	87	6	89	6	96	15	96	13	93	5

TABLE 12B. PHH Free Uptake Log Concentration

		AD-2315874.2		AD-2315875.2		AD-2315876.2		AD-2315877.2		AD-2315878.2		AD-2315879.2		AD-2315880.2	
siRNA Conc.(nM)	Log Conc.	% Message Remaining	SD	% Message Remaining	SD	% Message Remaining	SD	% Message Remaining	SD	% Message Remaining	SD	% Message Remaining	SD	% Message Remaining	SD
250	2	6	2	12	2	8	1	8	2	8	0	36	4	19	3
25	1	16	2	19	3	21	2	18	2	24	1	59	5	38	2
2.5	0	35	8	49	7	49	10	51	3	63	6	86	1	77	9
0.25	-1	88	15	79	7	91	7	89	6	95	4	112	8	105	5
0.025	-2	106	6	95	7	99	10	115	10	109	11	119	6	116	9
0.0025	-3	102	15	102	15	113	7	117	8	115	8	117	9	122	5
0.00025	-4	96	5	94	9	97	12	119	16	111	7	123	10	124	1
0.000025	-5	94	1	99	12	93	18	115	14	111	7	120	9	118	2
0.0000025	-6	87	7	93	5	92	13	115	8	105	15	109	11	122	9
0.00000025	-7	95	4	110	16	109	10	113	3	120	7	121	8	122	11
		AD-2315881.2		AD-2315882.2		AD-2315883.2		AD-2315884.2		AD-2315885.2		AD-2315886.2		AD-2315887.2	
siRNA Conc.(nM)	Log Conc.	% Message Remaining	SD	% Message Remaining	SD	% Message Remaining	SD	% Message Remaining	SD	% Message Remaining	SD	% Message Remaining	SD	% Message Remaining	SD
250	2	35	4	26	4	24	3	15	2	16	2	17	3	21	2
25	1	60	8	47	4	50	3	38	7	38	8	36	10	48	1
2.5	0	84	7	83	8	81	9	79	8	78	13	81	7	83	15
0.25	-1	101	14	100	6	115	6	109	5	96	18	116	7	108	15
0.025	-2	89	12	118	3	118	5	126	7	119	6	120	13	120	7
0.0025	-3	117	13	108	20	119	6	116	8	114	8	112	17	121	10
0.00025	-4	97	18	99	8	101	16	130	8	113	11	113	9	124	9
0.000025	-5	93	3	101	14	105	18	131	16	121	11	124	8	132	13
0.0000025	-6	99	6	105	12	103	5	127	7	116	11	128	10	133	16
0.00000025	-7	103	17	98	21	118	6	118	18	116	16	121	15	131	3

TABLE 12C. PHH Transfection Log Concentration

		AD-2315874.2		AD-2315875.2		AD-2315876.2		AD-2315877.2		AD-2315878.2		AD-2315879.2		AD-2315880.2	
siRNA Conc.(nM)	Log Conc.	% Message Remaining	SD	% Message Remaining	SD	% Message Remaining	SD	% Message Remaining	SD	% Message Remaining	SD	% Message Remaining	SD	% Message Remaining	SD
10	1	12	2	14	4	14	3	20	4	18	4	26	4	21	2
1	0	19	3	19	6	16	4	26	3	17	2	38	8	29	6
0.1	-1	31	2	38	7	33	8	38	6	41	7	71	17	46	10
0.01	-2	89	26	83	22	77	10	76	13	98	22	124	9	127	32
0.001	-3	117	26	125	30	105	40	117	27	132	9	119	27	135	7
0.0001	-4	107	26	82	13	120	20	107	19	110	25	112	11	123	21
0.00001	-5	126	32	112	33	108	41	127	31	107	15	150	12	108	28
0.000001	-6	96	4	121	19	98	22	135	23	128	15	141	16	121	18
0.0000001	-7	85	14	93	17	114	11	132	21	103	23	99	8	92	17
0.00000001	-8	83	9	106	20	100	17	118	25	119	15	112	22	144	11
		AD-2315881.2		AD-2315882.2		AD-2315883.2		AD-2315884.2		AD-2315885.2		AD-2315886.2		AD-2315887.2	
siRNA Conc.(nM)	Log Conc.	% Message Remaining	SD	% Message Remaining	SD	% Message Remaining	SD	% Message Remaining	SD	% Message Remaining	SD	% Message Remaining	SD	% Message Remaining	SD
10	1	25	4	16	1	21	2	22	3	18	2	17	2	20	1
1	0	31	8	19	3	29	3	22	4	19	1	25	4	23	2
0.1	-1	58	12	42	6	55	8	48	6	42	5	44	5	47	13
0.01	-2	87	21	80	5	94	15	92	5	87	11	91	11	89	13
0.001	-3	100	21	97	16	102	11	104	20	110	9	104	19	95	17
0.0001	-4	89	17	89	22	112	15	116	9	104	22	103	16	105	15
0.00001	-5	98	23	118	2	107	9	115	11	115	6	109	17	102	22
0.000001	-6	84	21	85	22	107	6	115	19	111	16	100	16	105	14
0.0000001	-7	93	12	105	7	102	13	121	8	111	7	110	8	106	26
0.00000001	-8	103	4	100	10	104	13	110	6	109	10	108	9	122	11

