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(54) PCSK9 IRNA COMPOSITIONS AND METHODS OF USE THEREOF

PCSK9-IRNA-ZUSAMMENSETZUNGEN UND VERFAHREN ZUR VERWENDUNG DAVON

COMPOSITIONS D'ARNI DE PCSK9 ET MÉTHODES D'UTILISATION ASSOCIÉES

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Description

[0001] Proprotein convertase subtilisin kexin 9 (PCSK9) is a member of the subtilisin serine protease family. The other eight mammalian subtilisin proteases, PCSK1-PCSK8 (also called PC1/3, PC2, furin, PC4, PC5/6, PACE4, PC7, and S1P/SKI-1) are proprotein convertases that process a wide variety of proteins in the secretory pathway and play roles in diverse biological processes (Bergeron, F. (2000) J. Mol. Endocrinol. 24, 1-22, Gensberg, K., (1998) Semin. Cell Dev. Biol. 9, 11-17, Seidah, N. G. (1999) Brain Res. 848, 45-62, Taylor, N. A., (2003) FASEB J. 17, 1215-1227, and Zhou, A., (1999) J. Biol. Chem. 274, 20745-20748).

[0002] PCSK9 has been proposed to play a role in cholesterol metabolism. PCSK9 mRNA expression is down-regulated by dietary cholesterol feeding in mice (Maxwell, K. N., (2003) J. Lipid Res. 44, 2109-2119), up-regulated by statins in HepG2 cells (Dubuc, G., (2004) Arterioscler. Thromb. Vasc. Biol. 24, 1454-1459), and up-regulated in sterol regulatory element binding protein (SREBP) transgenic mice (Horton, J. D., (2003) Proc. Natl. Acad. Sci. USA 100, 12027-12032), similar to the cholesterol biosynthetic enzymes and the low-density lipoprotein receptor (LDLR). Furthermore, PCSK9 missense mutations have been found to be associated with a form of autosomal dominant hypercholesterolemia (Hchola3) (Abifadel, M., et al. (2003) Nat. Genet. 34,154-156, Timms, K. M., (2004) Hum. Genet. 114, 349-353, Leren, T. P. (2004) Clin. Genet. 65, 419-422). PCSK9 may also play a role in determining LDL cholesterol levels in the general population, because single-nucleotide polymorphisms (SNPs) have been associated with cholesterol levels in a Japanese population (Shioji, K., (2004) J. Hum. Genet. 49, 109-114).

[0003] Autosomal dominant hypercholesterolemias (ADHs) are monogenic diseases in which patients exhibit elevated total and LDL cholesterol levels, tendon xanthomas, and premature atherosclerosis (Rader, D. J., (2003) J. Clin. Invest. 111, 1795-1803). The pathogenesis of ADHs and a recessive form, autosomal recessive hypercholesterolemia (ARH) (Cohen, J. C., (2003) Curr. Opin. Lipidol. 14, 121-127), is due to defects in LDL uptake by the liver. ADH may be caused by LDLR mutations, which prevent LDL uptake, or by mutations in the protein on LDL, apolipoprotein B, which binds to the LDLR. ARH is caused by mutations in the ARH protein that are necessary for endocytosis of the LDLR-LDL complex via its interaction with clathrin. Therefore, if PCSK9 mutations are causative in Hchola3 families, it seems likely that PCSK9 plays a role in receptor-mediated LDL uptake.

[0004] Overexpression studies point to a role for PCSK9 in controlling LDLR levels and, hence, LDL uptake by the liver (Maxwell, K. N. (2004) Proc. Natl. Acad. Sci. USA 101, 7100-7105, Benjannet, S., et al. (2004) J. Biol. Chem. 279, 48865-48875, Park, S. W., (2004) J. Biol. Chem. 279, 50630-50638). Adenoviral-mediated overexpression of mouse or human PCSK9 for 3 or 4 days in mice results in elevated total and LDL cholesterol levels; this effect is not seen in LDLR knockout animals (Maxwell, K. N. (2004) Proc. Natl. Acad. Sci. USA 101, 7100-7105, Benjannet, S., et al. (2004) J. Biol. Chem. 279, 48865-48875, Park, S. W., (2004) J. Biol. Chem. 279, 50630-50638). In addition, PCSK9 overexpression results in a severe reduction in hepatic LDLR protein, without affecting LDLR mRNA levels, SREBP protein levels, or SREBP protein nuclear to cytoplasmic ratio.

[0005] While hypercholesterolemia itself is asymptomatic, longstanding elevation of serum cholesterol can lead to atherosclerosis. Over a period of decades, chronically elevated serum cholesterol contributes to formation of atheromatous plaques in the arteries which can lead to progressive stenosis or even complete occlusion of the involved arteries. In addition, smaller plaques may rupture and cause a clot to form and obstruct blood flow resulting in, for example, myocardial infarction and/or stroke. If the formation of the stenosis or occlusion is gradual, blood supply to the tissues and organs slowly diminishes until organ function becomes impaired.

[0006] Accordingly, there is a need in the art for effective treatments for PCSK9-associated diseases, such as a hyperlipidemia, *e.g.*, hypercholesterolemia.

[0007] As described in more detail below, disclosed herein are compositions comprising RNAi agents, *e.g.*, double-stranded iRNA agents, targeting PCSK9. Also disclosed are methods using the compositions of the invention for inhibiting PCSK9 expression and for treating pathologies related to PCSK9 expression, *e.g.*, hypercholesterolemia.

[0008] Accordingly, in one aspect, the present invention provides a double stranded RNAi agent capable of inhibiting the expression of Proprotein convertase subtilisin kexin 9 (PCSK9) in a cell, wherein said double stranded RNAi agent comprises:

(a) a sense strand complementary to an antisense strand, wherein said antisense strand comprises a region complementary to part of an mRNA encoding PCSK9, wherein each strand is about 17 to about 30 nucleotides in length, wherein said antisense strand comprises at least 17 nucleotides from the nucleobase sequence ACAAAAG-CAAAACAGGUCUAG (SEQ ID NO: 412) and the double stranded RNAi agent is represented by formula (III):

$$\begin{array}{ll} \text{sense:} & 5'\ n_p\text{-}N_a\text{-}(X\ X\ X)_i\text{-}N_b\text{-}Y\ Y\ Y\text{-}N_b\text{-}(Z\ Z\ Z)_j\text{-}N_a\text{-}n_q\ 3' \\ \text{antisense:} & 3'\ n_p'\text{-}N_a'\text{-}(X'X'X')_k\text{-}N_b'\text{-}Y'Y'Y'\text{-}N_b'\text{-}(Z'Z'Z')_l\text{-}N_a'\text{-}n_q'\ 5' \end{array} \qquad \text{(III)}$$

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';
wherein the modifications on the nucleotides are 2'-O-methyl or 2'-fluoro modifications; and
wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker; or

(b) an antisense strand consisting of the nucleotide sequence asCfsaAfAfAfgCfaAfaAfcAfgGfuCfuagsasa and a sense strand consisting of the nucleotide sequence csusagacCfuGfudTuugcuuuugu,
wherein a, g, c, and u are 2'-O-methyl (2'-OMe) modified A, G, C, and U nucleotides, respectively: Af, Gf, Cf and Uf are 2'fluoro A, G, C and U modified nucleotides, respectively; dT is a deoxy-thymine nucleotide and s is a phosphorothioate linkage;
and wherein the sense strand is conjugated to at least one ligand.

[0009] In one implementation, 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 implementation, k is 0; 1 is 0; k is 1; l is 1; both k and 1 are 0; or both k and l are 1.

[0010] In one implementation, XXX is complementary to X'X'X', YYY is complementary to Y'Y'Y', and ZZZ is complementary to Z'Z'Z'.

[0011] In one implementation, YYY motif occurs at or near the cleavage site of the sense strand.

[0012] In one implementation, Y'Y'Y' motif occurs at the 11, 12 and 13 positions of the antisense strand from the 5'-end.

[0013] In one implementation, Y' is 2'-O-methyl.

[0014] In one implementation, formula (III) is represented by formula (IIIa):

$$\begin{array}{ll} \text{sense:} & 5'\ n_p\text{-}N_a\text{-}Y\ Y\ Y\text{-}N_a\text{-}n_q\ 3' \\ \text{antisense:} & 3'\ n_{p'}\text{-}N_{a'}\text{-}Y'Y'Y'\text{-}N_{a'}\text{-}n_{q'}\ 5' \end{array} \quad \text{(IIIa).}$$

[0015] In another implementation, formula (III) is represented by formula (IIIb):

$$\begin{array}{ll} \text{sense:} & 5'\ n_p\text{-}N_a\text{-}Y\ Y\ Y\text{-}N_b\text{-}Z\ Z\ Z\text{-}N_a\text{-}n_q\ 3' \\ \text{antisense:} & 3'\ n_{p'}\text{-}N_{a'}\text{-}Y'Y'Y'\text{-}N_{b'}\text{-}Z'Z'Z'\text{-}N_{a'}\text{-}n_{q'}\ 5' \end{array} \quad \text{(IIIb)}$$

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

[0016] In yet another implementation, formula (III) is represented by formula (IIIc):

$$\begin{array}{ll} \text{sense:} & 5'\ n_p\text{-}N_a\text{–}X\ X\ X\text{-}N_b\text{-}Y\ Y\ Y\text{-}N_a\text{-}n_q\ 3' \\ \text{antisense:} & 3'\ n_{p'}\text{-}N_{a'}\text{-}X'X'X'\text{-}N_{b'}\text{-}Y'Y'Y'\text{-}N_{a'}\text{-}n_{q'}\ 5' \end{array} \quad \text{(IIIc)}$$

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

[0017] In one implementation, formula (III) is represented by formula (IIId):

sense: $5'\ n_p\text{-}N_a\text{–}X\ X\ X\text{-}\ N_b\text{-}Y\ Y\ Y\text{-}N_b\text{-}Z\ Z\ Z\text{-}N_a\text{-}\ n_q\ 3'$

antisense: $3'\ n_{p'}\text{-}N_{a'}\text{-}\ X'X'X'\text{-}\ N_{b'}\text{-}Y'Y'Y'\text{-}N_{b'}\text{-}Z'Z'Z'\text{-}\ N_{a'}\text{-}\ n_{q'}\ 5'$

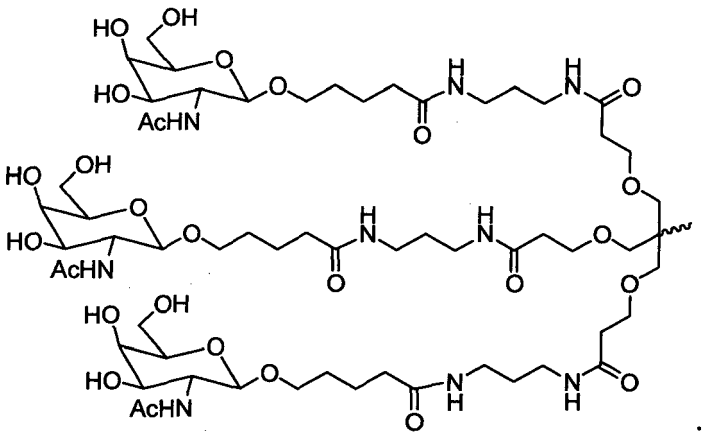
(IIId)

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.

[0018] In one implementation, the double-stranded region is 15-30 nucleotide pairs in length. In another embodiment, the double-stranded region is 17-23 nucleotide pairs in length. In yet another embodiment, the double-stranded region is 17-25 nucleotide pairs in length. In one embodiment, the double-stranded region is 23-27 nucleotide pairs in length. In another embodiment, the double-stranded region is 19-21 nucleotide pairs in length. In another embodiment, the double-stranded region is 21-23 nucleotide pairs in length. In one implementation, each strand has 15-30 nucleotides.

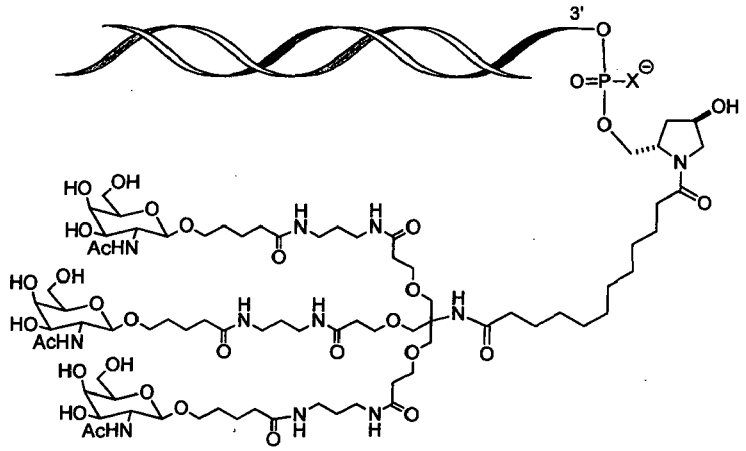
[0019] In one implementation, the modifications on the nucleotides are selected from the group consisting of LNA, HNA, CeNA, 2'-methoxyethyl, 2'-O-alkyl, 2'-O-allyl, 2'-C-allyl, 2'-fluoro, 2'-deoxy, 2'-hydroxyl, and combinations thereof. In another embodiment, the modifications on the nucleotides are 2'-O-methyl or 2'-fluoro modifications.

[0020] In one embodiment, the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker. In another embodiment, the ligand is



[0021] In one embodiment, the ligand is attached to the 3' end of the sense strand.

[0022] In one embodiment, the RNAi agent is conjugated to the ligand as shown in the following schematic



wherein X is O or S. In a specific implementation, X is O.

[0023] In one implementation, the agent further comprises at least one phosphorothioate or methylphosphonate internucleotide linkage.

[0024] In one implementation, the phosphorothioate or methylphosphonate internucleotide linkage is at the 3'-terminus of one strand. In one implementation, the strand is the antisense strand. In another implementation, the strand is the

sense strand.

[0025] In one implementation, the phosphorothioate or methylphosphonate internucleotide linkage is at the 5'-terminus of one strand. In one implementation, the strand is the antisense strand. In another embodiment, the strand is the sense strand.

[0026] In one implementation, the phosphorothioate or methylphosphonate internucleotide linkage is at the both the 5'- and 3'-terminus of one strand. In one embodiment, the strand is the antisense strand.

[0027] In one implementation, the base pair at the 1 position of the 5'-end of the antisense strand of the duplex is an AU base pair.

[0028] In one implementation, the Y nucleotides contain a 2'-fluoro modification.

[0029] In one implementation, the Y' nucleotides contain a 2'-O-methyl modification.

[0030] In one implementation, p'>0. In another embodiment, p'=2.

[0031] In one implementation, q'=0, p=0, q=0, and p' overhang nucleotides are complementary to the target mRNA. In another implementation, q'=0, p=0, q=0, and p' overhang nucleotides are non-complementary to the target mRNA.

[0032] In one implementation, the sense strand has a total of 21 nucleotides and the antisense strand has a total of 23 nucleotides.

[0033] In one implementation, at least one n_p' is linked to a neighboring nucleotide via a phosphorothioate linkage.

[0034] In one implementation, all n_p' are linked to neighboring nucleotides via phosphorothioate linkages.

[0035] In one implementation, the RNAi agent is selected from the group of RNAi agents listed in Table 1, Table 2, Table 9, Table 10, Table 12, and Figure 12.

[0036] In one implementation, the RNAi agent is selected from the group consisting of AD-53815, AD-56663, AD-56658, AD-56676, AD-56666, AD-57928, and AD-60212.

[0037] In another aspect, the present disclosure provides RNAi agents, *e.g.*, double stranded RNAi agents, capable of inhibiting the expression of Proprotein Convertase Subtilisin Kexin 9 (PCSK9) in a cell, wherein the double stranded RNAi agent comprises a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding PCSK9, wherein each strand is about 14 to about 30 nucleotides in length, wherein the double stranded RNAi agent is represented by formula (III):

$$\begin{array}{ll} \text{sense:} & 5'\ n_p\text{-}N_a\text{-}(X\,X\,X)_i\text{-}N_b\text{-}Y\,Y\,Y\text{-}N_b\text{-}(Z\,Z\,Z)_j\text{-}N_a\text{-}n_q\ 3' \\ \text{antisense:} & 3'\ n_p'\text{-}N_a'\text{-}(X'X'X')_k\text{-}N_b'\text{-}Y'Y'Y'\text{-}N_b'\text{-}(Z'Z'Z')_l\text{-}N_a'\text{-}n_q'\ 5' \end{array} \quad \text{(III)}$$

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 np, 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.

[0038] In yet another aspect, the present disclosure provides RNAi agents, *e.g.*, double stranded RNAi agents, capable of inhibiting the expression of Proprotein Convertase Subtilisin Kexin 9 (PCSK9) in a cell, wherein the double stranded RNAi agent comprises a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding PCSK9, wherein each strand is about 14 to about 30 nucleotides in length, wherein the double stranded RNAi agent is represented by formula (III):

$$\begin{array}{ll} \text{sense:} & 5'\ n_p\text{-}N_a\text{-}(X\,X\,X)_i\text{-}N_b\text{-}Y\,Y\,Y\text{-}N_b\text{-}(Z\,Z\,Z)_j\text{-}N_a\text{-}n_q\ 3' \\ \text{antisense:} & 3'\ n_p'\text{-}N_a'\text{-}(X'X'X')_k\text{-}N_b'\text{-}Y'Y'Y'\text{-}N_b'\text{-}(Z'Z'Z')_l\text{-}N_a'\text{-}n_q'\ 5' \end{array} \quad \text{(III)}$$

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.

[0039] In a further aspect, the present disclosure provides RNAi agents, *e.g.*, double stranded RNAi agents, capable of inhibiting the expression of Proprotein Convertase Subtilisin Kexin 9 (PCSK9) in a cell, wherein the double stranded RNAi agent comprises a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding PCSK9, wherein each strand is about 14 to about 30 nucleotides in length, wherein the double stranded RNAi agent is represented by formula (III):

$$\begin{array}{ll} \text{sense:} & 5'\ n_p\text{-}N_a\text{-}(X\,X\,X)_i\text{-}N_b\text{-}Y\,Y\,Y\text{-}N_b\text{-}(Z\,Z\,Z)_j\text{-}N_a\text{-}n_q\ 3' \\ \text{antisense:} & 3'\ n_p'\text{-}N_a'\text{-}(X'X'X')_k\text{-}N_b'\text{-}Y'Y'Y'\text{-}N_b'\text{-}(Z'Z'Z')_l\text{-}N_a'\text{-}n_q'\ 5' \end{array} \quad \text{(III)}$$

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 bivalent or trivalent branched linker.

[0040] In another aspect, the present disclosure provides RNAi agents, *e.g.*, double stranded RNAi agents capable of inhibiting the expression of Proprotein Convertase Subtilisin Kexin 9 (PCSK9) in a cell, wherein the double stranded RNAi agent comprises a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding PCSK9, wherein each strand is about 14 to about 30 nucleotides in length, wherein the double stranded RNAi agent is represented by formula (III):

$$\begin{array}{ll} \text{sense:} & 5'\ n_p\text{-}N_a\text{-}(X\,X\,X)_i\text{-}N_b\text{-}Y\,Y\,Y\text{-}N_b\text{-}(Z\,Z\,Z)_j\text{-}N_a\text{-}n_q\ 3' \\ \text{antisense:} & 3'\ n_p'\text{-}N_a'\text{-}(X'X'X')_k\text{-}N_b'\text{-}Y'Y'Y'\text{-}N_b'\text{-}(Z'Z'Z')_l\text{-}N_a'\text{-}n_q'\ 5' \end{array} \quad \text{(III)}$$

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 bivalent or trivalent branched linker.

[0041] In yet another aspect, the present disclosure provides RNAi agents, *e.g.*, double stranded RNAi agents, capable of inhibiting the expression of Proprotein Convertase Subtilisin Kexin 9 (PCSK9) in a cell, wherein the double stranded RNAi agent comprises a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding PCSK9, wherein each strand is about 14 to about 30 nucleotides in length, wherein the double stranded RNAi agent is represented by formula (III):

$$\begin{array}{ll} \text{sense:} & 5'\ n_p\text{-}N_a\text{-}Y\ Y\ Y\text{-}N_a\text{-}n_q\ 3' \\ \text{antisense:} & 3'\ n_p'\text{-}N_a'\text{-}Y'Y'Y'\text{-}N_a'\text{-}n_q'\ 5' \end{array} \quad \text{(IIIa)}$$

wherein:

each n_p, n_q, and n_q', each of which may or may riot 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 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 bivalent or trivalent branched linker.