TABLE 13. LogIC50 for PCH Free Uptake, PHH Free Uptake, and PHH Transfection

Duplex ID	PCH Free Uptake LogIC50	PHH Free Uptake LogIC50	PHH Transfection LogIC50
AD-2315874.2	-0.2573	-0.2817	-1.455
AD-2315875.2	-0.3135	-0.1777	-1.482
AD-2315876.2	-0.3371	-0.0897	-1.657
AD-2315877.2	0.0306	-0.2479	-1.906
AD-2315878.2	0.0065	0.1145	-1.419
AD-2315879.2	0.3894	0.4763	-1.059
AD-2315880.2	0.3065	0.2611	-1.098
AD-2315881.2	19.7000	0.9393	-1.039
AD-2315882.2	0.2335	0.5559	-1.386
AD-2315883.2	0.3199	0.5153	-1.179
AD-2315884.2	30.6600	0.3130	-1.439
AD-2315885.2	27.5500	0.4254	-1.474
AD-2315886.2	18.1700	0.2900	-1.361
AD-2315887.2	0.4277	0.7792	-1.365

Example 3. *In vivo* Single Dose Study in PXB mice

PXB mice having a humanized liver were administered a single dose, 0.5mg/kg, of selected dsRNA duplexes. The baseline level of plasma human PLG was used as the control. Blood was obtained by retro-orbital bleed and plasma was tested by ELISA (Abcam, Human PLG ELISA ab108893) for human PLG levels at various time points after administration. The results in FIG. 2 are presented as percent plasma PLG remaining relative to the baseline (pre-dose) control.

PBX mice were administered an exemplary siRNA duplex, AD-2315878, at either 1 mg/kg or 3 mg/kg subcutaneous in a single dose at day 0. Blood was obtained and plasma hPLG levels were determined at days 0, 7, and 14 as described above. The results in FIG. 3 are presented as percent plasma PLG remaining relative to the baseline (pre-dose) control.

PBX mice were administered exemplary siRNA duplexes AD-2137018 or AD-2136718 at 0.3 mg/kg, 1 mg/kg, or 3 mg/kg subcutaneous in a single dose at day 0. Blood was obtained and plasma hPLG levels were determined at days 0, 7, 14, 21, 28, 35, 42, 49, 57, and 63 as described above. The percent plasma PLB remaining was determined. The results for AD-2137018 are presented in FIG. 4 and the results for AD-2136718 are presented in FIG. 5.

PLG Sequences

SEQ ID NO:1
>NM_000301.5 Homo sapiens plasminogen (PLG), transcript variant 1, mRNA

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SEQ ID NO:2
>Reverse complement of SEQ ID NO:1

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SEQ ID NO: 3
>NM_001168338.1 Homo sapiens plasminogen (PLG), transcript variant 2, mRNA
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>Reverse complement of SEQ ID NO:3
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SEQ ID NO: 685
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SEQ ID NO: 686
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SEQ ID NO: 687
>NM_008877.3 Mus musculus plasminogen (Plg), mRNA
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SEQ ID NO: 688

>Reverse complement of SEQ ID NO:687

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SEQ ID NO: 689
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SEQ ID NO: 690
>Reverse complement of SEQ ID NO:689
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We claim:

1. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of plasminogen (PLG) in a cell, wherein said dsRNA agent comprises 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 PLG which comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense sequences listed in any one of Tables 3, 4, 5, 6, 7, 8A, or 8B.

2. The dsRNA agent of claim 1, wherein said dsRNA agent comprises at least one modified nucleotide.

3. The dsRNA agent of claim 1 or 2, wherein substantially all of the nucleotides of the sense strand comprise a modification.

4. The dsRNA agent of claim 1 or 2, wherein substantially all of the nucleotides of the antisense strand comprise a modification.

5. The dsRNA agent of claim 1 or 2, wherein substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand comprise a modification.

6. The dsRNA agent of any one of claims 1-5, wherein the antisense strand is chosen from the antisense strands of AD-2315878 (SEQ ID NO:1291), AD-2315874 (SEQ ID NO:1287), or AD-2315875 (SEQ ID NO:1288).

7. The dsRNA agent of any one of claims 1-6, wherein the sense strand is chosen from the sense strands of AD-2315878 (SEQ ID NO:1277), AD-2315874 (SEQ ID NO:1273), or AD-2315875 (SEQ ID NO:1274).

8. The dsRNA of any one of claims 1-7, wherein the dsRNA agent is AD-2315878, AD-2315874, or AD-2315875.

9. A double stranded RNA (dsRNA) agent for inhibiting expression of plasminogen (PLG) in a cell, wherein the double stranded RNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the sense sequences listed in any one of Tables 3, 4, 5, 6, 7, 8A, or 8B and the

antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense sequences listed in any one of Tables 3, 4, 5, 6, 7, 8A, or 8B,

wherein substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand are modified nucleotides, and

wherein the sense strand is conjugated to a ligand attached at the 3'-terminus.

10. The dsRNA agent of claim 9, wherein all of the nucleotides of the sense strand comprise a modification.

11. The dsRNA agent of claim 9, wherein all of the nucleotides of the antisense strand comprise a modification.

12. The dsRNA agent of claim 9, wherein all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand comprise a modification.

13. The dsRNA agent of any one of claims 2-12, wherein 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.

14. The dsRNA agent of claim 13, wherein the nucleotide modifications are 2'-O-methyl and/or 2'-fluoro modifications.

15. The dsRNA agent of any one of claims 1-14, wherein the region of complementarity is at least 17 nucleotides in length.

16. The dsRNA agent of any one of claims 1-15, wherein the region of complementarity is 19 to 30 nucleotides in length.

17. The dsRNA agent of claim 16, wherein the region of complementarity is 19-25 nucleotides in length.

18. The dsRNA agent of claim 17, wherein the region of complementarity is 21 to 23 nucleotides in length.

19. The dsRNA agent of any one of claims 1-18, wherein each strand is independently no more than 30 nucleotides in length.

20. The dsRNA agent of any one of claims 1-19, wherein each strand is independently 19-30 nucleotides in length.

21. The dsRNA agent of claim 20, wherein each strand is independently 19-25 nucleotides in length.

22. The dsRNA agent of claim 20, wherein each strand is independently 21-23 nucleotides in length.

23. The dsRNA agent of any one of claims 1-22, wherein at least one strand comprises a 3' overhang of at least 1 nucleotide.

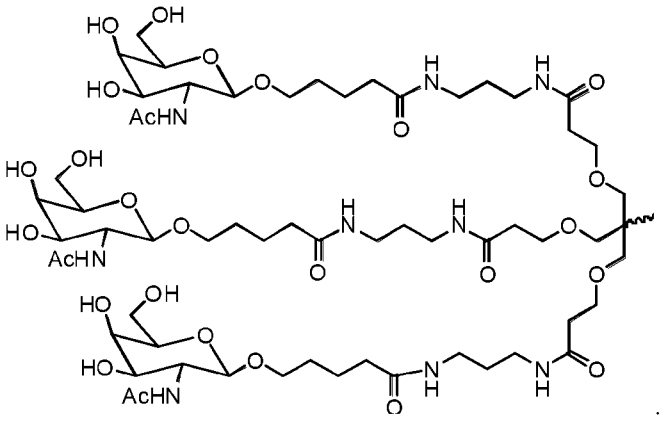
24. The dsRNA agent of claim 23, wherein at least one strand comprises a 3' overhang of at least 2 nucleotides.