[0042] The present invention also provides in vitro cells and pharmaceutical compositions comprising the double stranded RNAi agents of the invention.

[0043] Also described is an RNAi agent selected from the group of RNAi agents listed in Table 1, Table 2, Table 9, Table 10, Table 12, and Figure 12.

[0044] In some implementations, the RNAi agent is administered using a pharmaceutical composition.

[0045] In preferred implementations, the RNAi agent is administered in a solution. In some such implementations, the siRNA is administered in an unbuffered solution. In one implementation, the siRNA is administered in water. In other implementations, the siRNA is administered with a buffer solution, such as an acetate buffer, a citrate buffer, a prolamine buffer, a carbonate buffer, or a phosphate buffer or any combination thereof. In some implementations, the buffer solution is phosphate buffered saline (PBS).

[0046] In one implementation, the pharmaceutical compositions further comprise a lipid formulation. In one implementation, the lipid formulation comprises a LNP, or XTC. In another embodiment, the lipid formulation comprises a MC3.

[0047] In one aspect, the present invention provides a method of inhibiting PCSK9 expression in a cell, the method including contacting the cell with an RNAi agent, *e.g.,* a double stranded RNAi agent of the invention; and maintaining the cell produced in step (a) for a time sufficient to obtain degradation of the mRNA transcript of a PCSK9 gene, thereby inhibiting expression of the PCSK9 gene in the cell, wherein methods for treatment of the human or animal body by theraphy are excluded.

[0048] In one implementation, the PCSK9 expression is inhibited by at least about 30% 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95%.

[0049] In another aspect, the present disclosure provides methods of treating a subject having a disorder mediated by PCSK9 expression. The methods include administering to the subject a therapeutically effective amount of an RNAi agent, *e.g.*, a double stranded RNAi agent, or the vector of of the invention, thereby treating the subject.

[0050] In one implementation, the subject is a human.

[0051] In one implementation, the human has hypercholesterolemia.

[0052] In one implementation, the RNAi agent, *e.g.*, double stranded RNAi agent, is administered at a dose of about 0.01 mg/kg to about 10 mg/kg, about 0.5 mg/kg to about 50 mg/kg, about 10 mg/kg to about 30 mg/kg, about 10 mg/kg to about 20 mg/kg, about 15 mg/kg to about 20 mg/kg, about 15 mg/kg to about 25 mg/kg, about 15 mg/kg to about 30 mg/kg, or about 20 mg/kg to about 30 mg/kg.

[0053] In one implementation, the RNAi agent, *e.g.*, double stranded RNAi agent, is administered subcutaneously or intravenously.

[0054] In one implementation, the RNAi agent is administered in a dosing regimen that includes a loading phase followed by a maintenance phase, wherein the loading phase comprises administering a dose of 2 mg/kg, 1 mg/kg or 0.5 mg/kg five times a week, and wherein the maintenance phase comprises administering a dose of 2 mg/kg, 1 mg/kg or 0.5 mg/kg once, twice, or three times weekly, once every two weeks, once every three weeks, once a month, once every two months, once every three months, once every four months, once every five months, or once every six months.

[0055] In one implementation, the RNAi agent is administered in two or more doses. In a specific embodiment, the RNAi agent is administered at intervals selected from the group consisting of once every about 12 hours, once every about 24 hours, once every about 48 hours, once every about 72 hours, and once every about 96 hours.

[0056] In yet another aspect, the present disclosure provides methods of treating hypercholesterolemia in a subject. The methods include administering to the subject a therapeutically effective amount of an RNAi agent, *e.g.*, a double stranded RNAi agent, or the vector of the invention, thereby treating the subject.

[0057] In one implementation, the subject is a primate or rodent. In another implementation, the subject is a human.

[0058] In one implementation, the RNAi agent, *e.g.*, double stranded RNAi agent, is administered 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. In another embodiment, the double stranded RNAi agent is administered at a dose of about 10 mg/kg to about 30 mg/kg.

[0059] In one implementation, the RNAi agent, *e.g.*, double stranded RNAi agent, is administered subcutaneously or intravenously.

[0060] In one implementation, the RNAi agent is administered in a dosing regimen that includes a loading phase followed by a maintenance phase, wherein the loading phase comprises administering a dose of 2 mg/kg, 1 mg/kg or 0.5 mg/kg five times a week, and wherein the maintenance phase comprises administering a dose of 2 mg/kg, 1 mg/kg or 0.5 mg/kg once, twice, or three times weekly, once every two weeks, once every three weeks, once a month, once every two months, once every three months, once every four months, once every five months, or once every six months.

[0061] In one implementation, the RNAi agent is administered in two or more doses. In a specific embodiment, the RNAi agent is administered at intervals selected from the group consisting of once every about 12 hours, once every about 24 hours, once every about 48 hours, once every about 72 hours, and once every about 96 hours.

[0062] In one implementation, the methods further comprise determining an LDLR genotype or phenotype of the subject.

[0063] In one implementation, administering results in a decrease in serum cholesterol in the subject.

[0064] In one implementation, the methods further comprise determining the serum cholesterol level in the subject.

[0065] The present invention is further illustrated by the following detailed description and drawings.

Figure 1 is a graph depicting that there is a dose response effect with AD-48400 conjugated to GalNAc at all three dosages tested. AD-48399, conjugated to GalNAc, serves as a control.

Figures 2A and 2B are graphs depicting the *in vivo* efficacy and duration of response for the indicated siRNAs.

Figure 3 is a Table showing the sequences of the sense (SEQ ID NOS 1633-1642, respectively, in order of appearance) and antisense (SEQ ID NOS 1643-1652, respectively, in order of appearance) stands of the duplexes analyzed for *in vivo* efficacy and lead optimization.

Figure 4 is a graph depicting the results of the *in vivo* efficacy assays for lead optimization.

Figure 5 is a graph depicting the results of the *in vivo* dose response assays performed in PCSK9 trangenic mice. Seventy-two hours after a single dose of 10 mg/kg, 3 mg/kg, 1 mg/kg, and 0.3 mg/kg of AD-57928, PCSK9 protein levels were determined by ELISA.

Figure 6 is a graph depicting the levels of PCSK9 protein in serum of PCSK9 transgenic mice after administration of AD-57928 in 5x2 mg/kg doses during the "loading phase" and 1 x2 mg/kg or 2x2 mg/kg doses during the "maintenance phase".

Figure 7 is a graph depicting the levels of PCSK9 protein in serum of PCSK9 transgenic mice after administration

of AD-57928 in 5x1 mg/kg doses during the "loading phase" and 1 x mg/kg or 2x1 mg/kg doses during the "maintenance phase".

Figure 8 is a graph depicting the levels of PCSK9 protein in serum of PCSK9 transgenic mice after administration of AD-57928 in 5x0.5 mg/kg doses during the "loading phase" and 1 x0.5 mg/kg or 2x0.5 mg/kg doses during the "maintenance phase".

Figure 9 is a graph depicting the results of the *in vivo* dose response assays performed in PCSK9 trangenic mice. Seventy-two hours after a single dose of 0.3 mg/kg of siRNAs, PCSK9 protein levels were determined by ELISA.

Figure 10 is a graph showing the amount of AD-57928 and AD-58895 per nanogram of liver of C57B6 wild-type mice after administration of a single dose of 1 mg/kg of AD-57928 or AD-58895.

Figure 11 is a graph showing the amout of AD-57928 and AD-58895 expressed as a % of theoretical amount in the liver of C57B6 wild-type mice after administration of a single dose of 1 mg/kg of AD-57928 or AD-58895.

Figure 12A is a Table depicting iRNA agents of the invention containing optimized sequences as compared to AD-57928 sequences. Figure 12A discloses the "Sense" sequences as SEQ ID NOS 1653-1658, respectively, in order of appearance, and the "Antisense" sequences as SEQ ID NOS 1659-1664, respectively, in order of appearance.

Figure 12B is a graph showing the IC_{50} values of the indicated iRNA agents.

Figure 13 is a graph showing the level of the indicated iRNA agents in the liver of wild-type mice following administration of a single 1 mg/kg dose of the indicated iRNA agent.

Figure 14A is a graph showing the amount of PCSK9 protein in the serum of non-human primates expressed as percent of PCSK9 remaining relative to pre-bleed levels of PCSK9 after administration of the indicated iRNA agents at qdx5 + qwx3.

Figure 14B is a graph showing the absolute amount of PCSK9 protein in the serum of non-human primates after administration of the indicated iRNA agents at qdx5 + qwx3.

Figure 15 is a graph showing the amount of low density lipoprotein cholesterol (LDL or LDLc) in the serum of non-human primates expressed as a percent of LDL remaining relative to pre-bleed levels of LDL after administration of the indicated iRNA agents at qdx5 + qwx3.

Figure 16A is a graph showing the amount of low density lipoprotein cholesterol (LDL or LDLc) in the serum of non-human primates expressed as a percent of the average amount of pre-bleed levels of LDL after administration of AD-57928 at 2 mg/kg, q1w and 1 mg/kg, 2xw. ,

Figure 16B is a graph showing the amount of PCSK9 protein relative to the pre-bleed amount in the serum of non-human primates after administration of AD-57928 at 2 mg/kg, q1w and 1 mg/kg, 2xw.

Figure 17A is a graph showing the amount of low density lipoprotein cholesterol (LDL or LDLc) in the serum of non-human primates expressed as a percent of the average amount of pre-bleed levels of LDL after administration of AD-57928 at 2 mg/kg, 2xw and a single 25 mg/kg dose. The last dose for the 2 mg/kg, 2xw group was day 36.

Figure 17B is a graph showing the amount of PCSK9 protein relative to the pre-bleed amount in the serum of non-human primates after administration of AD-57928 at 2 mg/kg, 2xw and a single 25 mg/kg dose.

Figure 18 is a graph showing the amount of low density lipoprotein cholesterol (LDL or LDLc) in the serum of non-human primates expressed as a percent of LDL remaining relative to pre-bleed levels of LDL after administration of the indicated iRNA agents at qdx5 +qwx3.

Figure 19 is a graph showing the amount of low density lipoprotein cholesterol (LDL or LDLc) in the serum of non-human primates expressed as a percent of LDL remaining relative to pre-bleed levels of LDL after administration of the indicated iRNA agents at qdx5 + qwx3.

[0066] The present invention is defined by the claims. Also disclosed are methods using the compositions of the invention for inhibiting PCSK9 expression and for treating pathologies related to PCSK9 expression, *e.g.*, hypercholesterolemia.

I. Definitions

[0067] 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.

[0068] 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.

[0069] The term "including" is used herein to mean, and is used interchangeably with, the phrase "including but not limited to".

[0070] The term "or" is used herein to mean, and is used interchangeably with, the term "and/or," unless context clearly indicates otherwise.

[0071] As used herein, "PCSK9" refers to the proprotein convertase subtilisin kexin 9 gene or protein. PCSK9 is also known as FH3, HCHOLA3, NARC-1, or NARC1. The term PCSK9 includes human PCSK9, the amino acid and nucleotide sequence of which maybe found in, for example, GenBank Accession No. GI:299523249; mouse PCSK9, the amino acid and nucleotide sequence of which may be found in, for example, GenBank Accession No. GI:163644257; rat PCSK9, the amino acid and nucleotide sequence of which maybe found in, for example, GenBank Accession No. GI:77020249. Additional examples of PCSK9 mRNA sequences are readily available using, *e.g.*, GenBank.

[0072] As used herein, "target sequence" refers to a contiguous portion of the nucleotide sequence of an mRNA molecule formed during the transcription of a PCSK9 gene, including mRNA that is a product of RNA processing of a primary transcription product.

[0073] 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.

[0074] "G," "C," "A" and "U" each generally stand for a nucleotide that contains guanine, cytosine, adenine, and uracil as a base, respectively. "T" and "dT" are used interchangeably herein and refer to a deoxyribonucleotide wherein the nucleobase is thymine, e.g., deoxyribothymine, 2'-deoxythymidine or thymidine. However, it will be understood that the term "ribonucleotide" or "nucleotide" or "deoxyribonucleotide" can also refer to a modified nucleotide, as further detailed below, or a surrogate replacement moiety. The skilled person is well aware that guanine, cytosine, adenine, and uracil may be replaced by other moieties without substantially altering the base pairing properties of an oligonucleotide comprising a nucleotide bearing such replacement moiety. For example, without limitation, a nucleotide comprising inosine as its base may base pair with nucleotides containing adenine, cytosine, or uracil. Hence, nucleotides containing uracil, guanine, or adenine may be replaced in the nucleotide sequences of the invention by a nucleotide containing, for example, inosine. Sequences comprising such replacement moieties are embodiments of the invention.

[0075] 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 PCSK9 in a cell, *e.g.,* a cell within a subject, such as a mammalian subject.

[0076] In one implementation, an RNAi agent of the invention includes a single stranded RNA that interacts with a target RNA sequence, *e.g.*, a PCSK9 target mRNA sequence, to direct the cleavage of the target RNA. Without wishing to be bound by theory, it is believed that long double stranded RNA introduced into cells is broken down into siRNA by a Type III endonuclease known as Dicer (Sharp et al. (2001) Genes Dev. 15:485). Dicer, a ribonuclease-III-like enzyme, processes the dsRNA into 19-23 base pair short interfering RNAs with characteristic two base 3' overhangs (Bernstein, et al., (2001) Nature 409:363). The siRNAs are then incorporated into an RNA-induced silencing complex (RISC) where one or more helicases unwind the siRNA duplex, enabling the complementary antisense strand to guide target recognition (Nykanen, et al., (2001) Cell 107:309). Upon binding to the appropriate target mRNA, one or more endonucleases within the RISC cleave the target to induce silencing (Elbashir, et al., (2001) Genes Dev. 15:188). Thus, in one aspect the invention relates to a single stranded RNA (siRNA) generated within a cell and which promotes the formation of a RISC complex to effect silencing of the target gene, *i.e.,* a PCSK9 gene. Accordingly, the term "siRNA" is also used herein to refer to an RNAi as described above.

[0077] In another implementation, the RNAi agent may be a single-stranded siRNA that is introduced into a cell or organism to inhibit a target mRNA. Single-stranded RNAi agents bind to the RISC endonuclease Argonaute 2, which then cleaves the target mRNA. The single-stranded siRNAs are generally 15-30 nucleotides and are chemically modified. The design and testing of single-stranded siRNAs are described in U.S. Patent No. 8,101,348 and in Lima et al., (2012) Cell 150: 883-894, the entire contents of each of which are hereby incorporated herein by reference. Any of the antisense nucleotide sequences described herein may be used as a single-stranded siRNA as described herein or as chemically modified by the methods described in Lima et al., (2012) Cell 150:883-894.

[0078] In another implementation, an "iRNA" for use in the compositions, uses, and methods of the invention is a double-stranded RNA and is referred to herein as a "double stranded 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 PCSK9 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.

[0079] 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. Such modifications may 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.

[0080] 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." 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 agent may comprise one or more nucleotide overhangs.

[0081] In one implementation, an RNAi agent of the invention is a dsRNA of 24-30 nucleotides that interacts with a target RNA sequence, e.g., a PCSK9 target mRNA sequence, to direct the cleavage of the target RNA. Without wishing to be bound by theory, long double stranded RNA introduced into cells is broken down into siRNA by a Type III endonuclease known as Dicer (Sharp et al. (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). As used herein, a "nucleotide overhang" refers to the unpaired nucleotide or nucleotides that protrude from the duplex structure of an RNAi agent when a 3'-end of one strand of the RNAi agent extends beyond the 5'-end of the other strand, or vice versa. "Blunt" or "blunt end" means that there are no unpaired nucleotides at that end of the double stranded RNAi agent, i.e., no nucleotide overhang. A "blunt ended" RNAi agent is a dsRNA that is double-stranded over its entire length, i.e., no nucleotide overhang at either end of the molecule. The RNAi agents of the invention include RNAi agents with nucleotide overhangs at one end (*i.e.*, agents with one overhang and one blunt end) or with nucleotide overhangs at both ends.

[0082] The term "antisense strand" refers to the strand of a double stranded RNAi agent which includes a region that is substantially complementary to a target sequence (*e.g.*, a human PCSK9 mRNA). As used herein, the term "region complementary to part of an mRNA encoding transthyretin" refers to a region on the antisense strand that is substantially complementary to part of a PCSK9 mRNA sequence. Where the region of complementarity is not fully complementary to the target sequence, the mismatches are most tolerated in the terminal regions and, if present, are generally in a terminal region or regions, *e.g.*, within 6, 5, 4, 3, or 2 nucleotides of the 5' and/or 3' terminus.

[0083] The term "sense strand," as used herein, refers to the strand of a dsRNA that includes a region that is substantially complementary to a region of the antisense strand.

[0084] 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 implementations, the cleavage region comprises three bases on either end of, and immediately adjacent to, the cleavage site. In some implementations, the cleavage region comprises two bases on either end of, and immediately adjacent to, the cleavage site. In some implementations, 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.

[0085] 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 may include: 400 mM NaCl, 40 mM PIPES pH 6.4, 1 mM EDTA, 50oC or 70oC for 12-16 hours followed by washing. Other conditions, such as physiologically relevant conditions as may be encountered inside an organism, can apply. For example, a complementary sequence is sufficient to allow the relevant function of the nucleic acid to proceed, *e.g.*, RNAi. 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.

[0086] Sequences can be "fully complementary" with respect to each when there is base-pairing of the nucleotides of the first nucleotide sequence with the nucleotides of the second nucleotide sequence over the entire length of the first and second nucleotide sequences. However, where a first sequence is referred to as "substantially complementary" with respect to a second sequence herein, the two sequences can be fully complementary, or they may form one or more, but generally not more than 4, 3 or 2 mismatched base pairs upon hybridization, while retaining the ability to hybridize under the conditions most relevant to their ultimate application. However, where two oligonucleotides are designed to form, upon hybridization, one or more single stranded overhangs, such overhangs shall not be regarded as mismatches with regard to the determination of complementarity. For example, a dsRNA comprising one oligonucleotide 21 nucleotides in length and another oligonucleotide 23 nucleotides in length, wherein the longer oligonucleotide comprises a sequence of 21 nucleotides that is fully complementary to the shorter oligonucleotide, may yet be referred to

as "fully complementary" for the purposes described herein.

[0087] "Complementary" sequences, as used herein, may also include, or be formed entirely from, non-Watson-Crick base pairs and/or base pairs formed from non-natural and modified nucleotides, in as far as the above requirements with respect to their ability to hybridize are fulfilled. Such non-Watson-Crick base pairs includes, but not limited to, G:U Wobble or Hoogstein base pairing.

[0088] The terms "complementary," "fully complementary" and "substantially complementary" herein may 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 a dsRNA and a target sequence, as will be understood from the context of their use.

[0089] 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 PCSK9) including a 5' UTR, an open reading frame (ORF), or a 3' UTR. For example, a polynucleotide is complementary to at least a part of a PCSK9 mRNA if the sequence is substantially complementary to a non-interrupted portion of an mRNA encoding PCSK9.

[0090] The term "inhibiting," as used herein, is used interchangeably with "reducing," "silencing," "downregulating," "suppressing" and other similar terms, and includes any level of inhibition.

[0091] The phrase "inhibiting expression of a PCSK9," as used herein, includes inhibition of expression of any PCSK9 gene (such as, *e.g.,* a mouse PCSK9 gene, a rat PCSK9 gene, a monkey PCSK9 gene, or a human PCSK9 gene) as well as variants, (*e.g.*, naturally occurring variants), or mutants of a PCSK9 gene. Thus, the PCSK9 gene may be a wild-type PCSK9 gene, a mutant PCSK9 gene, or a transgenic PCSK9 gene in the context of a genetically manipulated cell, group of cells, or organism.

[0092] "Inhibiting expression of a PCSK9 gene" includes any level of inhibition of a PCSK9 gene, *e.g.*, at least partial suppression of the expression of a PCSK9 gene, such as an inhibition of at least about 5%, at least about 10%, at least about 15%, at least about 20%, 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%.

[0093] The expression of a PCSK9 gene may be assessed based on the level of any variable associated with PCSK9 gene expression, *e.g.*, PCSK9 mRNA level, PCSK9 protein level, or serum lipid levels. 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). '

[0094] The phrase "contacting a cell with a double stranded RNAi agent," as used herein, includes contacting a cell by any possible means. Contacting a cell with a double stranded RNAi agent includes contacting a cell *in vitro* with the RNAi agent or contacting a cell *in vivo* with the RNAi agent. 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.

[0095] 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, 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.,* a GalNAc3 ligand, that directs the RNAi agent to a site of interest, e.g., the liver. Combinations of i*n vitro* and *in vivo* methods of contacting are also possible. In connection with the methods of the invention, a cell might also be contacted *in vitro* with an RNAi agent and subsequently transplanted into a subject.

[0096] A "patient" or "subject," as used herein, is intended to include either a human or non-human animal, preferably a mammal, *e.g.*, a monkey. Most preferably, the subject or patient is a human.

[0097] A "PCSK9-associated disease," as used herein, is intended to include any disease associated with the PCSK9 gene or protein. Such a disease may be caused, for example, by excess production of the PCSK9 protein, by PCSK9 gene mutations, by abnormal cleavage of the PCSK9 protein, by abnormal interactions between PCSK9 and other proteins or other endogenous or exogenous substances. Exemplary PCSK9-associated diseases include lipidemias, *e.g.*, a hyperlipidemias, and other forms of lipid imbalance such as hypercholesterolemia, hypertriglyceridemia and the pathological conditions associated with these disorders such as heart and circulatory diseases.

[0098] "Therapeutically effective amount," as used herein, is intended to include the amount of an RNAi agent that, when administered to a patient for treating a PCSK9 associated disease, is sufficient to effect treatment of the disease (*e.g.*, by diminishing, ameliorating or maintaining the existing disease or one or more symptoms of disease). The "therapeutically effective amount" may vary depending on the RNAi agent, how the agent is administered, the disease and

its severity and the history, age, weight, family history, genetic makeup, stage of pathological processes mediated by PCSK9 expression, the types of preceding or concomitant treatments, if any, and other individual characteristics of the patient to be treated.

[0099] "Prophylactically effective amount," as used herein, is intended to include the amount of an RNAi agent that, when administered to a subject who does not yet experience or display symptoms of a PCSK9-associated disease, but who may be predisposed to the disease, is sufficient to prevent or ameliorate the disease or one or more symptoms of the disease. Ameliorating the disease includes, slowing the course of the disease or reducing the severity of later-developing disease. The "prophylactically effective amount" may vary depending on the RNAi agent, how the agent is administered, the degree of risk of disease, and the history, age, weight, family history, genetic makeup, the types of preceding or concomitant treatments, if any, and other individual characteristics of the patient to be treated.

[0100] A "therapeutically-effective amount" or "prophylacticaly effective amount" also includes an amount of an RNAi agent that produces some desired local or systemic effect at a reasonable benefit/risk ratio applicable to any treatment. RNAi gents 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.

[0101] 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 preferred embodiments, a "sample derived from a subject" refers to blood or plasma drawn from the subject. In further embodiments, a "sample derived from a subject" refers to liver tissue (or subcomponents thereof) derived from the subject.

II. iRNAs

[0102] Described herein are improved double-stranded RNAi agents which inhibit the expression of a PCSK9 gene in a cell, such as a cell within a subject, *e.g.*, a mammal, such as a human having a lipid disorder, *e.g.*, hypercholesterolemia and uses of such double-stranded RNAi agents.

[0103] The double-stranded RNAi agents of the disclosure include agents with chemical modifications as disclosed, for example, in U.S. Provisional Application No. 61/561,710, filed on November 18,2011, the entire contents of which are incorporated herein by reference.

[0104] As shown herein and in Provisional Application No. 61/561,710, a superior result may be obtained by introducing one or more motifs of three identical modifications on three consecutive nucleotides into a sense strand and/or antisense strand of a RNAi agent, particularly at or near the cleavage site. In some implementations, the sense strand and antisense strand of the RNAi agent may otherwise be completely modified. The introduction of these motifs interrupts the modification pattern, if present, of the sense and/or antisense strand. The RNAi agent may be optionally conjugated with a GalNAc derivative ligand, for instance on the sense strand. The resulting RNAi agents present superior gene silencing activity.

[0105] More specifically, it has been surprisingly discovered that when the sense strand and antisense strand of the double-stranded RNAi agent are completely modified to have one or more motifs of three identical modifications on three consecutive nucleotides at or near the cleavage site of at least one strand of an RNAi agent, the gene silencing acitivity of the RNAi agent was superiorly enhanced.

[0106] Accordingly, the disclosure provides double-stranded RNAi agents capable of inhibiting the expression of a target gene (*i.e.*, a Proprotein concertase subtilisin kexin 9 (PCSK9) 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.

[0107] 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.

[0108] In one implementation, 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.

[0109] In one implementation, 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.

[0110] The 5'- or 3'- overhangs at the sense strand, antisense strand or both strands of the RNAi agent may be phosphorylated. In some implementations, 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 implementation, 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 implementation, this 3'-overhang is present in the sense strand.

[0111] 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.

[0112] In one implementation, 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.

[0113] In another implementation, 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.

[0114] In yet another implementation, 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.

[0115] In one implementation, 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 implementation, 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 implementation, 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 implementation 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 $GalNAc_3$).

[0116] In one implementation, the RNAi agent comprises sense and antisense strands, wherein the RNAi agent comprises a first strand having a length which is at least 25 and at most 29 nucleotides and a second strand having a length which is at most 30 nucleotides with at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at position 11, 12, 13 from the 5' end; wherein the 3' end of the first strand and the 5' end of the second strand form a blunt end and the second strand is 1-4 nucleotides longer at its 3' end than the first strand, wherein the duplex region region which is at least 25 nucleotides in length, and the second strand is sufficiently complemenatary to a target mRNA along at least 19 nucleotide of the second strand length to reduce target gene expression when the RNAi agent is introduced into a mammalian cell, and wherein dicer cleavage of the RNAi agent preferentially results in an siRNA comprising the 3' end of the second strand, thereby reducing expression of the target gene in the mammal.

Optionally, the RNAi agent further comprises a ligand.

[0117] In one implementation, 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.

[0118] In one implementation, 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

[0119] For an RNAi agent having a duplex region of 17-23 nucleotide in length, the cleavage site of the antisense strand is typically around the 10, 11 and 12 positions from the 5'-end. Thus the motifs of three identical modifications may occur at the 9, 10, 11 positions; 10, 11, 12 positions; 11, 12, 13 positions; 12, 13, 14 positions; or 13, 14, 15 positions of the antisense strand, the count starting from the 1 st nucleotide from the 5'-end of the antisense strand, or, the count starting from the 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.

[0120] 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.

[0121] In one implementation, the sense strand of the RNAi agent may contain more than one motif of three identical modifications on three consecutive nucleotides. The first motif may occur at or near the cleavage site of the strand and the other motifs may be a wing modification. The term "wing modification" herein refers to a motif occurring at another portion of the strand that is separated from the motif at or near the cleavage site of the same strand. The wing modification is either adajacent to the first motif or is separated by at least one or more nucleotides. When the motifs are immediately adjacent to each other then the chemistry of the motifs are distinct from each other and when the motifs are separated by one or more nucleotide than the chemistries can be the same or different. Two or more wing modifications may be present. For instance, when two wing modifications are present, each wing modification may occur at one end relative to the first motif which is at or near cleavage site or on either side of the lead motif.

[0122] 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.

[0123] In one implementation, 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.

[0124] In another implementation, 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.

[0125] 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.

[0126] 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.

[0127] In one implementation, 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.

[0128] 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.

[0129] 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 implementations 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.

[0130] In one implementation, each residue of the sense strand and antisense strand is independently modified with LNA, HNA, CeNA, 2'-methoxyethyl, 2'- O-methyl, 2'-O-allyl, 2'-C-allyl, 2'-deoxy, 2'-hydroxyl, or 2'-fluoro. The strands can contain more than one modification. In one implementation, each residue of the sense strand and antisense strand is independently modified with 2'- O-methyl or 2'-fluoro.

[0131] 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.

[0132] In one implementation, 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.

[0133] 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.

[0134] In one implementation, the RNAi agent of the invention comprises the modification pattern for the alternating motif on the sense strand relative to the modification pattern for the alternating motif on the antisense strand is shifted. The shift may be such that the modified group of nucleotides of the sense strand corresponds to a differently modified group of nucleotides of the antisense strand and *vice versa*. For example, the sense strand when paired with the antisense strand in the dsRNA duplex, the alternating motif in the sense strand may start with "ABABAB" from 5'-3' of the strand and the alternating motif in the antisense strand may start with "BABABA" from 5'-3' of the strand within the duplex region. As another example, the alternating motif in the sense strand may start with "AABBAABB" from 5'-3' of the strand and the alternating motif in the antisenese strand may start with "BBAABBAA" from 5'-3' of the strand within the duplex region, so that there is a complete or partial shift of the modification patterns between the sense strand and the antisense strand.

[0135] In one implementation, 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.

[0136] The introduction of one or more motifs of three identical modifications on three consecutive nucleotides to the sense strand and/or antisense strand interrupts the initial modification pattern present in the sense strand and/or antisense strand. This interruption of the modification pattern of the sense and/or antisense strand by introducing one or more motifs of three identical modifications on three consecutive nucleotides to the sense and/or antisense strand surprisingly enhances the gene silencing acitivty to the target gene.

[0137] In one implementation, when the motif of three identical modifications on three consecutive nucleotides is introduced to any of the strands, the modification of the nucleotide next to the motif is a different modification than the modification of the motif For example, the portion of the sequence containing the motif is "...N_aYYYN_b...," where "Y" represents the modification of the motif of three identical modifications on three consecutive nucleotide, and "N_a" and "N_b" represent a modification to the nucleotide next to the motif "YYY" that is different than the modification of Y, and where N_a and N_b can be the same or different modifications. Altnernatively, N_a and/or N_b may be present or absent when there is a wing modification present.

[0138] 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.

[0139] In one implementation, 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 maybe 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.

[0140] In one implementation, 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.

[0141] In one implementation, the RNAi agent comprises mismatch(es) with the target, within the duplex, or combinations thereof. The mistmatch may occur in the overhang region or the duplex region. The base pair may be ranked on the basis of their propensity to promote dissociation or melting (*e.g.*, on the free energy of association or dissociation of a particular pairing, the simplest approach is to examine the pairs on an individual pair basis, though next neighbor or similar analysis can also be used). In terms of promoting dissociation: A:U is preferred over G:C; G:U is preferred over G:C; and I:C is preferred over G:C (I=inosine). Mismatches, *e.g.*, non-canonical or other than canonical pairings (as described elsewhere herein) are preferred over canonical (A:T, A:U, G:C) pairings; and pairings which include a universal base are preferred over canonical pairings.

[0142] In one implementation, 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.

[0143] In one implementation, 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.

[0144] 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 np 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.

[0145] In one implementation, the N_a and/or N_b comprise modifications of alternating pattern.

[0146] In one implementation, 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 1 ^{s}t nucleotide, from the 5'-end; or optionally, the count starting at the 1 ^{s}t paired nucleotide within the duplex region, from the 5'- end.

[0147] In one implementation, i is 1 and j is 0, or i is 0 and j is 1, or both i and j are 1. The sense strand can therefore be represented by the following formulas:

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

$$5' \; n_p\text{-}N_a\text{-}XXX\text{-}N_b\text{-}YYY\text{-}N_a\text{-}n_q \; 3' \qquad \text{(Ic)};$$

or

$$5' \; n_p\text{-}N_a\text{-}XXX\text{-}N_b\text{-}YYY\text{-}N_b\text{-}ZZZ\text{-}N_a\text{-}n_q \; 3' \qquad \text{(Id)}.$$

[0148] 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.

[0149] 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 O modified nucleotides. Each N_a can independently represent an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

[0150] 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.

[0151] Each of X, Y and Z may be the same or different from each other.

[0152] In other implementations, i is 0 and j is 0, and the sense strand may be represented by the formula:

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

[0153] 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.

[0154] In one implementation, the antisense strand sequence of the RNAi may be represented by formula (II):

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

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.

[0155] In one implementation, the N_a' and/or N_b' comprise modifications of alternating pattern.

[0156] 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.

[0157] In one implementation, Y'Y'Y' motif is all 2'-OMe modified nucleotides.

[0158] In one implementation, k is 1 and l is 0, or k is 0 and l is 1, or both k and l are 1.

[0159] The antisense strand can therefore be represented by the following formulas:

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

$$5' n_{q'}\text{-}N_a'\text{-}Y'Y'Y'\text{-}N_b'\text{-}X'X'X'\text{-}n_{p'}\ 3' \qquad \text{(IIc)};$$

or

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

[0160] 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.

[0161] 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.

[0162] 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.

[0163] In other implementations, k is 0 and 1 is 0 and the antisense strand may be represented by the formula:

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

[0164] 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.

[0165] Each of X', Y' and Z' may be the same or different from each other.

[0166] Each nucleotide of the sense strand and antisense strand may be independently modified with LNA, 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.

[0167] In one implementation, 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.

[0168] In one implementation 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.

[0169] The sense strand represented by any one of the above formulas (Ia), (Ib), (Ic), and (Id) forms a duplex with a antisense strand being represented by any one of formulas (IIa), (IIb), (IIc), and (IId), respectively.

[0170] Accordingly, the RNAi agents for use in the described methods may comprise a sense strand and an antisense strand, each strand having 14 to 30 nucleotides, the RNAi duplex represented by formula (III):

$$\begin{aligned} &\text{sense:} && 5'\ n_p\text{-}N_a\text{-}(X\,X\,X)_i\text{-}N_b\text{-}\,Y\,Y\,Y\,\text{-}N_b\text{-}(Z\,Z\,Z)_j\text{-}N_a\text{-}n_q\ 3' \\ &\text{antisense:} && 3'\ n_p'\text{-}N_a'\text{-}(X'X'X')_k\text{-}N_b'\text{-}Y'Y'Y'\text{-}N_b'\text{-}(Z'Z'Z')_l\text{-}N_a'\text{-}n_q'\ 5' \end{aligned} \qquad \text{(III)}$$

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 modified nucleotides, each sequence comprising at least two differently modified nucleotides;

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

wherein

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

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

[0171] 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 1 are 1.

[0172] Exemplary combinations of the sense strand and antisense strand forming a RNAi duplex include the formulas below:

$$\begin{array}{l} 5'\ n_p - N_a - Y\ Y\ Y - N_a - n_q\ 3' \\ 3'\ n_p' - N_a' - Y'Y'Y' - N_a' n_q'\ 5' \end{array}$$

(IIIa)

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

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

(IIIb)

$$\begin{array}{l} 5'\ n_p - N_a - X\ X\ X - N_b - Y\ Y\ Y - N_a - n_q\ 3' \\ 3'\ n_p' - N_a' - X'X'X' - N_b' - Y'Y'Y' - N_a' - n_q'\ 5' \end{array}$$

(IIIc)

$$\begin{array}{l} 5'\ n_p - N_a - X\ X\ X - N_b - Y\ Y\ Y - N_b - Z\ Z\ Z - N_a - n_q\ 3' \\ 3'\ n_p' - N_a' - X'X'X' - N_b' - Y'Y'Y' - N_b' - Z'Z'Z' - N_a - n_q'\ 5' \end{array}$$

(IIId)

[0173] When the RNAi agent is represented by formula (IIIa), each N_a independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

[0174] When the RNAi agent is represented by formula (IIIb), each N_b independently represents an oligonucleotide sequence comprising 1-10, 1-7, 1-5 or 1-4 modified nucleotides. Each N_a independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

[0175] When the RNAi agent is represented as formula (IIIc), each N_b, N_b' independently represents an oligonucleotide sequence comprising 0-10, 0-7, 0-10, 0-7, 0-5, 0-4, 0-2 or 0modified nucleotides. Each N_a independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

[0176] When the RNAi agent is represented as formula (IIId), each N_b, N_b' independently represents an oligonucleotide sequence comprising 0-10, 0-7, 0-10, 0-7, 0-5, 0-4, 0-2 or 0modified nucleotides. Each N_a, N_a' independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides. Each of N_a, N_a', N_b and N_b' independently comprises modifications of alternating pattern.

[0177] Each of X, Y and Z in formulas (III), (IIIa), (IIIb), (IIIc), and (IIId) may be the same or different from each other.

[0178] 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.

[0179] 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.

[0180] 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.

[0181] In one implementation, 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.

[0182] In one implementation, when the RNAi agent is represented by formula (IIId), the N_a modifications are 2'-O-methyl or 2'-fluoro modifications. In another embodiment, when the RNAi agent is represented by formula (IIId), the N_a modifications are 2'-O-methyl or 2'-fluoro modifications and n_p' >0 and at least one n_p' is linked to a neighboring nucleotide a via phosphorothioate linkage. In yet another embodiment, when the RNAi agent is represented by formula (IIId), the N_a modifications are 2'-O-methyl or 2'-fluoro modifications, n_p' >0 and at least one n_p' is linked to a neighboring nucleotide via phosphorothioate linkage, and the sense strand is conjugated to one or more GalNAc derivatives attached through a bivalent or trivalent branched linker. In another embodiment, when the RNAi agent is represented by formula (IIId), the N_a modifications are 2'-O-methyl or 2'-fluoro modifications , n_p' >0 and at least one n_p' is linked to a neighboring nucleotide via phosphorothioate linkage, the sense strand comprises at least one phosphorothioate linkage, and the sense strand is conjugated to one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

[0183] In one implementation, when the RNAi agent is represented by formula (IIIa), the N_a modifications are 2'-O-methyl or 2'-fluoro modifications , n_p' >0 and at least one n_p' is linked to a neighboring nucleotide via phosphorothioate linkage, the sense strand comprises at least one phosphorothioate linkage, and the sense strand is conjugated to one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

[0184] In one implementation, 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.

[0185] In one implementation, 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.

[0186] In one implementation, two RNAi agents represented by formula (III), (IIIa), (IIIb), (IIIc), and (IIId) are linked to each other at the 5' end, and one or both of the 3' ends and are optionally conjugated to to a ligand. Each of the agents can target the same gene or two different genes; or each of the agents can target same gene at two different target sites.

[0187] 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.

[0188] 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.

[0189] 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.

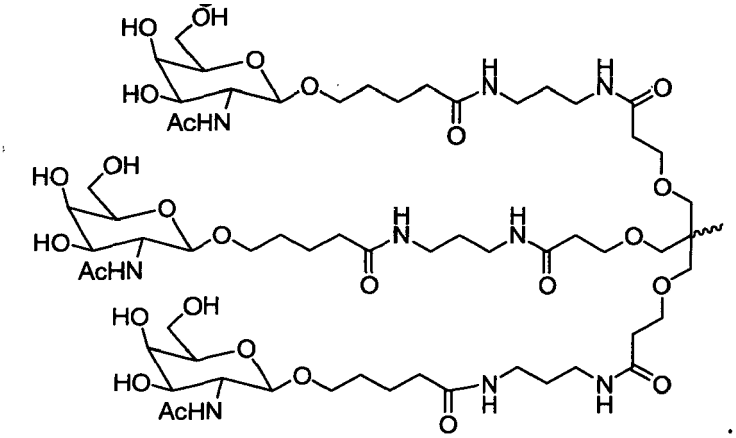
[0190] The RNAi agents may be conjugated to a ligand *via* a carrier, wherein the carrier can be cyclic group or acyclic group; preferably, the cyclic group is selected from pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, [1,3]dioxolane, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl, tetrahydrofuryl and and decalin; preferably, the acyclic group is selected from serinol backbone or diethanolamine backbone.

[0191] In certain specific implementations, the RNAi agent for use in the methods of the invention is an agent selected from the group of agents listed in Table 1 and Table 2.