25. The dsRNA agent of any one of claims 1-8 or 13-24 further comprising a ligand.

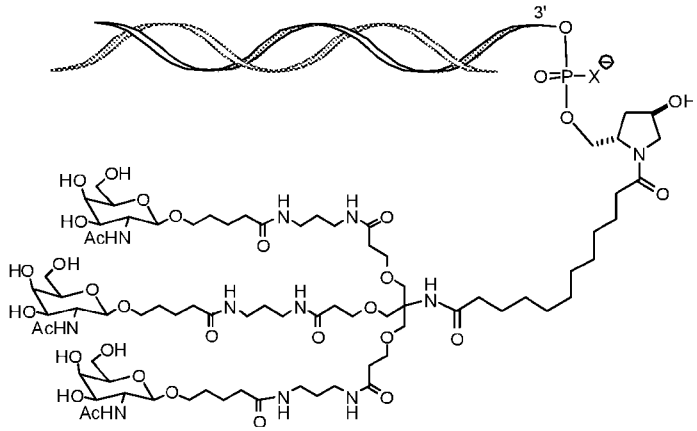
26. The dsRNA agent of claim 25, wherein the ligand is conjugated to the 3' end of the sense strand of the dsRNA agent.

27. The dsRNA agent of claim 9 or 26, wherein the ligand is an N-acetylgalactosamine (GalNAc) derivative.

28. The dsRNA agent of claim 27, wherein the ligand is



29. The dsRNA agent of claim 28, wherein the dsRNA agent is conjugated to the ligand as shown in the following schematic



and, wherein X is O or S.

30. The dsRNA agent of claim 29, wherein the X is O.

31. The dsRNA agent of any one of claims 1-8 or 15-30, wherein the region of complementarity comprises any one of the antisense sequences in any one of Tables 3, 4, 5, 6, 7, 8A, or 8B.

32. The dsRNA agent of any one of claims 1-8, wherein

(a) the sense strand comprises the sequence and all of the modifications of SEQ ID NO: 881, and the antisense strand comprises the sequence and all the modifications of SEQ ID NO:1265;

(b) the sense strand comprises the sequence and all of the modifications of SEQ ID NO: 914, and the antisense strand comprises the sequence and all the modifications of SEQ ID NO:1266; or

(c) the sense strand comprises the sequence and all of the modifications of SEQ ID NO: 907, and the antisense strand comprises the sequence and all the modifications of SEQ ID NO:1272.

33. A double stranded ribonucleic acid (dsRNA) agent for inhibiting the expression of plasminogen (PLG) in a cell, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the sense sequences listed in any one of Tables 3, 4, 5, 6, 7, 8A, or 8B and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense sequences listed in any one of Tables 3, 4, 5, 6, 7, 8A, or 8B,

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.

34. The dsRNA agent of claim 33, wherein all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand are modified nucleotides.

35. The dsRNA agent of claim 33 or 34, wherein the antisense sequence comprises any one of the antisense sequences listed in any one of Tables 3, 4, 5, 6, 7, 8A, or 8B.

36. The dsRNA agent of any one of claims 1-35, wherein 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 3, 4, 5, 6, 7, 8A, or 8B.

37. The dsRNA of any one of claims 1-36 wherein the dsRNA agent targets a hotspot region of an mRNA encoding PLG.

38. A dsRNA agent that targets a hotspot region of a plasminogen (PLG) mRNA.

39. A cell containing the dsRNA agent of any one of claims 1-38.

40. A vector encoding at least one strand of the dsRNA agent of any one of claims 1-38.

41. A pharmaceutical composition for inhibiting expression of the plasminogen (PLG) gene comprising the dsRNA agent of any one of claims 1-38.

42. The pharmaceutical composition of claim 41, wherein the agent is formulated in an unbuffered solution.

43. The pharmaceutical composition of claim 42, wherein the unbuffered solution is saline or water.

44. The pharmaceutical composition of claim 41, wherein the agent is formulated with a buffered solution.

45. The pharmaceutical composition of claim 44, wherein said buffered solution comprises acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof.

46. The pharmaceutical composition of claim 44, wherein the buffered solution is phosphate buffered saline (PBS).

47. A method of inhibiting plasminogen (PLG) expression in a cell, the method comprising contacting the cell with the agent of any one of claims 1-38, or a pharmaceutical composition of any one of claims 41-46, thereby inhibiting expression of PLG in the cell.

48. The method of claim 47, wherein said cell is within a subject.

49. The method of claim 48, wherein the subject is a human.

50. The method of any one of claims 47-49, wherein the PLG expression is inhibited by at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or to below the level of detection of PLG expression.