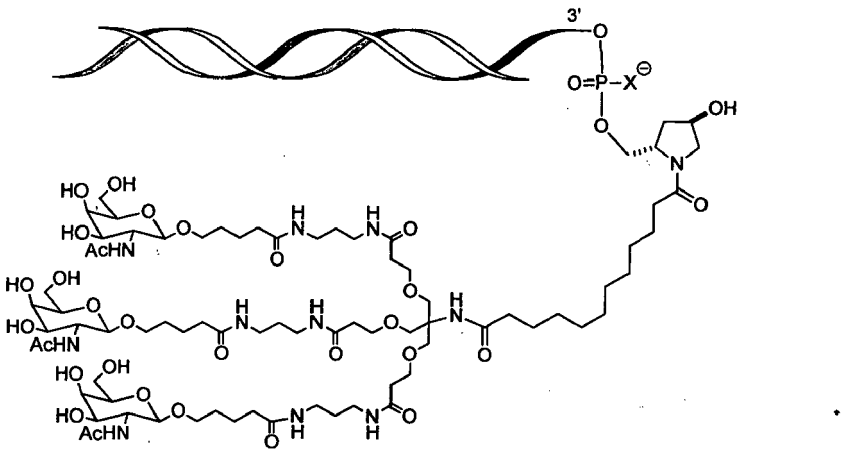
[0192] These agents may further comprise a ligand.

A. Ligands

[0193] The double-stranded RNA (dsRNA) agents may optionally be conjugated to one or more ligands. The ligand can be attached to the sense strand, antisense strand or both strands, at the 3'-end, 5'-end or both ends. For instance, the ligand may be conjugated to the sense strand. In preferred embodiments, the ligand is conjgated to the 3'-end of the sense strand. In one preferred embodiment, the ligand is a GalNAc ligand. In particularly preferred embodiments, the ligand is $GalNAc_3$:



[0194] In some embodiments, the ligand, e.g., GalNAc ligand, is attached to the 3' end of the RNAi agent. In one embodiment, the RNAi agent is conjugated to the ligand, e.g., GalNAc ligand, as shown in the following schematic



wherein X is O or S. In one implementation, X is O.

[0195] A wide variety of entities can be coupled to the RNAi agents of the present invention. Preferred moieties are ligands, which are coupled, preferably covalently, either directly or indirectly *via* an intervening tether.

[0196] In preferred implementations, a ligand alters the distribution, targeting or lifetime of the molecule into which it is incorporated. In preferred implementations a ligand provides an enhanced affinity for a selected target, *e.g.*, molecule, cell or cell type, compartment, receptor *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. Ligands providing enhanced affinity for a selected target are also termed targeting ligands.

[0197] Some ligands can have endosomolytic properties. The endosomolytic ligands promote the lysis of the endosome and/or transport of the composition of the invention, or its components, from the endosome to the cytoplasm of the cell. The endosomolytic ligand may be a polyanionic peptide or peptidomimetic which shows pH-dependent membrane activity and fusogenicity. In one embodiment, the endosomolytic ligand assumes its active conformation at endosomal pH. The "active" conformation is that conformation in which the endosomolytic ligand promotes lysis of the endosome and/or transport of the composition of the invention, or its components, from the endosome to the cytoplasm of the cell. Exemplary

endosomolytic ligands include the GALA peptide (Subbarao et al., Biochemistry, 1987, 26: 2964-2972), the EALA peptide (Vogel et al., J. Am. Chem. Soc., 1996, 118: 1581-1586), and their derivatives (Turk et al., Biochem. Biophys. Acta, 2002, 1559: 56-68). In one embodiment, the endosomolytic component may contain a chemical group (*e.g.*, an amino acid) which will undergo a change in charge or protonation in response to a change in pH. The endosomolytic component may be linear or branched.

[0198] Ligands can improve transport, hybridization, and specificity properties and may also improve nuclease resistance of the resultant natural or modified oligoribonucleotide, or a polymeric molecule comprising any combination of monomers described herein and/or natural or modified ribonucleotides.

[0199] Ligands in general can include therapeutic modifiers, *e.g.*, for enhancing uptake; diagnostic compounds or reporter groups *e.g.*, for monitoring distribution; cross-linking agents; and nuclease-resistance conferring moieties. General examples include lipids, steroids, vitamins, sugars, proteins, peptides, polyamines, and peptide mimics.

[0200] Ligands can include a naturally occurring substance, such as a protein (*e.g.*, human serum albumin (HSA), low-density lipoprotein (LDL), high-density lipoprotein (HDL), or globulin); a carbohydrate (*e.g.*, a dextran, pullulan, chitin, chitosan, inulin, cyclodextrin or hyaluronic acid); or a lipid. The ligand may also be a recombinant or synthetic molecule, such as a synthetic polymer, *e.g.,* a synthetic polyamino acid, an oligonucleotide (*e.g.*, an aptamer). 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.

[0201] 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, biotin, an RGD peptide, an RGD peptide mimetic or an aptamer.

[0202] Other examples of ligands include dyes, intercalating agents (*e.g.*, acridines), crosslinkers (*e.g.*, psoralene, mitomycin C), porphyrins (TPPC4, texaphyrin, Sapphyrin), polycyclic aromatic hydrocarbons (*e.g.*, phenazine, dihydrophenazine), artificial endonucleases or a chelator (*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.

[0203] 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 cancer cell, endothelial cell, or bone cell. Ligands may also include hormones and hormone receptors. They can also include non-peptidic species, such as lipids, lectins, carbohydrates, vitamins, cofactors, multivalent lactose, multivalent galactose, N-acetylgalactosamine, N-acetyl-gulucosamine multivalent mannose, multivalent fucose, or aptamers. The ligand can be, for example, a lipopolysaccharide, an activator of p38 MAP kinase, or an activator of NF-κB.

[0204] 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.

[0205] The ligand can increase the uptake of the oligonucleotide into the cell by, for example, activating an inflammatory response. Exemplary ligands that would have such an effect include tumor necrosis factor alpha (TNFalpha), interleukin-1 beta, or gamma interferon.

[0206] In one aspect, the ligand 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, naproxen 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.

[0207] A lipid based ligand can be used to modulate, *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.

[0208] In a preferred implementation, 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.

[0209] In another preferred implementation, 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.

[0210] In another aspect, the ligand is a moiety, *e.g.*, a vitamin, which is taken up by a target cell, *e.g.,* a proliferating cell. These are particularly useful for treating disorders characterized by unwanted cell proliferation, *e.g.,* of the malignant or non-malignant type, e.g., cancer cells. Exemplary vitamins include vitamin A, E, and K. Other exemplary vitamins include B vitamins, *e.g.*, folic acid, B12, riboflavin, biotin, pyridoxal or other vitamins or nutrients taken up by cancer cells. Also included are HAS, low density lipoprotein (LDL) and high-density lipoprotein (HDL).

[0211] 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.

[0212] The ligand can be a peptide or peptidomimetic. A peptidomimetic (also referred to herein as an oligopeptido-mimetic) is a molecule capable of folding into a defined three-dimensional structure similar to a natural peptide. The peptide or peptidomimetic moiety can be about 5-50 amino acids long, *e.g.,* about 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 amino acids long. A peptide or peptidomimetic can be, for example, a cell permeation peptide, cationic peptide, amphipathic peptide, or hydrophobic peptide (*e.g.*, consisting primarily of Tyr, Trp or Phe). The peptide moiety can be a dendrimer peptide, constrained peptide or crosslinked peptide. In another alternative, the peptide moiety can include a hydrophobic membrane translocation sequence (MTS). An exemplary hydrophobic MTS-containing peptide is RFGF having the amino acid sequence AAVALLPAVLLALLAP (SEQ ID NO: 1). An RFGF analogue (*e.g.*, amino acid sequence AALLPVLLAAP (SEQ ID NO: 2)) 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: 3)) and the Drosophila Antennapedia protein (RQIKIWFQNRRMKWKK (SEQ ID NO: 4)) 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). Preferably the peptide or peptidomimetic tethered to an iRNA agent via an incorporated monomer unit is a cell targeting peptide such as an arginine-glycine-aspartic acid (RGD)-peptide, or RGD mimic. A peptide moiety can range in length from about 5 amino acids to about 40 amino acids. The peptide moieties can have a structural modification, such as to increase stability or direct conformational properties. Any of the structural modifications described below can be utilized.An RGD peptide moiety can be used to target a tumor cell, such as an endothelial tumor cell or a breast cancer tumor cell (Zitzmann et al., Cancer Res., 62:5139-43, 2002). An RGD peptide can facilitate targeting of an iRNA agent to tumors of a variety of other tissues, including the lung, kidney, spleen, or liver (Aoki et al., Cancer Gene Therapy 8:783-787, 2001). Preferably, the RGD peptide will facilitate targeting of an iRNA agent to the kidney. The RGD peptide can be linear or cyclic, and can be modified, *e.g.*, glycosylated or methylated to facilitate targeting to specific tissues. For example, a glycosylated RGD peptide can deliver an iRNA agent to a tumor cell expressing $\alpha_V ß_3$ (Haubner et al., Jour. Nucl. Med., 42:326-336, 2001). Peptides that target markers enriched in proliferating cells can be used. For example, RGD containing peptides and peptidomimetics can target cancer cells, in particular cells that exhibit an integrin. Thus, one could use RGD peptides, cyclic peptides containing RGD, RGD peptides that include D-amino acids, as well as synthetic RGD mimics. In addition to RGD, one can use other moieties that target the integrin ligand. Generally, such ligands can be used to control proliferating cells and angiogeneis. Preferred conjugates of this type of ligand target PECAM-1, VEGF, or other cancer gene, *e.g.,* a cancer gene described herein.

[0213] A "cell permeation peptide" is capable of permeating a cell, *e.g.,* a microbial cell, such as a bacterial or fungal cell, or a mammalian cell, such as a human cell. A microbial cell-permeating peptide can be, for example, an α-helical linear peptide (*e.g.*, LL-37 or Ceropin P1), a disulfide bond-containing peptide (*e.g.*, α-defensin, β-defensin or bactenecin), or a peptide containing only one or two dominating amino acids (*e.g.*, PR-39 or indolicidin). A cell permeation peptide can also include a nuclear localization signal (NLS). For example, a cell permeation peptide can be a bipartite amphipathic peptide, such as MPG, which is derived from the fusion peptide domain of HIV-1 gp41 and the NLS of SV40 large T antigen (Simeoni et al., Nucl. Acids Res. 31:2717-2724, 2003).

[0214] In one implementation, a targeting peptide can be an amphipathic α-helical peptide. Exemplary amphipathic α-helical peptides include, but are not limited to, cecropins, lycotoxins, paradaxins, buforin, CPF, bombinin-like peptide

(BLP), cathelicidins, ceratotoxins, S. clava peptides, hagfish intestinal antimicrobial peptides (HFIAPs), magainines, brevinins-2, dermaseptins, melittins, pleurocidin, H_2A peptides, Xenopus peptides, esculentinis-1, and caerins. A number of factors will preferably be considered to maintain the integrity of helix stability. For example, a maximum number of helix stabilization residues will be utilized (*e.g.*, leu, ala, or lys), and a minimum number helix destabilization residues will be utilized (*e.g.*, proline, or cyclic monomeric units. The capping residue will be considered (for example Gly is an exemplary N-capping residue and/or C-terminal amidation can be used to provide an extra H-bond to stabilize the helix. Formation of salt bridges between residues with opposite charges, separated by i $\pm$ 3, or i $\pm$ 4 positions can provide stability. For example, cationic residues such as lysine, arginine, homo-arginine, ornithine or histidine can form salt bridges with the anionic residues glutamate or aspartate.

[0215] Peptide and peptidomimetic ligands include those having naturally occurring or modified peptides, *e.g.,* D or L peptides; α, β, or γ peptides; N-methyl peptides; azapeptides; peptides having one or more amide, *i.e.,* peptide, linkages replaced with one or more urea, thiourea, carbamate, or sulfonyl urea linkages; or cyclic peptides.

[0216] The targeting ligand can be any ligand that is capable of targeting a specific receptor. Examples are: folate, GalNAc, galactose, mannose, mannose-6P, clusters of sugars such as GalNAc cluster, mannose cluster, galactose cluster, or an apatamer. A cluster is a combination of two or more sugar units. The targeting ligands also include integrin receptor ligands, Chemokine receptor ligands, transferrin, biotin, serotonin receptor ligands, PSMA, endothelin, GCPII, somatostatin, LDL and HDL ligands. The ligands can also be based on nucleic acid, e.g., an aptamer. The aptamer can be unmodified or have any combination of modifications disclosed herein.

[0217] Endosomal release agents include imidazoles, poly or oligoimidazoles, PEIs, peptides, fusogenic peptides, polycaboxylates, polyacations, masked oligo or poly cations or anions, acetals, polyacetals, ketals/polyketyals, orthoesters, polymers with masked or unmasked cationic or anionic charges, dendrimers with masked or unmasked cationic or anionic charges.

[0218] PK modulator stands for pharmacokinetic modulator. PK modulators include lipophiles, bile acids, steroids, phospholipid analogues, peptides, protein binding agents, PEG, vitamins etc. Examplary 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 phosphorothioate linkages in the backbaone are also amenable to the present invention as ligands (*e.g.,* as PK modulating ligands).

[0219] In addition, aptamers that bind serum components (*e.g.*, serum proteins) are also amenable to the present invention as PK modulating ligands.

[0220] Other ligand conjugates amenable to the invention are described in U.S. Patent Applications USSN: 10/916,185, filed August 10, 2004; USSN: 10/946,873, filed September 21, 2004; USSN: 10/833,934, filed August 3, 2007; USSN: 11/115,989 filed April 27, 2005 and USSN: 11/944,227 filed November 21, 2007.

[0221] When two or more ligands are present, the ligands can all have same properties, all have different properties or some ligands have the same properties while others have different properties. For example, a ligand can have targeting properties, have endosomolytic activity or have PK modulating properties. In a preferred embodiment, all the ligands have different properties.

[0222] Ligands can be coupled to the oligonucleotides at various places, for example, 3'-end, 5'-end, and/or at an internal position. In preferred embodiments, the ligand is attached to the oligonucleotides *via* an intervening tether, *e.g.,* a carrier described herein. The ligand or tethered ligand may be present on a monomer when the monomer is incorporated into the growing strand. In some embodiments, the ligand may be incorporated via coupling to a "precursor" monomer after the "precursor" monomer has been incorporated into the growing strand. For example, a monomer having, *e.g.,* an amino-terminated tether (*i.e.*, having no associated ligand), *e.g.*, TAP-$(CH_2)_nNH_2$ maybe incorporated into a growing oligonucelotide strand. In a subsequent operation, *i.e.,* after incorporation of the precursor monomer into the strand, a ligand having an electrophilic group, *e.g.*, a pentafluorophenyl ester or aldehyde group, can subsequently be attached to the precursor monomer by coupling the electrophilic group of the ligand with the terminal nucleophilic group of the precursor monomer's tether.

[0223] In another example, a monomer having a chemical group suitable for taking part in Click Chemistry reaction may be incorporated, *e.g.*, an azide or alkyne terminated tether/linker. In a subsequent operation, *i.e.,* after incorporation of the precursor monomer into the strand, a ligand having complementary chemical group, *e.g.* an alkyne or azide can be attached to the precursor monomer by coupling the alkyne and the azide together.

[0224] For double- stranded oligonucleotides, ligands can be attached to one or both strands. In some embodiments, a double-stranded iRNA agent contains a ligand conjugated to the sense strand. In other embodiments, a double-stranded iRNA agent contains a ligand conjugated to the antisense strand.

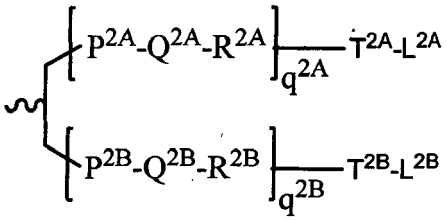
[0225] In some implementations, ligand can be conjugated to nucleobases, sugar moieties, or internucleosidic linkages of nucleic acid molecules. Conjugation to purine nucleobases or derivatives thereof can occur at any position including, endocyclic and exocyclic atoms. In some embodiments, the 2-, 6-, 7-, or 8-positions of a purine nucleobase are attached

to a conjugate moiety. Conjugation to pyrimidine nucleobases or derivatives thereof can also occur at any position. In some embodiments, the 2-, 5-, and 6-positions of a pyrimidine nucleobase can be substituted with a conjugate moiety. Conjugation to sugar moieties of nucleosides can occur at any carbon atom. Example carbon atoms of a sugar moiety that can be attached to a conjugate moiety include the 2', 3', and 5' carbon atoms. The 1' position can also be attached to a conjugate moiety, such as in an abasic residue. Internucleosidic linkages can also bear conjugate moieties. For phosphorus-containing linkages (*e.g.*, phosphodiester, phosphorothioate, phosphorodithiotate, phosphoroamidate, and the like), the conjugate moiety can be attached directly to the phosphorus atom or to an O, N, or S atom bound to the phosphorus atom. For amine- or amide-containing internucleosidic linkages *(e.g.,* PNA), the conjugate moiety can be attached to the nitrogen atom of the amine or amide or to an adjacent carbon atom.

[0226] Any suitable ligand in the field of RNA interference may be used, although the ligand is typically a carbohydrate *e.g.* monosaccharide (such as GalNAc), disaccharide, trisaccharide, tetrasaccharide, polysaccharide.

[0227] Linkers that conjugate the ligand to the nucleic acid include those discussed above. For example, the ligand can be one or more GalNAc (*N*-acetylglucosamine) derivatives attached through a bivalent or trivalent branched linker.

[0228] In one implementation, the dsRNA of the invention is conjugated to a bivalent and trivalent branched linkers include the structures shown in any of formula (IV) - (VII):



Formula (IV)

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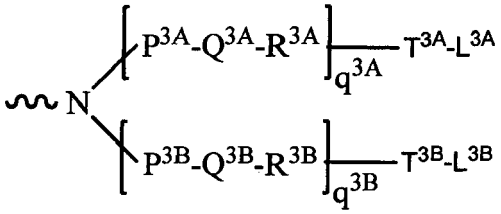

Formula (V)

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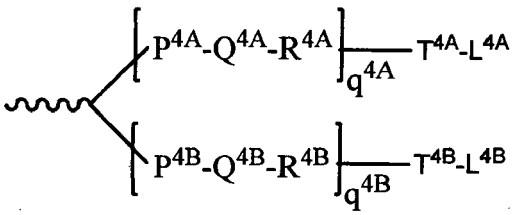
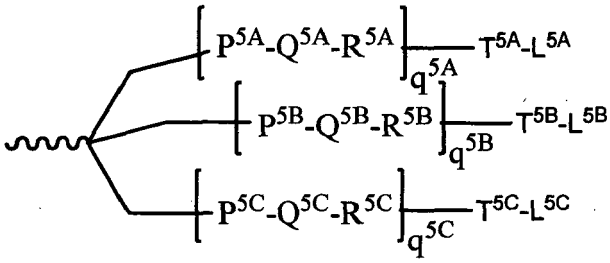


Formula (VI)

, or



Formula (VII)

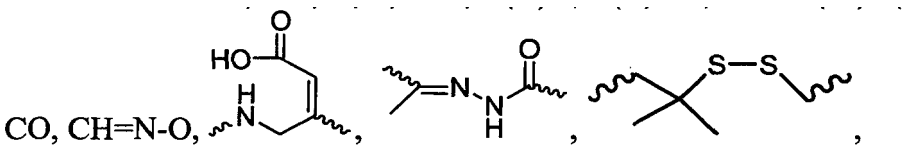
;

wherein:

q^{2A}, q^{2B}, q^{3A}, q^{3B}, $q4^{A}$ q^{4B}, q^{5A}, q^{5B} and q^{5C} represent independently for each occurrence 0-20 and wherein the repeating unit can be the same or different; P^{2A}, P^{2B}, P^{3A}, P^{3B}, P^{4A}, P^{4B}, P^{5A}, P^{5B}, P^{5C}, T^{2A}, T^{2B}, T^{3A}, T^{3B}, T^{4A}, T^{4B}, T^{4A}, T^{5B}, T^{5C} are each independently for each occurrence absent, CO, NH, O, S, OC(O), NHC(O), CH_2, CH_2NH or CH_2O;

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

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



CO, CH=N-O,

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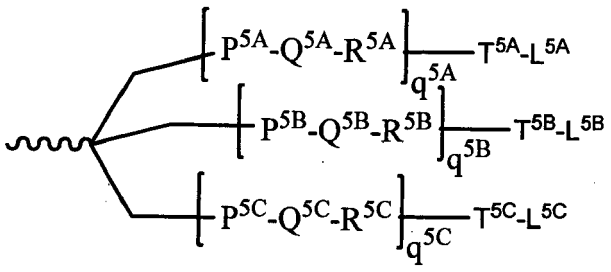
or heterocyclyl;

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

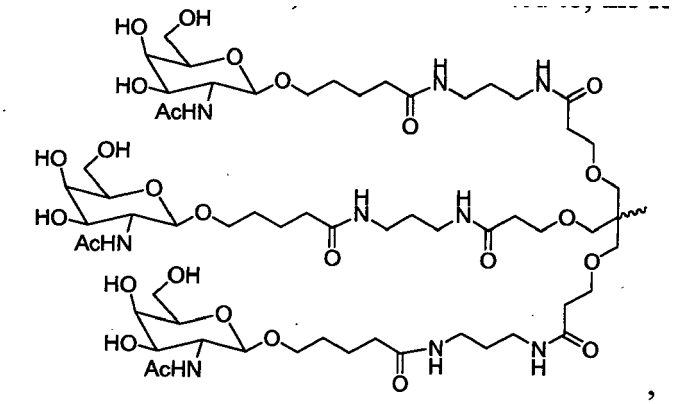
R^a is H or amino acid side chain.