51. The method of claim 50, wherein the human subject suffers from a PLG-associated disease, disorder, or condition.

52. The method of claim 51, wherein the PLG-associated disease, disorder, or condition is a bleeding disorder.

53. The method of claim 52, wherein the bleeding disorder is hereditary hemorrhagic telangiectasia (HHT).

54. The method of claim 51, wherein the PLG-associated disease, disorder, or condition is melasma or hyperpigmentation of the skin or wherein the subject is treated pre-surgery to prevent excessive bleeding.

55. The method of claim 52, wherein the bleeding disorder is selected from the group consisting of heavy menstrual bleeding (HMB), PAI-1 deficiency, von Willebrand disease, low factor XI levels, platelet defects, hemophilia A, hemophilia B, afibrinogenemia, parahemophilia, low factor VIII levels, low factor IX levels, low factor VII levels, low factor XIII levels, low factor X levels, low factor V levels, low factor II levels, nose bleeds, bleeding gums, easy bruising, postpartum bleeding, and excessive bleeding following surgery.

56. The method of claim 52, wherein the bleeding disorder is a mucocutaneous bleeding disorder (MCB).

57. The method of claim 56, wherein the mucocutaneous bleeding disorder is selected from the group consisting of inherited platelet disorders (IPD), hereditary hemorrhagic telangiectasia (HHT), hypermobility spectrum disorders (HSD), Ehlers-Danlos syndromes (EDS), and von Willebrand disease (VWD).

58. A method of inhibiting the expression of PLG in a subject, the method comprising administering to the subject a therapeutically effective amount of the dsRNA agent of any one of claims 1-38, or a pharmaceutical composition of any one of claims 41-46, thereby inhibiting the expression of PLG in said subject.

59. A method of treating a subject suffering from a PLG-associated disease, disorder, or condition, comprising administering to the subject a therapeutically effective amount of the agent of any one of claims 1-38, or a pharmaceutical composition of any one of claims 41-46, thereby treating the subject suffering from a PLG-associated disease, disorder, or condition.

60. 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 a PLG gene, comprising administering to the subject a prophylactically effective amount of the agent of any one of claims 1-38, or a pharmaceutical composition of any one of claims 41-46, thereby preventing at least one symptom in a subject having a disease, disorder or condition that would benefit from reduction in expression of a PLG gene.

61. The method of any one of claims 58-60, wherein the PLG-associated disease, disorder, or condition is a bleeding disorder.

62. The method of claim 61, wherein a symptom of the bleeding disorder is heavy menstrual bleeding (HMB).

63. The method of claim 61, wherein the bleeding disorder is selected from the group consisting of hereditary hemorrhagic telangiectasia (HHT), heavy menstrual bleeding (HMB), PAI-1 deficiency, von Willebrand disease, low factor XI levels, platelet defects, hemophilia A, hemophilia B, afibrinogenemia, parahemophilia, low factor VIII levels, low factor IX levels, low factor VII levels, low factor XIII levels, low factor X levels, low factor V levels, low factor II levels, nose bleeds, bleeding gums, easy bruising, postpartum bleeding, and excessive bleeding following surgery.

64. The method of claim 59 or 60, wherein the PLG-associated disease, disorder, or condition is melasma or hyperpigmentation of the skin or wherein the subject is treated pre-surgery to prevent excessive bleeding.

65. The method of claim 61, wherein the bleeding disorder is a mucocutaneous bleeding disorder (MCB).

66. The method of claim 65, wherein the mucocutaneous bleeding disorder is selected from the group consisting of inherited platelet disorders (IPD), hereditary hemorrhagic telangiectasia (HHT), hypermobility spectrum disorders (HSD), Ehlers-Danlos syndromes (EDS), and von Willebrand disease (VWD).

67. The method of any one of claims 48-66, further comprising administering an additional therapeutic to the subject.

68. The method of any one of claims 48-67, wherein 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.

69. The method of any one of claims 48-68, wherein the agent is administered to the subject intravenously, intramuscularly, or subcutaneously.

70. The method of any one of claims 48-69, further comprising determining the level of PLG in the subject.

71. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of plasminogen (PLG) 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 3, 4, 5, 6, 7, 8A, or 8B and the antisense strand comprises a nucleotide sequence of any one of the agents in any one of Tables 3, 4, 5, 6, 7, 8A, or 8B,

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.