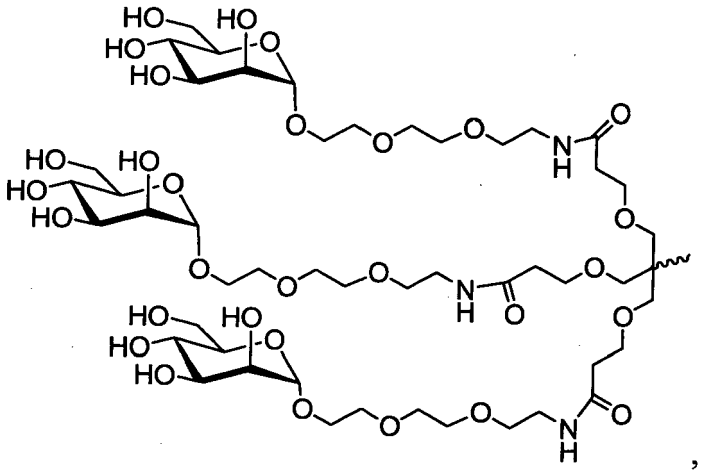
[0229] Trivalent conjugating GalNAc derivatives are particularly useful for use with RNAi agents for inhibiting the expression of a target gene, such as those of formula (VII):



Formula (VII)

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 following compounds:





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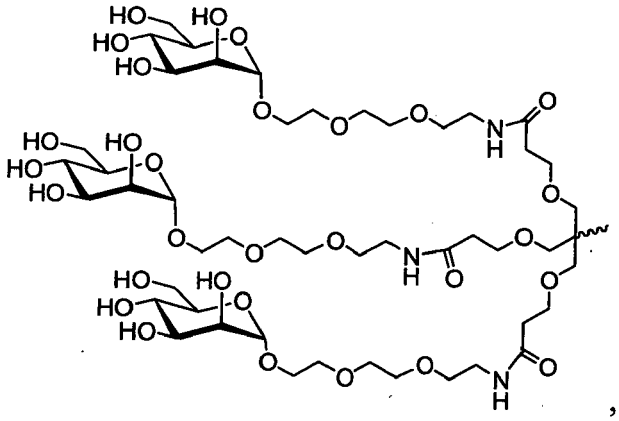

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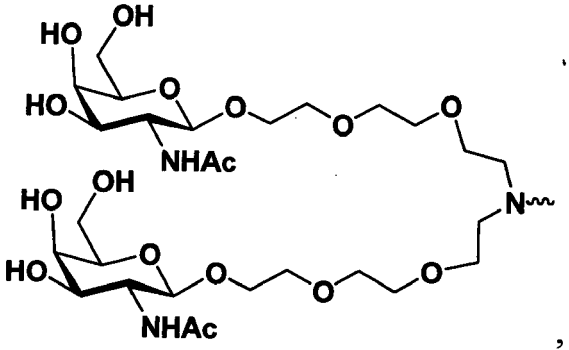

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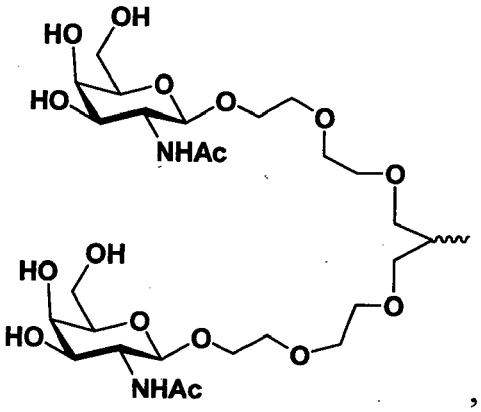

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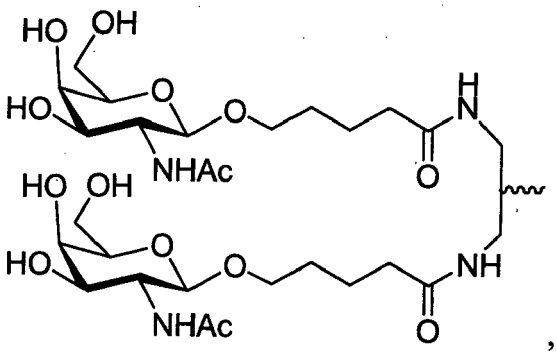

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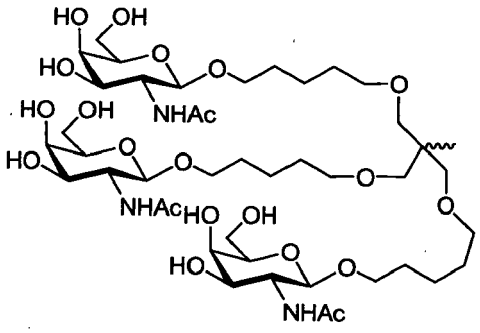

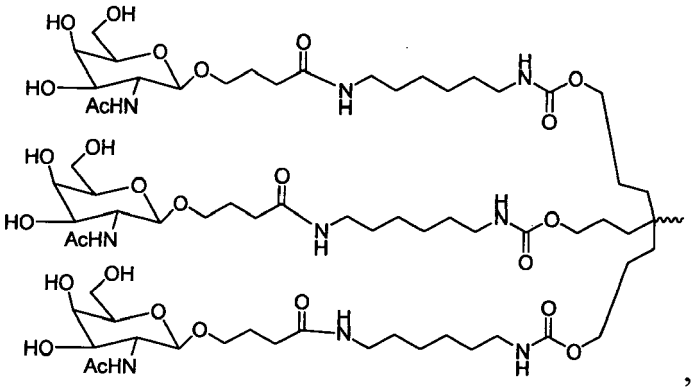

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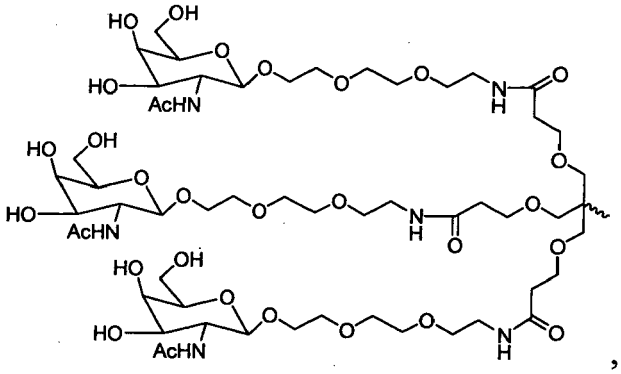

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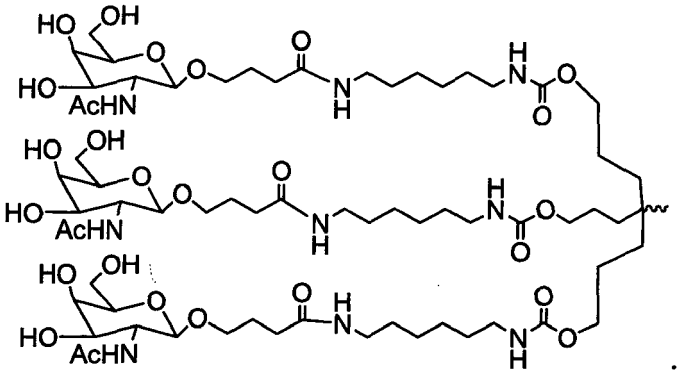
or



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[0230] In other implementations, the RNAi agent for use in the methods of the invention is an agent selected from the group consisting of AD-53815, AD-56663, AD-56658, AD-56676, AD-56666, AD-57928, and AD-60212.

III. Delivery of an iRNA of the Invention

[0231] The delivery of an iRNA agent 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 lipid disorder, such as a hyperlipidemia) 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.

[0232] 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 implementations, 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.

A. Vector encoded iRNAs of the Invention

[0233] iRNA targeting the PCSK9 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., Proc. Natl. Acad. Sci. USA (1995) 92:1292).

[0234] 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.

[0235] 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.

[0236] iRNA expression plasmids can be transfected into target cells as a complex with cationic lipid carriers (*e.g.*, Oligofectamine) or non-cationic lipid-based carriers (*e.g.*, Transit-TKO™). Multiple lipid transfections for iRNA-mediated knockdowns targeting different regions of a target RNA over a period of a week or more are also contemplated by the invention. Successful introduction of vectors into host cells can be monitored using various known methods. For example, transient transfection can be signaled with a reporter, such as a fluorescent marker, such as Green Fluorescent Protein (GFP). Stable transfection of cells *ex vivo* can be ensured using markers that provide the transfected cell with resistance to specific environmental factors (*e.g.*, antibiotics and drugs), such as hygromycin B resistance.

[0237] 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 further described below.

[0238] Vectors useful for the delivery of an iRNA will include regulatory elements (promoter, enhancer, *etc.*) sufficient for expression of the iRNA in the desired target cell or tissue. The regulatory elements can be chosen to provide either constitutive or regulated/inducible expression.

[0239] Expression of the iRNA can be precisely regulated, for example, by using an inducible regulatory sequence that is sensitive to certain physiological regulators, e.g., circulating glucose levels, or hormones (Docherty et al., 1994, FASEB J. 8:20-24). Such inducible expression systems, suitable for the control of dsRNA expression in cells or in mammals include, for example, regulation by ecdysone, by estrogen, progesterone, tetracycline, chemical inducers of dimerization, and isopropyl-beta-D1 - thiogalactopyranoside (IPTG). A person skilled in the art would be able to choose the appropriate regulatory/promoter sequence based on the intended use of the iRNA transgene.

[0240] Viral vectors that contain nucleic acid sequences encoding an iRNA can be used. For example, a retroviral vector can be used (see Miller et al., Meth. Enzymol. 217:581-599 (1993)). These retroviral vectors contain the components necessary for the correct packaging of the viral genome and integration into the host cell DNA. The nucleic acid sequences encoding an iRNA are cloned into one or more vectors, which facilitate delivery of the nucleic acid into a patient. More detail about retroviral vectors can be found, for example, in Boesen et al., Biotherapy 6:291-302 (1994), which describes the use of a retroviral vector to deliver the mdr1 gene to hematopoietic stem cells in order to make the stem cells more resistant to chemotherapy. Other references illustrating the use of retroviral vectors in gene therapy are: Clowes et al., J. Clin. Invest. 93:644-651 (1994); Kiem et al., Blood 83:1467-1473 (1994); Salmons and Gunzberg, Human Gene Therapy 4:129-141 (1993); and Grossman and Wilson, Curr. Opin. in Genetics and Devel. 3:110-114 (1993). Lentiviral vectors contemplated for use include, for example, the HIV based vectors described in U.S. Patent Nos. 6,143,520; 5,665,557; and 5,981,276.

[0241] Adenoviruses are also contemplated for use in delivery of iRNAs of the invention. Adenoviruses are especially attractive vehicles, *e.g.,* for delivering genes to respiratory epithelia. Adenoviruses naturally infect respiratory epithelia

where they cause a mild disease. Other targets for adenovirus-based delivery systems are liver, the central nervous system, endothelial cells, and muscle. Adenoviruses have the advantage of being capable of infecting non-dividing cells. Kozarsky and Wilson, Current Opinion in Genetics and Development 3:499-503 (1993) present a review of adenovirus-based gene therapy. Bout et al., Human Gene Therapy 5:3-10 (1994) demonstrated the use of adenovirus vectors to transfer genes to the respiratory epithelia of rhesus monkeys. Other instances of the use of adenoviruses in gene therapy can be found in Rosenfeld et al., Science 252:431-434 (1991); Rosenfeld et al., Cell 68:143-155 (1992); Mastrangeli et al., J. Clin. Invest. 91:225-234 (1993); PCT Publication WO94/12649; and Wang, et al., Gene Therapy 2:775-783 (1995). A suitable AV vector for expressing an iRNA featured in the invention, a method for constructing the recombinant AV vector, and a method for delivering the vector into target cells, are described in Xia H et al. (2002), Nat. Biotech. 20: 1006-1010.

[0242] Adeno-associated virus (AAV) vectors may also be used to delivery an iRNA of the invention (Walsh et al., Proc. Soc. Exp. Biol. Med. 204:289-300 (1993); U.S. Pat. No. 5,436,146). In one embodiment, the iRNA can be expressed as two separate, complementary single-stranded RNA molecules from a recombinant AAV vector having, for example, either the U6 or H1 RNA promoters, or the cytomegalovirus (CMV) promoter. Suitable AAV vectors for expressing the dsRNA featured in the invention, methods for constructing the recombinant AV vector, and methods for delivering the vectors into target cells are described in Samulski R et al. (1987), J. Virol. 61: 3096-3101; Fisher K J et al. (1996), J. Virol, 70: 520-532; Samulski R et al. (1989), J. Virol. 63: 3822-3826; U.S. Pat. No. 5,252,479; U.S. Pat. No. 5,139,941; International Patent Application No. WO 94/13788; and International Patent Application No. WO 93/24641, the entire disclosures of which are herein incorporated by reference.

[0243] Another viral vector suitable for delivery of an iRNA of the inevtion is a pox virus such as a vaccinia virus, for example an attenuated vaccinia such as Modified Virus Ankara (MVA) or NYVAC, an avipox such as fowl pox or canary pox.

[0244] The tropism of viral vectors can be modified by pseudotyping the vectors with envelope proteins or other surface antigens from other viruses, or by substituting different viral capsid proteins, as appropriate. For example, lentiviral vectors can be pseudotyped with surface proteins from vesicular stomatitis virus (VSV), rabies, Ebola, Mokola, and the like. AAV vectors can be made to target different cells by engineering the vectors to express different capsid protein serotypes; see, *e.g.,* Rabinowitz J E et al. (2002), J Virol 76:791-801.

[0245] The pharmaceutical preparation of a vector can include the vector in an acceptable diluent, or can include a slow release matrix in which the gene delivery vehicle is imbedded. Alternatively, where the complete gene delivery vector can be produced intact from recombinant cells, *e.g.*, retroviral vectors, the pharmaceutical preparation can include one or more cells which produce the gene delivery system.

V. Pharmaceutical Compositions of the Invention

[0246] The present invention also includes pharmaceutical compositions and formulations which include the iRNAs of the invention. In one implementation, provided herein are pharmaceutical compositions containing an iRNA, as described herein, and a pharmaceutically acceptable carrier. The pharmaceutical compositions containing the iRNA are useful for treating a disease or disorder associated with the expression or activity of a PCSK9 gene, *e.g.* a lipid 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) delivery. Another example is compositions that are formulated for direct delivery into the brain parenchyma, *e.g.*, by infusion into the brain, such as by continuous pump infusion.

[0247] The pharmaceutical compositions comprising RNAi agents of the invention may be, for example, solutions with or without a buffer, or compositions containing pharmaceutically acceptable carriers. Such compositions include, for example, aqueous or crystalline compositions, liposomal formulations, micellar formulations, emulsions, and gene therapy vectors.

[0248] In the described methods , the RNAi agent may be administered in a solution. A free RNAi agent may be administered in an unbuffered solution, e.g., in saline or in water. Alternatively, the free siRNA may also be administred in a suitable buffer solution. The buffer solution may comprise acetate, citrate, prolamine, carbonate, or phosphate, or any combination thereof. In a preferred embodiment, the buffer solution is phosphate buffered saline (PBS). The pH and osmolarity of the buffer solution containing the RNAi agent can be adjusted such that it is suitable for administering to a subject.

[0249] In some implementations, the buffer solution further comprises an agent for controlling the osmolarity of the solution, such that the osmolarity is kept at a desired value, *e.g.,* at the physiologic values of the human plasma. Solutes which can be added to the buffer solution to control the osmolarity include, but are not limited to, proteins, peptides, amino acids, non-metabolized polymers, vitamins, ions, sugars, metabolites, organic acids, lipids, or salts. In some embodiments, the agent for controlling the osmolarity of the solution is a salt. In certain implementations, the agent for controlling the osmolarity of the solution is sodium chloride or potassium chloride.

[0250] The pharmaceutical compositions of the invention may be administered in dosages sufficient to inhibit expression of a PCSK9 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. For example, the dsRNA can be administered at about 0.01 mg/kg, about 0.05 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 1.5 mg/kg, about 2 mg/kg, about 3 mg/kg, about 10 mg/kg, about 20 mg/kg, about 30 mg/kg, about 40 mg/kg, or about 50 mg/kg per single dose.

[0251] For example, the RNAi agent, e.g., dsRNA, may be administered at a dose of about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, or about 10 mg/kg. Values and ranges intermediate to the recited values are also intended to be part of this invention.

[0252] In another implementation, the RNAi agent, e.g., dsRNA, is administered at a dose of about 0.1 to about 50 mg/kg, about 0.25 to about 50 mg/kg, about 0.5 to about 50 mg/kg, about 0.75 to about 50 mg/kg, about 1 to about 50 mg/mg, about 1.5 to about 50 mg/kb, about 2 to about 50 mg/kg, about 2.5 to about 50 mg/kg, about 3 to about 50 mg/kg, about 3.5 to about 50 mg/kg, about 4 to about 50 mg/kg, about 4.5 to about 50 mg/kg, about 5 to about 50 mg/kg, about 7.5 to about 50 mg/kg, about 10 to about 50 mg/kg, about 15 to about 50 mg/kg, about 20 to about 50 mg/kg, about 20 to about 50 mg/kg, about 25 to about 50 mg/kg, about 25 to about 50 mg/kg, about 30 to about 50 mg/kg, about 35 to about 50 mg/kg, about 40 to about 50 mg/kg, about 45 to about 50 mg/kg, about 0.1 to about 45 mg/kg, about 0.25 to about 45 mg/kg, about 0.5 to about 45 mg/kg, about 0.75 to about 45 mg/kg, about 1 to about 45 mg/mg, about 1.5 to about 45 mg/kb, about 2 to about 45 mg/kg, about 2.5 to about 45 mg/kg, about 3 to about 45 mg/kg, about 3.5 to about 45 mg/kg, about 4 to about 45 mg/kg, about 4.5 to about 45 mg/kg, about 5 to about 45 mg/kg, about 7.5 to about 45 mg/kg, about 10 to about 45 mg/kg, about 15 to about 45 mg/kg, about 20 to about 45 mg/kg, about 20 to about 45 mg/kg, about 25 to about 45 mg/kg, about 25 to about 45 mg/kg, about 30 to about 45 mg/kg, about 35 to about 45 mg/kg, about 40 to about 45 mg/kg, about 0.1 to about 40 mg/kg, about 0.25 to about 40 mg/kg, about 0.5 to about 40 mg/kg, about 0.75 to about 40 mg/kg, about 1 to about 40 mg/mg, about 1.5 to about 40 mg/kb, about 2 to about 40 mg/kg, about 2.5 to about 40 mg/kg, about 3 to about 40 mg/kg, about 3.5 to about 40 mg/kg, about 4 to about 40 mg/kg, about 4.5 to about 40 mg/kg, about 5 to about 40 mg/kg, about 7.5 to about 40 mg/kg, about 10 to about 40 mg/kg, about 15 to about 40 mg/kg, about 20 to about 40 mg/kg, about 20 to about 40 mg/kg, about 25 to about 40 mg/kg, about 25 to about 40 mg/kg, about 30 to about 40 mg/kg, about 35 to about 40 mg/kg, about 0.1 to about 30 mg/kg, about 0.25 to about 30 mg/kg, about 0.5 to about 30 mg/kg, about 0.75 to about 30 mg/kg, about 1 to about 30 mg/mg, about 1.5 to about 30 mg/kb, about 2 to about 30 mg/kg, about 2.5 to about 30 mg/kg, about 3 to about 30 mg/kg, about 3.5 to about 30 mg/kg, about 4 to about 30 mg/kg, about 4.5 to about 30 mg/kg, about 5 to about 30 mg/kg, about 7.5 to about 30 mg/kg, about 10 to about 30 mg/kg, about 15 to about 30 mg/kg, about 20 to about 30 mg/kg, about 20 to about 30 mg/kg, about 25 to about 30 mg/kg, about 0.1 to about 20 mg/kg, about 0.25 to about 20 mg/kg, about 0.5 to about 20 mg/kg, about 0.75 to about 20 mg/kg, about 1 to about 20 mg/mg, about 1.5 to about 20 mg/kb, about 2 to about 20 mg/kg, about 2.5 to about 20 mg/kg, about 3 to about 20 mg/kg, about 3.5 to about 20 mg/kg, about 4 to about 20 mg/kg, about 4.5 to about 20 mg/kg, about 5 to about 20 mg/kg, about 7.5 to about 20 mg/kg, about 10 to about 20 mg/kg, or about 15 to about 20 mg/kg. Values and ranges intermediate to the recited values are also intended to be part of this invention.

[0253] For example, the RNAi agent, e.g., dsRNA, may be administered at a dose of about 0..01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, or about 10 mg/kg. Values and ranges intermediate to the recited values are also intended to be part of this disclosure.

[0254] In another implementation, the RNAi agent, *e.g.*,dsRNA, is administered at a dose of about 0.5 to about 50 mg/kg, about 0.75 to about 50 mg/kg, about 1 to about 50 mg/mg, about 1.5 to about 50 mg/kg, about 2 to about 50 mg/kg, about 2.5 to about 50 mg/kg, about 3 to about 50 mg/kg, about 3.5 to about 50 mg/kg, about 4 to about 50 mg/kg, about 4.5 to about 50 mg/kg, about 5 to about 50 mg/kg, about 7.5 to about 50 mg/kg, about 10 to about 50 mg/kg, about 15 to about 50 mg/kg, about 20 to about 50 mg/kg, about 20 to about 50 mg/kg, about 25 to about 50 mg/kg, about 25 to about 50 mg/kg, about 30 to about 50 mg/kg, about 35 to about 50 mg/kg, about 40 to about 50 mg/kg, about 45 to about 50 mg/kg, about 0.5 to about 45 mg/kg, about 0.75 to about 45 mg/kg, about 1 to about 45 mg/mg, about 1.5 to about 45 mg/kb, about 2 to about 45 mg/kg, about 2.5 to about 45 mg/kg, about 3 to about 45 mg/kg, about 3.5 to about 45 mg/kg, about 4 to about 45 mg/kg, about 4.5 to about 45 mg/kg, about 5 to about 45 mg/kg, about 7.5 to about 45 mg/kg, about 10 to about 45 mg/kg, about 15 to about 45 mg/kg, about 20 to about 45 mg/kg, about 20 to about 45 mg/kg, about 25 to about 45 mg/kg, about 25 to about 45 mg/kg, about 30 to about 45 mg/kg, about 35 to about 45 mg/kg, about 40 to about 45 mg/kg, about 0.5 to about 40 mg/kg, about 0.75 to about 40 mg/kg, about 1 to about 40

mg/mg, about 1.5 to about 40 mg/kb, about 2 to about 40 mg/kg, about 2.5 to about 40 mg/kg, about 3 to about 40 mg/kg, about 3.5 to about 40 mg/kg, about 4 to about 40 mg/kg, about 4.5 to about 40 mg/kg, about 5 to about 40 mg/kg, about 7.5 to about 40 mg/kg, about 10 to about 40 mg/kg, about 15 to about 40 mg/kg, about 20 to about 40 mg/kg, about 20 to about 40 mg/kg, about 25 to about 40 mg/kg, about 25 to about 40 mg/kg, about 30 to about 40 mg/kg, about 35 to about 40 mg/kg, about 0.5 to about 30 mg/kg, about 0.75 to about 30 mg/kg, about 1 to about 30 mg/mg, about 1.5 to about 30 mg/kb, about 2 to about 30 mg/kg, about 2.5 to about 30 mg/kg, about 3 to about 30 mg/kg, about 3.5 to about 30 mg/kg, about 4 to about 30 mg/kg, about 4.5 to about 30 mg/kg, about 5 to about 30 mg/kg, about 7.5 to about 30 mg/kg, about 10 to about 30 mg/kg, about 15 to about 30 mg/kg, about 20 to about 30 mg/kg, about 20 to about 30 mg/kg, about 25 to about 30 mg/kg, about 0.5 to about 20 mg/kg, about 0.75 to about 20 mg/kg, about 1 to about 20 mg/mg, about 1.5 to about 20 mg/kb, about 2 to about 20 mg/kg, about 2.5 to about 20 mg/kg, about 3 to about 20 mg/kg, about 3.5 to about 20 mg/kg, about 4 to about 20 mg/kg, about 4.5 to about 20 mg/kg, about 5 to about 20 mg/kg, about 7.5 to about 20 mg/kg, about 10 to about 20 mg/kg, or about 15 to about 20 mg/kg. In one embodiment, the dsRNA is administered at a dose of about 10mg/kg to about 30 mg/kg. Values and ranges intermediate to the recited values are also intended to be part of this disclosure.

[0255] For example, subjects can be administered a therapeutic amount of iRNA, such as about 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10, 10.5, 11, 11.5, 12, 12.5, 13, 13.5, 14, 14.5, 15, 15.5, 16, 16.5, 17, 17.5, 18, 18.5, 19, 19.5, 20, 20.5, 21, 21.5, 22, 22.5, 23, 23.5, 24, 24.5, 25, 25.5, 26, 26.5, 27, 27.5, 28, 28.5, 29, 29.5, 30, 31, 32, 33, 34, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or about 50 mg/kg. Values and ranges intermediate to the recited values are also intended to be part of this disclosure.

[0256] The pharmaceutical composition can be administered once daily, or the iRNA can be administered as two, three, or more sub-doses at appropriate intervals throughout the day or even using continuous infusion or delivery through a controlled release formulation. In that case, the iRNA contained in each sub-dose must be correspondingly smaller in order to achieve the total daily dosage. The dosage unit can also be compounded for delivery over several days, e.g., using a conventional sustained release formulation which provides sustained release of the iRNA over a several day period. Sustained release formulations are well known in the art and are particularly useful for delivery of agents at a particular site, such as could be used with the agents of the present invention. In this implementation, the dosage unit contains a corresponding multiple of the daily dose.

[0257] In other implementations, a single dose of the pharmaceutical compositions can be long lasting, such that subsequent doses are administered at not more than 3, 4, or 5 day intervals, or at not more than 1,2,3, or 4 week intervals. In some implementations , a single dose of the pharmaceutical compositions of the invention is administered once per week. In other implementations , a single dose of the pharmaceutical compositions of the invention is administered bi-monthly.

[0258] 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.

[0259] Advances in mouse genetics have generated a number of mouse models for the study of various human diseases, such as a bleeding disorder that would benefit from reduction in the expression of PCSK9. 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, a mouse containing a transgene expressing human PCSK9.

[0260] 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.

[0261] The iRNA can be delivered in a manner to target a particular tissue, such as the liver (*e.g.,* the hepatocytes of the liver).

[0262] 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.

A. iRNA Formulations Comprising Membranous Molecular Assemblies

[0263] 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. As used herein, the term "liposome" refers to a vesicle composed of amphiphilic lipids arranged in at least one bilayer, *e.g.*, one bilayer or a plurality of bilayers. Liposomes include unilamellar and multilamellar vesicles that have a membrane formed from a lipophilic material and an aqueous interior. The aqueous portion contains the iRNA composition. 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. 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 liposomal bilayer fuses with bilayer of the cellular membranes. As the merging of the liposome and cell progresses, the internal aqueous contents that include the iRNA are delivered into the cell where the iRNA can specifically bind to a target RNA and can mediate RNAi. In some cases the liposomes are also specifically targeted, *e.g.*, to direct the iRNA to particular cell types.

[0264] A liposome containing a RNAi 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 RNAi agent preparation is then added to the micelles that include the lipid component. The cationic groups on the lipid interact with the RNAi agent and condense around the RNAi agent to form a liposome. After condensation, the detergent is removed, *e.g.*, by dialysis, to yield a liposomal preparation of RNAi agent.

[0265] 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 adjusted to favor condensation.

[0266] 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. 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; U.S. Pat. No. 4,897,355; U.S. Pat. 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 RNAi agent preparations into liposomes.

[0267] Liposomes fall into two broad classes. Cationic liposomes are positively charged liposomes which interact with the negatively charged nucleic acid molecules to form a stable complex. The positively charged nucleic acid/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).

[0268] Liposomes which are pH-sensitive or negatively-charged, entrap nucleic acids rather than complex with it. Since both the nucleic acid and the lipid are similarly charged, repulsion rather than complex formation occurs. Nevertheless, some nucleic acid is entrapped within the aqueous interior of these liposomes. pH-sensitive liposomes have been used to deliver nucleic acids 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).

[0269] 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 phosphati-

dylglycerol, 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.

[0270] Examples of other methods to introduce liposomes into cells *in vitro* and *in vivo* include U.S. Pat. No. 5,283,185; U.S. Pat. No. 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.

[0271] 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 cyclosporine A into different layers of the skin (Hu et al. S.T.P.Pharma. Sci., 1994, 4(6) 466).

[0272] 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).

[0273] 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).

[0274] In one implementation, 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 RNAi agents to macrophages.

[0275] 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 RNAi agents 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.

[0276] 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 RNAi agent (see, e.g., Felgner, P. L. et al., Proc. Natl. Acad. Sci., USA 8:7413-7417, 1987 and U.S. Pat. No. 4,897,355 for a description of DOTMA and its use with DNA).

[0277] 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.

[0278] 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., U.S. Pat. No. 5,171,678).

[0279] 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 trans-

fection 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.

[0280] 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 RNAi agent into the skin. In some implementations, liposomes are used for delivering RNAi agent to epidermal cells and also to enhance the penetration of RNAi 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).

[0281] 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 RNAi agent are useful for treating a dermatological disorder.

[0282] 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 RNAi agent can be delivered, for example, subcutaneously by infection in order to deliver RNAi agent 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.

[0283] Other formulations amenable to the present invention are described in United States provisional application serial Nos. 61/018,616, filed January 2,2008; 61/018,611, filed January 2,2008; 61/039,748, filed March 26,2008; 61/047,087, filed April 22, 2008 and 61/051,528, filed May 8, 2008. PCT application no PCT/US2007/080331, filed October 3, 2007 also describes formulations that are amenable to the present invention.

[0284] Transfersomes are yet another type of liposomes, and are highly deformable lipid aggregates which are attractive candidates for drug delivery vehicles. Transfersomes can 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.

[0285] 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).

[0286] 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.

[0287] 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.

[0288] 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.

[0289] 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.

[0290] 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).

[0291] 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.

[0292] A mixed micellar formulation suitable for delivery through transdermal membranes may be prepared by mixing an aqueous solution of the siRNA composition, 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.

[0293] In one method a first micellar composition is prepared which contains the siRNA composition 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 siRNA composition, 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.

[0294] Phenol and/or m-cresol may be added to the mixed micellar composition to stabilize the formulation and protect against bacterial growth. Alternatively, phenol and/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.

[0295] 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.

[0296] 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.

[0297] 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*

[0298] iRNAs, *e.g.*, dsRNAs of in the invention may be fully encapsulated in a lipid formulation, *e.g.*, a LNP, or other nucleic acid-lipid particle.

[0299] As used herein, the term "LNP" refers to a stable nucleic acid-lipid particle. LNPs 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). 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; U.S. Publication No. 2010/0324120 and PCT Publication No. WO 96/40964.

[0300] In one implementation, 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.

[0301] The cationic lipid can be, for example, N,N-dioleyl-N,N-dimethylammonium chloride (DODAC), N,N-distearyl-N,N-dimethylammonium bromide (DDAB), N-(l-(2,3-dioleoyloxy)propyl)-N,N,N-trimethylammonium chloride (DOTAP), N-(l-(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 can comprise from about 20 mol % to about 50 mol % or about 40 mol % of the total lipid present in the particle.

[0302] In another implementation, 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.

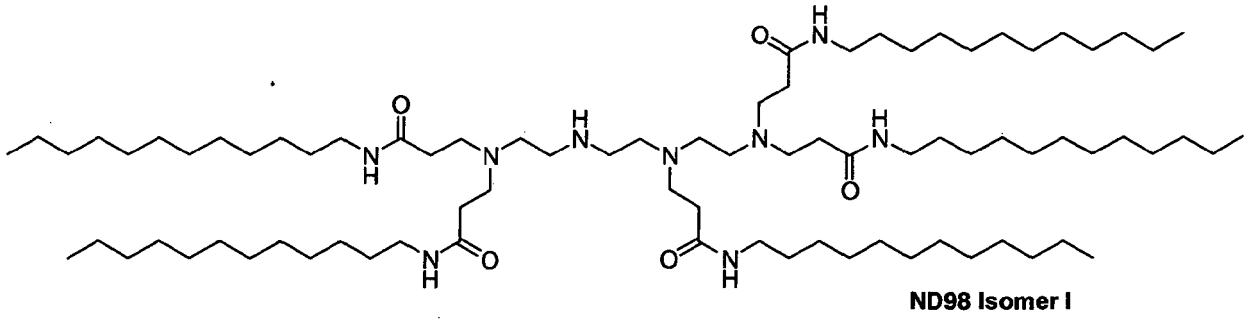
In one implementation, the lipid-siRNA particle includes 40% 2, 2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane: 10% DSPC: 40% Cholesterol: 10% PEG-C-DOMG (mole percent) with a particle size of 63.0 $\pm$ 20 nm and a 0.027 siRNA/Lipid Ratio.

[0303] The ionizable/non-cationic lipid can 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-1-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 can 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.

[0304] The conjugated lipid that inhibits aggregation of particles can 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 can be, for example, a PEG-dilauryloxypropyl (Ci_2), a PEG-dimyristyloxypropyl (Ci_4), a PEG-dipalmityloxypropyl (Ci_6), or a PEG-distearyloxypropyl ($C]_8$). The conjugated lipid that prevents aggregation of particles can be from 0 mol % to about 20 mol % or about 2 mol % of the total lipid present in the particle.

[0305] In some implementations, 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.

[0306] In one implementation, the lipidoid ND98·4HCl (MW 1487) (see U.S. Patent Application No. 12/056,230, filed 3/26/2008, which is incorporated herein by reference), Cholesterol (Sigma-Aldrich), and PEG-Ceramide C16 (Avanti Polar Lipids) can be used to prepare lipid-dsRNA nanoparticles (*i.e.,* LNP01 particles). Stock solutions of each in ethanol can be prepared as follows: ND98, 133 mg/ml; Cholesterol, 25 mg/ml, PEG-Ceramide C16, 100 mg/ml. The ND98, Cholesterol, and PEG-Ceramide C16 stock solutions can then be combined in a, *e.g.,* 42:48:10 molar ratio. The combined lipid solution can be mixed with aqueous dsRNA (*e.g.*, in sodium acetate pH 5) such that the final ethanol concentration is about 35-45% and the final sodium acetate concentration is about 100-300 mM. Lipid-dsRNA nanoparticles typically form spontaneously upon mixing. Depending on the desired particle size distribution, the resultant nanoparticle mixture can be extruded through a polycarbonate membrane (*e.g.*, 100 nm cut-off) using, for example, a thermobarrel extruder, such as Lipex Extruder (Northern Lipids, Inc). In some cases, the extrusion step can be omitted. Ethanol removal and simultaneous buffer exchange can be accomplished by, for example, dialysis or tangential flow filtration. Buffer can be exchanged with, for example, phosphate buffered saline (PBS) at about pH 7, *e.g.*, about pH 6.9, about pH 7.0, about pH 7.1, about pH 7.2, about pH 7.3, or about pH 7.4.



Formula 1

[0307] LNP01 formulations are described, *e.g.*, in International Application Publication No. WO 2008/042973.

[0308] Additional exemplary lipid-dsRNA formulations are described in Table A.

Table A.

	Ionizable/Cationic Lipid	**cationic lipid/non-cationic lipid/cholesterol/PEG-lipid conjugate Lipid:siRNA ratio**
LNP-1	1,2-Dilinolenyloxy-N,N-dimethylaminopropane (DLinDMA)	DLinDMA/DPPC/Cholesterol/PEG-cDMA (57.1/7.1/34.4/1.4) lipid:siRNA ~ 7:1
2-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

(continued)

	Ionizable/Cationic Lipid	cationic lipid/non-cationic lipid/cholesterol/PEG-lipid conjugate Lipid:siRNA ratio
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 (Tech G1)	Tech G1/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

(continued)

	Ionizable/Cationic Lipid	cationic lipid/non-cationic lipid/cholesterol/PEG-lipid conjugate Lipid:siRNA ratio
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)
LNP (1,2-Dilinolenyloxy-N,N-dimethylaminopropane (DLinDMA)) comprising formulations are described in International Publication No. WO2009/127060, filed April 15, 2009.
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. 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.
MC3 comprising formulations are described, *e.g.*, in U.S. Publication No. 2010/0324120, filed June 10, 2010.
ALNY-100 comprising formulations are described, *e.g.*, International patent application number PCT/US09/63933, filed on November 10, 2009.
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.

Synthesis of ionizable/cationic lipids

[0309] Any of the compounds, *e.g.*, cationic lipids and the like, used in the nucleic acid-lipid particles can be prepared by known organic synthesis techniques, including the methods described in more detail in the Examples. All substituents are as defined below unless indicated otherwise.

[0310] "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.

[0311] "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.

[0312] "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.

[0313] "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.

[0314] "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 can be optionally oxidized, and the nitrogen heteroatom can be optionally quaternized, including bicyclic rings in which any of the above heterocycles are fused to a benzene ring. The heterocycle can 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.

[0315] 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

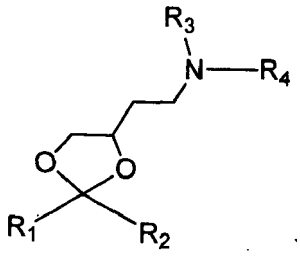
regard, substituents include oxo, halogen, heterocycle, -CN, -ORx, -NRxRy, -NRxC(=O)Ry, -NRxSO2Ry, -C(=O)Rx, -C(=O)ORx, -C(=O)NRxRy, -SOnRx and -SOnNRxRy, wherein n is 0, 1 or 2, Rx and Ry are the same or different and independently hydrogen, alkyl or heterocycle, and each of said alkyl and heterocycle substituents can be further substituted with one or more of oxo, halogen, -OH, -CN, alkyl, -ORx, heterocycle, -NRxRy, -NRxC(=O)Ry, -NRxSO2Ry, -C(=O)Rx, -C(=O)ORx, -C(=O)NRxRy, -SOnRx and -SOnNRxRy.

[0316] "Halogen" means fluoro, chloro, bromo and iodo.

[0317] In some implementations, the described methods can 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.

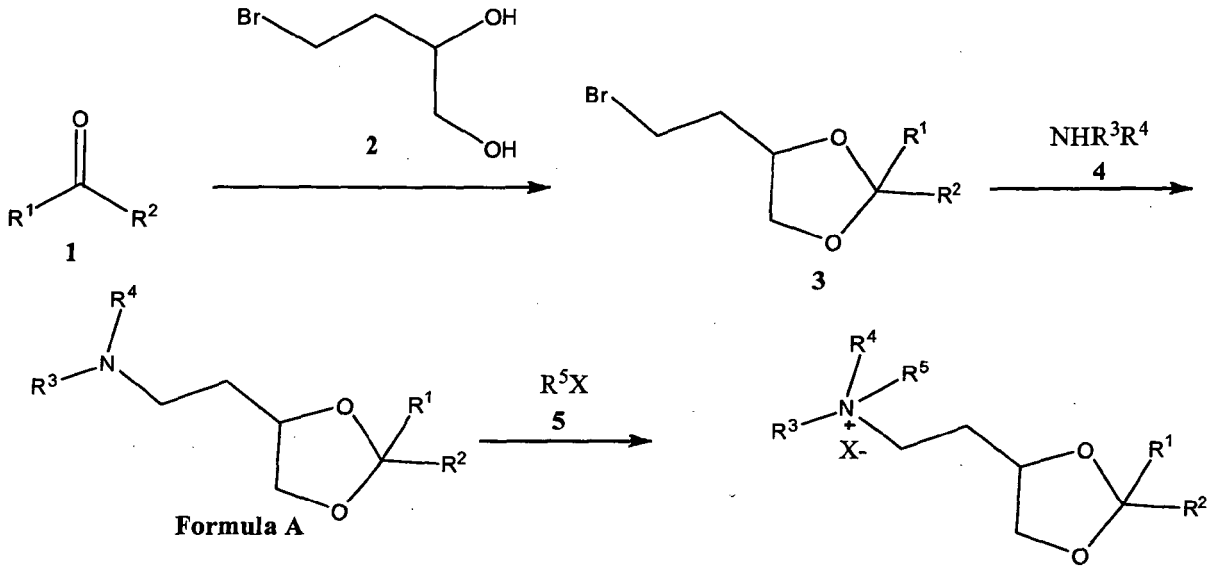
Synthesis of Formula A

[0318] In some implementations, nucleic acid-lipid particles of 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 implementations, the cationic lipid is XTC (2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane). In general, the lipid of formula A above can be made by the following Reaction Schemes 1 or 2, wherein all substituents are as defined above unless indicated otherwise.

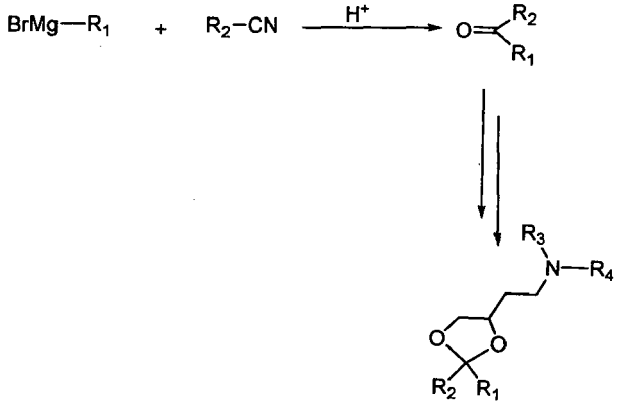
Scheme 1



[0319] Lipid 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, 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

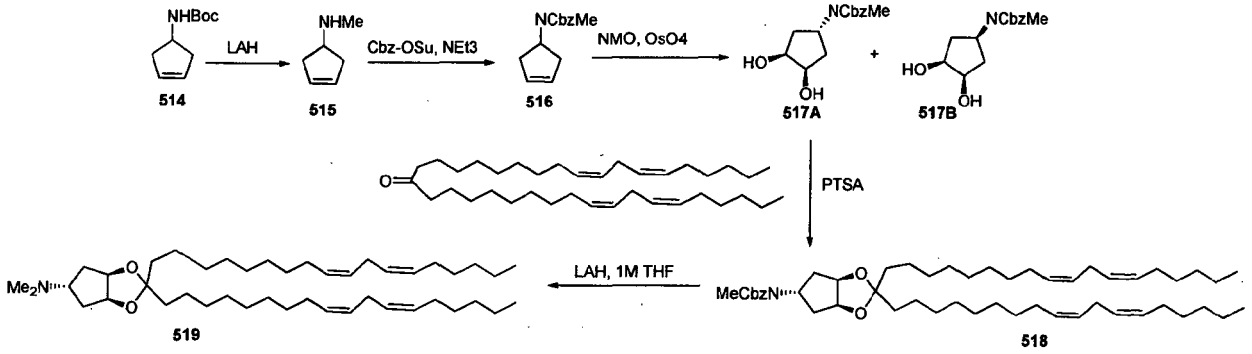


[0320] Alternatively, the ketone 1 starting material can be prepared according to Scheme 2. Grignard reagent 6 and cyanide 7 can be purchased or prepared according to methods known to those of ordinary skill in the art. Reaction of 6 and 7 yields ketone 1. Conversion of ketone 1 to the corresponding lipids of formula A is as described in Scheme 1.

Synthesis of MC3

[0321] 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*

[0322] Synthesis of ketal 519 [ALNY-100] was performed using the following scheme 3:



Synthesis of 515

[0323] 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

[0324] 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

[0325] The cyclopentene 516 (5 g, 0.02164 mol) was dissolved in a solution of 220 mL acetone and water (10:1) in a single neck 500 mL RBF and to it was added N-methyl morpholine-N-oxide (7.6 g, 0.06492 mol) followed by 4.2 mL of 7.6% solution of OsO4 (0.275 g, 0.00108 mol) in tert-butanol at room temperature. After completion of the reaction (~ 3 h), the mixture was quenched with addition of solid Na2SO3 and resulting mixture was stirred for 1.5 h at room temperature. Reaction mixture was diluted with DCM (300 mL) and washed with water (2 x 100 mL) followed by saturated NaHCO3 (1 x 50 mL) solution, water (1 x 30 mL) and finally with brine (1x 50 mL). Organic phase was dried over an.Na2SO4 and solvent was removed in vacuum. Silica gel column chromatographic purification of the crude material was afforded a mixture of diastereomers, which were separated by prep HPLC.
Yield: - 6 g crude
517A - Peak-1 (white solid), 5.13 g (96%). 1H-NMR (DMSO, 400MHz): δ= 7.39-7.31(m, 5H), 5.04(s, 2H), 4.78-4.73 (m, 1H), 4.48-4.47(d, 2H), 3.94-3.93(m, 2H), 2.71(s, 3H), 1.72-1.67(m, 4H). LC-MS - [M+H]-266.3, [M+NH4 +]-283.5 present, HPLC-97.86%. Stereochemistry confirmed by X-ray.

Synthesis of 518

[0326] 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 (CDC13, 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

[0327] 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 40oC over 0.5 h then cooled again on an ice bath. The mixture was carefully hydrolyzed with saturated aqueous Na2SO4 then filtered through celite and reduced to an oil. Column chromatography provided the pure 519 (1.3 g, 68%) which was obtained as a colorless oil. 13C NMR δ = 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.

[0328] 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 LNP 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.

[0329] 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 Publn. No. 20030027780, and U.S. Patent No. 6,747,014, each of which is incorporated herein by reference.

[0330] 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.

[0331] 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.

[0332] 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.

[0333] 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.

C. Additional Formulations

Emulsions

[0334] 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 the aqueous phase, oily phase or itself as a separate phase. Pharmaceutical excipients such as emulsifiers, stabilizers, dyes, and antioxidants 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.

[0335] 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).

[0336] 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).

[0337] 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.

[0338] 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).

[0339] 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.

[0340] 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.

[0341] 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

[0342] In one implementation, 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).

[0343] 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.

[0344] 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.

[0345] 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.

[0346] Microemulsions 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

[0347] 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

[0348] In one implementation, 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.

[0349] 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.

[0350] 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).

[0351] 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).

[0352] 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), tauro-

cholic 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).

[0353] 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).

[0354] 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).

[0355] 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.

[0356] 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

[0357] 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

[0358] 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*).

[0359] 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.

[0360] 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.

[0361] 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

[0362] 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.

[0363] 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.

[0364] 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 bleeding disorder. Examples of such agents include, but are not lmited to an anti-inflammatory agent, anti-steatosis agent, anti-viral, and/or anti-fibrosis agent. In addition, other substances commonly used to protect the liver, such as silymarin, can also be used in conjunction with the *iRNAs described herein.* Other agents useful for treating liver diseases include telbivudine, entecavir, and protease inhibitors such as telaprevir and other disclosed, for example, in Tung et al., U.S. Application Publication Nos. 2005/0148548, 2004/0167116, and 2003/0144217; and in Hale et al., U.S. Application Publication No. 2004/0127488.

[0365] Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic

effects is the therapeutic index and it can be expressed as the ratio LD50/ED50. Compounds that exhibit high therapeutic indices are preferred.

[0366] 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 ED50 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.

[0367] 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 PCSK9 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.

IV. Methods For Inhibiting PCSK9 Expression

[0368] The present disclosure provides methods of inhibiting expression of a Proprotein Convertase Subtilisin Kexin 9 (PCSK9) in a cell. The methods include contacting a cell with an RNAi agent, *e.g.*, a double stranded RNAi agent, in an amount effective to inhibit expression of the PCSK9 in the cell, thereby inhibiting expression of the PCSK9 in the cell.

[0369] Contacting of a cell with a double stranded RNAi agent may be done *in vitro* or *in vivo.* Contacting a cell *in vivo* with the RNAi agent includes contacting a cell or group of cells within a subject, *e.g.,* a human subject, with the RNAi agent. Combinations of *in vitro* and *in vivo* methods of contacting are also possible. Contacting may be direct or indirect, as discussed above. Furthermore, contacting a cell may be accomplished via a targeting ligand, including any ligand described herein or known in the art. In preferred implementations, the targeting ligand is a carbohydrate moiety, *e.g.*, a $GalNAc_3$ ligand, or any other ligand that directs the RNAi agent to a site of interest, *e.g.*, the liver of a subject.

[0370] The term "inhibiting," as used herein, is used interchangeably with "reducing," "silencing," "downregulating" and other similar terms, and includes any level of inhibition.

[0371] The phrase "inhibiting expression of a PCSK9" is intended to refer to inhibition of expression of any PCSK9 gene (such as, *e.g.,* a mouse PCSK9 gene, a rat PCSK9 gene, a monkey PCSK9 gene, or a human PCSK9 gene) as well as variants or mutants of a PCSK9 gene. Thus, the PCSK9 gene may be a wild-type PCSK9 gene, a mutant PCSK9 gene, or a transgenic PCSK9 gene in the context of a genetically manipulated cell, group of cells, or organism.

[0372] "Inhibiting expression of a PCSK9 gene" includes any level of inhibition of a PCSK9 gene, *e.g.*, at least partial suppression of the expression of a PCSK9 gene. The expression of the PCSK9 gene may be assessed based on the level, or the change in the level, of any variable associated with PCSK9 gene expression, *e.g.*, PCSK9 mRNA level, PCSK9 protein level, or lipid levels. This level may be assessed in an individual cell or in a group of cells, including, for example, a sample derived from a subject.

[0373] Inhibition may be assessed by a decrease in an absolute or relative level of one or more variables that are associated with PCSK9 expression 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).

[0374] In some implementations of the methods of the invention, expression of a PCSK9 gene is inhibited by at least about 5%, at least about 10%, at least about 15%, at least about 20%, 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%.

[0375] Inhibition of the expression of a PCSK9 gene may be manifested by a reduction of the amount of mRNA expressed by a first cell or group of cells (such cells may be present, for example, in a sample derived from a subject) in which a PCSK9 gene is transcribed and which has or have been treated (*e.g.*, by contacting the cell or cells with an RNAi agent of the invention, or by administering an RNAi agent of the invention to a subject in which the cells are or were present) such that the expression of a PCSK9 gene is inhibited, as compared to a second cell or group of cells substantially identical to the first cell or group of cells but which has not or have not been so treated (control cell(s)). In preferred embodiments, the inhibition is assessed by expressing the level of mRNA in treated cells as a percentage of the level of mRNA in control cells, using the following formula:

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

[0376] Alternatively, inhibition of the expression of a PCSK9 gene may be assessed in terms of a reduction of a parameter that is functionally linked to PCSK9 gene expression, *e.g.*, PCSK9 protein expression, such as lipid levels, cholesterol levels, *e.g.*, LDLc levels. PCSK9 gene silencing may be determined in any cell expressing PCSK9, either constitutively or by genomic engineering, and by any assay known in the art. The liver is the major site of PCSK9 expression. Other significant sites of expression include the pancreas, kidney, and intestines.

[0377] Inhibition of the expression of a PCSK9 protein may be manifested by a reduction in the level of the PCSK9 protein that is expressed by a cell or group of cells (*e.g.,* the level of protein expressed in a sample derived from a subject). As explained above for the assessment of mRNA suppression, the inhibiton of protein expression levels in a treated cell or group of cells may similarly be expressed as a percentage of the level of protein in a control cell or group of cells.

[0378] A control cell or group of cells that may be used to assess the inhibition of the expression of a PCSK9 gene includes a cell or group of cells that has not yet been contacted with an RNAi agent of the invention. For example, the control cell or group of cells may be derived from an individual subject (*e.g.*, a human or animal subject) prior to treatment of the subject with an RNAi agent.

[0379] The level of PCSK9 mRNA that is expressed by a cell or group of cells may be determined using any method known in the art for assessing mRNA expression. In one embodiment, the level of expression of PCSK9 in a sample is determined by detecting a transcribed polynucleotide, or portion thereof, *e.g.*, mRNA of the PCSK9 gene. RNA may be extracted from cells using RNA extraction techniques including, for example, using acid phenol/guanidine isothiocyanate extraction (RNAzol B; Biogenesis), RNeasy RNA preparation kits (Qiagen) or PAXgene (PreAnalytix, Switzerland). Typical assay formats utilizing ribonucleic acid hybridization include nuclear run-on assays, RT-PCR, RNase protection assays (Melton et al., Nuc. Acids Res. 12:7035), Northern blotting, *in situ* hybridization, and microarray analysis.

[0380] In one implementation, the level of expression of PCSK9 is determined using a nucleic acid probe. The term "probe", as used herein, refers to any molecule that is capable of selectively binding to a specific PCSK9. Probes can be synthesized by one of skill in the art, or derived from appropriate biological preparations. Probes may be specifically designed to be labeled. Examples of molecules that can be utilized as probes include, but are not limited to, RNA, DNA, proteins, antibodies, and organic molecules.

[0381] Isolated mRNA can be used in hybridization or amplification assays that include, but are not limited to, Southern or Northern analyses, polymerase chain reaction (PCR) analyses and probe arrays. One method for the determination of mRNA levels involves contacting the isolated mRNA with a nucleic acid molecule (probe) that can hybridize to PCSK9 mRNA. In one embodiment, the mRNA is immobilized on a solid surface and contacted with a probe, for example by running the isolated mRNA on an agarose gel and transferring the mRNA from the gel to a membrane, such as nitrocellulose. In an alternative implementation, the probe(s) are immobilized on a solid surface and the mRNA is contacted with the probe(s), for example, in an Affymetrix gene chip array. A skilled artisan can readily adapt known mRNA detection methods for use in determining the level of PCSK9 mRNA.

[0382] An alternative method for determining the level of expression of PCSK9 in a sample involves the process of nucleic acid amplification and/or reverse transcriptase (to prepare cDNA) of for example mRNA in the sample, *e.g.*, by RT-PCR (the experimental embodiment set forth in Mullis, 1987, U.S. Pat. No. 4,683,202), ligase chain reaction (Barany (1991) Proc. Natl. Acad. Sci. USA 88:189-193), self sustained sequence replication (Guatelli et al. (1990) Proc. Natl. Acad. Sci. USA 87:1874-1878), transcriptional amplification system (Kwoh et al. (1989) Proc. Natl. Acad. Sci. USA 86:1173-1177), Q-Beta Replicase (Lizardi et al. (1988) Bio/Technology 6:1197), rolling circle replication (Lizardi et al., U.S. Pat. No. 5,854,033) or any other nucleic acid amplification method, followed by the detection of the amplified molecules using techniques well known to those of skill in the art. These detection schemes are especially useful for the detection of nucleic acid molecules if such molecules are present in very low numbers. In particular aspects of the invention, the level of expression of PCSK9 is determined by quantitative fluorogenic RT-PCR (*i.e.,* the TaqMan™ System).

[0383] The expression levels of PCSK9 mRNA may be monitored using a membrane blot (such as used in hybridization analysis such as Northern, Southern, dot, and the like), or microwells, sample tubes, gels, beads or fibers (or any solid support comprising bound nucleic acids). See U.S. Pat. Nos. 5,770,722, 5,874,219, 5,744,305, 5,677,195 and 5,445,934, which are incorporated herein by reference. The determination of PCSK9 expression level may also comprise using nucleic acid probes in solution.

[0384] In preferred implementations, the level of mRNA expression is assessed using branched DNA (bDNA) assays or real time PCR (qPCR). The use of these methods is described and exemplified in the Examples presented herein.

[0385] The level of PCSK9 protein expression may be determined using any method known in the art for the meas-

urement of protein levels. Such methods include, for example, electrophoresis, capillary electrophoresis, high performance liquid chromatography (HPLC), thin layer chromatography (TLC), hyperdiffusion chromatography, fluid or gel precipitin reactions, absorption spectroscopy, a colorimetric assays, spectrophotometric assays, flow cytometry, immunodiffusion (single or double), immunoelectrophoresis, Western blotting, radioimmunoassay (RIA), enzyme-linked immunosorbent assays (ELISAs), immunofluorescent assays, electrochemiluminescence assays, and the like.

[0386] The term "sample" as used herein refers to 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, lymph, urine, cerebrospinal fluid, saliva, ocular fluids, 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 implementations, 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 preferred embodiments, a "sample derived from a subject" refers to blood or plasma drawn from the subject. In further implementations, a "sample derived from a subject" refers to liver tissue derived from the subject.

[0387] In some implementations of the methods of the invention, the RNAi agent is administered to a subject such that the RNAi agent is delivered to a specific site within the subject. The inhibition of expression of PCSK9 may be assessed using measurements of the level or change in the level of PCSK9 mRNA or PCSK9 protein in a sample derived from fluid or tissue from the specific site within the subject. In preferred implementations, the site is the liver. The site may also be a subsection or subgroup of cells from any one of the aforementioned sites. The site may also include cells that express a particular type of receptor.

V. Methods for Treating or Preventing a PCSK9-Associated Disease

[0388] The present disclosure also provides methods for treating or preventing diseases and conditions that can be modulated by down regulating PCSK9 gene expression. For example, the compositions described herein can be used to treat lipidemia, *e.g.*, a hyperlipidemia and other forms of lipid imbalance such as hypercholesterolemia, hypertriglyceridemia and the pathological conditions associated with these disorders such as heart and circulatory diseases. Other diseases and conditions that can be modulated by down regulating PCSK9 gene expression include lysosomal storage diseases including, but not limited to, Niemann-Pick disease, Tay-Sachs disease, Lysosomal acid lipase deficiency, and Gaucher Disease. The methods include administering to the subject a therapeutically effective amount or prophylactically effective amount of an RNAi agent of the invention. In some implementations, the method includes administering an effective amount of a PCSK9 siRNA to a patient having a heterozygous LDLR genotype.

[0389] The effect of the decreased PCSK9 gene preferably results in a decrease in LDLc (low density lipoprotein cholesterol) levels in the blood, and more particularly in the serum, of the mammal. In some implementations, LDLc levels are decreased by at least 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more, as compared to pretreatment levels.

[0390] As used herein, a "subject" includes a human or non-human animal, preferably a vertebrate, and more preferably a mammal. A subject may include a transgenic organism. Most preferably, the subject is a human, such as a human suffering from or predisposed to developing a PCSK9-associated disease.

[0391] In some implementations of the methods of the invention, PCSK9 expression is decreased for an extended duration, *e.g.*, at least one week, two weeks, three weeks, or four weeks or longer. For example, in certain instances, expression of the PCSK9 gene is suppressed by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% by administration of an iRNA agent described herein. In some implementations, the PCSK9 gene is suppressed by at least about 60%, 70%, or 80% by administration of the iRNA agent. In some embodiments, the PCSK9 gene is suppressed by at least about 85%, 90%, or 95% by administration of the double-stranded oligonucleotide.

[0392] The RNAi agents of the invention may be administered to a subject using any mode of administration known in the art, including, but not limited to subcutaneous, intravenous, intramuscular, intraocular, intrabronchial, intrapleural, intraperitoneal, intraarterial, lymphatic, cerebrospinal, and any combinations thereof. In preferred embodiments, the agents are administered subcutaneously.

[0393] In some implementations, the administration is via a depot injection. A depot injection may release the RNAi agent 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 PCSK9, 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 implementations, the depot injection is a subcutaneous injection.

[0394] In some implementations, the administration is via a pump. The pump may be an external pump or a surgically implanted pump. In certain implementations, the pump is a subcutaneously implanted osmotic pump. In other implementations, the pump is an infusion pump. An infusion pump may be used for intravenous, subcutaneous, arterial, or epidural infusions. In preferred implementations, the infusion pump is a subcutaneous infusion pump. In other implementations, the pump is a surgically implanted pump that delivers the RNAi agent to the liver.

[0395] Other modes of administration include epidural, intracerebral, intracerebroventricular, nasal administration, intraarterial, intracardiac, intraosseous infusion, intrathecal, and intravitreal, and pulmonary. 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.

[0396] The method includes administering an iRNA agent, *e.g.,* a dose sufficient to depress levels of PCSK9 mRNA for at least 5, more preferably 7, 10, 14, 21, 25, 30 or 40 days; and optionally, administering a second single dose of dsRNA, wherein the second single dose is administered at least 5, more preferably 7, 10, 14, 21, 25, 30 or 40 days after the first single dose is administered, thereby inhibiting the expression of the PCSK9 gene in a subject.

[0397] In one implementation, doses of iRNA agent of the invention are administered not more than once every four weeks, not more than once every three weeks, not more than once every two weeks, or not more than once every week. In another implementation, the administrations can be maintained for one, two, three, or six months, or one year or longer.

[0398] In another implementation, administration can be provided when Low Density Lipoprotein cholesterol (LDLc) levels reach or surpass a predetermined minimal level, such as greater than 70mg/dL, 130 mg/dL, 150 mg/dL, 200 mg/dL, 300 mg/dL, or 400 mg/dL.

[0399] In general, the iRNA agent does not activate the immune system, *e.g*., it does not increase cytokine levels, such as TNF-alpha or IFN-alpha levels. For example, when measured by an assay, such as an in vitro PBMC assay, such as described herein, the increase in levels of TNF-alpha or IFN-alpha, is less than 30%, 20%, or 10% of control cells treated with a control dsRNA, such as a dsRNA that does not target PCSK9.

[0400] For example, a subject can be administered a therapeutic amount of an iRNA agent, such as 0.5 mg/kg, 1.0 mg/kg, 1.5 mg/kg, 2.0 mg/kg, or 2.5 mg/kg dsRNA. The iRNA agent can be administered by intravenous infusion over a period of time, such as over a 5 minute, 10 minute, 15 minute, 20 minute, or 25 minute period. The administration is repeated, for example, on a regular basis, such as biweekly (*i.e.,* every two weeks) for one month, two months, three months, four months or longer. After an initial treatment regimen, the treatments can be administered on a less frequent basis. For example, after administration biweekly for three months, administration can be repeated once per month, for six months or a year or longer. Administration of the iRNA agent can reduce PCSK9 levels, *e.g.,* in a cell, tissue, blood, urine or other compartment of the patient by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80 % or at least 90% or more.

[0401] Before administration of a full dose of the iRNA agent, patients can be administered a smaller dose, such as a 5%> infusion reaction, and monitored for adverse effects, such as an allergic reaction, or for elevated lipid levels or blood pressure. In another example, the patient can be monitored for unwanted immunostimulatory effects, such as increased cytokine (e.g., TNF-alpha or INF-alpha) levels.

[0402] 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 agent of the invention or formulation of that iRNA agent can also be judged using an experimental animal model for the given disease as known in the art. When using an experimental animal model, efficacy of treatment is evidenced when a statistically significant reduction in a marker or symptom is observed.

[0403] In one implementation, the RNAi agent is administered at a dose of between about 0.25 mg/kg to about 50 mg/kg, e.g., between about 0.25 mg/kg to about 0.5 mg/kg, between about 0.25 mg/kg to about 1 mg/kg, between about 0.25 mg/kg to about 5 mg/kg, between about 0.25 mg/kg to about 10 mg/kg, between about 1 mg/kg to about 10 mg/kg, between about 5 mg/kg to about 15 mg/kg, between about 10 mg/kg to about 20 mg/kg, between about 15 mg/kg to about 25 mg/kg, between about 20 mg/kg to about 30 mg/kg, between about 25 mg/kg to about 35 mg/kg, or between about 40 mg/kg to about 50 mg/kg.

[0404] In some implementations, the RNAi agent is administered at a dose of about 0.25 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 2 mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 6 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg, about 10 mg/kg, about 11 mg/kg, about 12 mg/kg, about 13 mg/kg, about 14 mg/kg, about 15 mg/kg, about 16 mg/kg, about 17 mg/kg, about 18 mg/kg, about 19 mg/kg, about 20 mg/kg, about 21 mg/kg, about 22 mg/kg, about 23 mg/kg, about 24 mg/kg, about 25 mg/kg, about 26 mg/kg, about 27 mg/kg, about 28 mg/kg, about 29 mg/kg, 30 mg/kg, about 31 mg/kg, about 32 mg/kg, about 33 mg/kg, about 34 mg/kg, about 35 mg/kg, about 36 mg/kg, about 37 mg/kg, about 38 mg/kg, about 39 mg/kg, about 40 mg/kg, about 41 mg/kg, about 42 mg/kg, about 43 mg/kg, about 44 mg/kg, about 45 mg/kg, about 46 mg/kg, about 47 mg/kg, about 48 mg/kg, about 49 mg/kg or about 50 mg/kg. In one implementation, iRNA agent is administered at a dose of about 25 mg/kg.

[0405] The dose of an RNAi agent that is administered to a subject may be tailored to balance the risks and benefits of a particular dose, for example, to achieve a desired level of PCSK9 gene suppression (as assessed, *e.g*., based on PCSK9 mRNA suppression, PCSK9 protein expression, or a reduction in lipid levels) or a desired therapeutic or prophylactic effect, while at the same time avoiding undesirable side effects.

[0406] In some implementations, the RNAi agent is administered in two or more doses. If desired to facilitate repeated

or frequent infusions, implantation of a delivery device, *e.g.,* a pump, semi-permanent stent (*e.g.*, intravenous, intraperitoneal, intracisternal or intracapsular), or reservoir may be advisable. In some implementations, the number or amount of subsequent doses is dependent on the achievement of a desired effect, *e.g.*, the suppression of a PCSK9 gene, or the achievement of a therapeutic or prophylactic effect, *e.g.*, reducing reducing a symptom of hypercholesterolemia. In some implementations , the RNAi agent is administered according to a schedule. For example, the RNAi agent may be administered once per week, twice per week, three times per week, four times per week, or five times per week. In some implementations, the schedule involves regularly spaced administrations, *e.g.*, hourly, every four hours, every six hours, every eight hours, every twelve hours, daily, every 2 days, every 3 days, every 4 days, every 5 days, weekly, biweekly, or monthly. In other embodiments, the schedule involves closely spaced administrations followed by a longer period of time during which the agent is not administered. For example, the schedule may involve an initial set of doses that are administered in a relatively short period of time (*e.g.*, about every 6 hours, about every 12 hours, about every 24 hours, about every 48 hours, or about every 72 hours) followed by a longer time period (*e.g.*, about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, or about 8 weeks) during which the RNAi agent is not administered. In one implementation, the RNAi agent is initially administered hourly and is later administered at a longer interval (*e.g.*, daily, weekly, biweekly, or monthly). In another implementation, the RNAi agent is initially administered daily and is later administered at a longer interval (*e.g.*, weekly, biweekly, or monthly). In certain implementations, the longer interval increases over time or is determined based on the achievement of a desired effect. In a specific implementation, the RNAi agent is administered once daily during a first week, followed by weekly dosing starting on the eighth day of administration. In another specific implementation, the RNAi agent is administered every other day during a first week followed by weekly dosing starting on the eighth day of administration.

[0407] In one implementation, the iRNA agent is administered two times per week. In one implementation, iRNA agent is administered two times per week at a dose of 1 mg/kg. In another implementation, iRNA agent is administered two times per week at a dose of 2 mg/kg.

[0408] In one implementation, the iRNA agent is administered once every two weeks. In one implementation, iRNA agent is administered once every two week at a dose of 1 mg/kg. In another implementation, iRNA agent is administered once every two week at a dose of 2 mg/kg.

[0409] In one implementation, the iRNA agent is administered once a week. In one implementation, iRNA agent is administered once a week at a dose of 0.5 mg/kg. In one implementation, iRNA agent is administered once a week at a dose of 1 mg/kg. In another implementation, iRNA agent is administered once a week at a dose of 2 mg/kg.

[0410] In some implementations, the RNAi agent is administered in a dosing regimen that includes a "loading phase" of closely spaced administrations that may be followed by a "maintenance phase", in which the RNAi agent is administred at longer spaced intervals. In one implementation, the loading phase comprises five daily administrations of the RNAi agent during the first week. In another implementation, the maintenance phase comprises one or two weekly administrations of the RNAi agent. In a further implementation, the maintenance phase lasts for 5 weeks. In one implementation, the loading phase comprises administration of a dose of 2 mg/kg, 1 mg/kg or 0.5 mg/kg five times a week. In another implementation, the maintenance phase comprises administration of a dose of 2 mg/kg, 1 mg/kg or 0.5 mg/kg once, twice, or three times weekly, once every two weeks, once every three weeks, once a month, once every two months, once every three months, once every four months, once every five months, or once every six months.

[0411] Any of these schedules may optionally be repeated for one or more iterations. The number of iterations may depend on the achievement of a desired effect, *e.g.*, the suppression of a PCSK9 gene, and/or the achievement of a therapeutic or prophylactic effect, *e.g.*, reducing serum cholesterol levels or reducing a symptom of hypercholesterolemia.

[0412] In further implementations, administration of a siRNA is administered in combination an additional therapeutic agent. The siRNA and an additional therapeutic agent can be administered in combination in the same composition, e.g., parenterally, or the additional therapeutic agent can be administered as part of a separate composition or by another method described herein.

[0413] Examples of additional therapeutic agents include those known to treat an agent known to treat a lipid disorders, such as hypercholesterolemia, atherosclerosis or dyslipidemia. For example, a siRNA featured in the invention can be administered with, *e.g.*, an HMG-CoA reductase inhibitor (*e.g.*, a statin), a fibrate, a bile acid sequestrant, niacin, an antiplatelet agent, an angiotensin converting enzyme inhibitor, an angiotensin II receptor antagonist (*e.g.*, losartan potassium, such as Merck & Co. 's Cozaar®), an acylCoA cholesterol acetyltransferase (ACAT) inhibitor, a cholesterol absorption inhibitor, a cholesterol ester transfer protein (CETP) inhibitor, a microsomal triglyceride transfer protein (MTTP) inhibitor, a cholesterol modulator, a bile acid modulator, a peroxisome proliferation activated receptor (PPAR) agonist, a gene-based therapy, a composite vascular protectant (*e.g.,* AGI-1067, from Atherogenics), a glycoprotein IIb/IIIa inhibitor, aspirin or an aspirin-like compound, an IBAT inhibitor (*e.g.*, S-8921, from Shionogi), a squalene synthase inhibitor, or a monocyte chemoattractant protein (MCP)-I inhibitor. Exemplary HMG-CoA reductase inhibitors include atorvastatin (Pfizer's Lipitor®/Tahor/Sortis/Torvast/Cardyl), pravastatin (Bristol-Myers Squibb's Pravachol, Sankyo's Mevalotin/Sanaprav), simvastatin (Merck's Zocor®/Sinvacor, Boehringer Ingelheim's Denan, Banyu's Lipovas), lovastatin (Merck's Mevacor/Mevinacor, Bexal's Lovastatina, Cepa; Schwarz Pharma's Liposcler), fluvastatin (Novartis' Les-

col®/Locol/Lochol, Fujisawa's Cranoc, Solvay's Digaril), cerivastatin (Bayer's Lipobay/GlaxoSmithKline's Baycol), rosuvastatin (AstraZeneca' s Crestor®), and pitivastatin (itavastatin/risivastatin) (Nissan Chemical, Kowa Kogyo, Sankyo, and Novartis). Exemplary fibrates include, *e.g.,* bezafibrate (*e.g.,* Roche's Befizal®/Cedur®/Bezalip®, Kissei's Bezatol), clofibrate (*e.g*., Wyeth's Atromid-S®), fenofibrate (*e.g*., Fournier's Lipidil/Lipantil, Abbott's Tricor®, Takeda's Lipantil, generics), gemfibrozil (*e.g*., Pfizer' s Lopid/Lipur) and ciprofibrate (Sanofi-Synthelabo's Modalim®). Exemplary bile acid sequestrants include, *e.g*., cholestyramine (Bristol-Myers Squibb's Questran® and Questran Light™), colestipol (*e.g*., Pharmacia's Colestid), and colesevelam (Genzyme/Sankyo's WelChol™). Exemplary niacin therapies include, *e.g*., immediate release formulations, such as Aventis' Nicobid, Upsher-Smith's Niacor, Aventis' Nicolar, and Sanwakagaku's Perycit. Niacin extended release formulations include, *e.g*., Kos Pharmaceuticals' Niaspan and Upsher-Smith's SIo-Niacin. Exemplary antiplatelet agents include, *e.g.,* aspirin (*e.g.,* Bayer's aspirin), clopidogrel (Sanofi-Synthelabo/Bristol-Myers Squibb's Plavix), and ticlopidine (*e.g*., Sanofi-Synthelabo's Ticlid and Daiichi's Panaldine). Other aspirin-like compounds useful in combination with a dsRNA targeting PCSK9 include, *e.g*., Asacard (slow-release aspirin, by Pharmacia) and Pamicogrel (Kanebo/Angelini Ricerche/CEPA). Exemplary angiotensin-converting enzyme inhibitors include, *e.g*., ramipril (*e.g.,* Aventis' Altace) and enalapril (*e.g.,* Merck & Co.'s Vasotec). Exemplary acyl CoA cholesterol acetyltransferase (AC AT) inhibitors include, *e.g*., avasimibe (Pfizer), eflucimibe (BioMsrieux Pierre Fabre/Eli Lilly), CS-505 (Sankyo and Kyoto), and SMP-797 (Sumito). Exemplary cholesterol absorption inhibitors include, *e.g*., ezetimibe (Merck/Schering-Plough Pharmaceuticals Zetia®) and Pamaqueside (Pfizer). Exemplary CETP inhibitors include, *e.g*., Torcetrapib (also called CP-529414, Pfizer), JTT-705 (Japan Tobacco), and CETi-1 (Avant Immunotherapeutics). Exemplary microsomal triglyceride transfer protein (MTTP) inhibitors include, *e.g*., implitapide (Bayer), R-103757 (Janssen), and CP-346086 (Pfizer). Other exemplary cholesterol modulators include, *e.g*., NO- 1886 (Otsuka/TAP Pharmaceutical), CI-1027 (Pfizer), and WAY- 135433 (Wyeth-Ayerst).

[0414] Exemplary bile acid modulators include, *e.g*., HBS-107 (Hisamitsu/Banyu), Btg-511 (British Technology Group), BARI-1453 (Aventis), S-8921 (Shionogi), SD-5613 (Pfizer), and AZD- 7806 (AstraZeneca). Exemplary peroxisome proliferation activated receptor (PPAR) agonists include, *e.g*., tesaglitazar (AZ-242) (AstraZeneca), Netoglitazone (MCC-555) (Mitsubishi/ Johnson & Johnson), GW-409544 (Ligand Pharniaceuticals/GlaxoSmithKline), GW-501516 (Ligand Pharmaceuticals/GlaxoSmithKline), LY-929 (Ligand Pharmaceuticals and Eli Lilly), LY-465608 (Ligand Pharmaceuticals and Eli Lilly), LY-518674 (Ligand Pharmaceuticals and Eli Lilly), and MK-767 (Merck and Kyorin). Exemplary gene-based therapies include, *e.g*., AdGWEGF 121.10 (GenVec), ApoAl (UCB Pharma/Groupe Fournier), EG-004 (Trinam) (Ark Therapeutics), and ATP -binding cassette transporter- A1 (ABCA1) (CV Therapeutics/Incyte, Aventis, Xenon). Exemplary Glycoprotein IIb/IIIa inhibitors include, *e.g*., roxifiban (also called DMP754, Bristol-Myers Squibb), Gantofiban (Merck KGaA/Yamanouchi), and Cromafiban (Millennium Pharmaceuticals). Exemplary squalene synthase inhibitors include, *e.g*., BMS- 1884941 (Bristol-Myers Squibb), CP-210172 (Pfizer), CP-295697 (Pfizer), CP-294838 (Pfizer), and TAK-475 (Takeda). An exemplary MCP-I inhibitor is, *e.g.,* RS-504393 (Roche Bioscience). The anti-atherosclerotic agent BO-653 (Chugai Pharmaceuticals), and the nicotinic acid derivative Nyclin (Yamanouchi Pharmacuticals) are also appropriate for administering in combination with a dsRNA featured in the invention. Exemplary combination therapies suitable for administration with a dsRNA targeting PCSK9 include, *e.g*., advicor (Niacin/lovastatin from Kos Pharmaceuticals), amlodipine/atorvastatin (Pfizer), and ezetimibe/simvastatin (*e.g*., Vytorin® 10/10, 10/20, 10/40, and 10/80 tablets by Merck/Schering-Plough Pharmaceuticals). Agents for treating hypercholesterolemia, and suitable for administration in combination with a dsRNA targeting PCSK9 include, *e.g*., lovastatin, niacin Altoprev® Extended-Release Tablets (Andrx Labs), lovastatin Caduet® Tablets (Pfizer), amlodipine besylate, atorvastatin calcium Crestor® Tablets (AstraZeneca), rosuvastatin calcium Lescol® Capsules (Novartis), fluvastatin sodium Lescol® (Reliant, Novartis), fluvastatin sodium Lipitor® Tablets (Parke-Davis), atorvastatin calcium Lofibra® Capsules (Gate), Niaspan Extended-Release Tablets (Kos), niacin Pravachol Tablets (Bristol-Myers Squibb), pravastatin sodium TriCor® Tablets (Abbott), fenofibrate Vytorin® 10/10 Tablets (Merck/Schering-Plough Pharmaceuticals), ezetimibe, simvastatin WelChol™ Tablets (Sankyo), colesevelam hydrochloride Zetia® Tablets (Schering), ezetimibe Zetia® Tablets (Merck/Schering-Plough Pharmaceuticals), and ezetimibe Zocor® Tablets (Merck).

[0415] In one implementation, an iRNA agent is administered in combination with an ezetimibe/simvastatin combination (*e.g*., Vytorin® (Merck/Schering-Plough Pharmaceuticals)). In one implementation, the iRNA agent is administered to the patient, and then the additional therapeutic agent is administered to the patient (or *vice versa*). In another implementation, the iRNA agent and the additional therapeutic agent are administered at the same time.

[0416] In another aspect, the disclosure features, a method of instructing an end user, *e.g.,* a caregiver or a subject, on how to administer an iRNA agent described herein. The method includes, optionally, providing the end user with one or more doses of the iRNA agent, and instructing the end user to administer the iRNA agent on a regimen described herein, thereby instructing the end user.

[0417] In one aspect, the disclosure provides a method of treating a patient by selecting a patient on the basis that the patient is in need of LDL lowering, LDL lowering without lowering of HDL, ApoB lowering, or total cholesterol lowering. The method includes administering to the patient a siRNA in an amount sufficient to lower the patient's LDL levels or ApoB levels, *e.g*., without substantially lowering HDL levels.

[0418] Genetic predisposition plays a role in the development of target gene associated diseases, *e.g.*, hyperlipidemia. Therefore, a patient in need of a siRNA can be identified by taking a family history, or, for example, screening for one or more genetic markers or variants. Examples of genes involved in hyperlipidemia include but are not limited to, *e.g.,* LDL receptor (LDLR), the apoliproteins (ApoAI, ApoB, ApoE, and the like), Cholesteryl ester transfer protein (CETP), Lipoprotein lipase (LPL), hepatic lipase (LIPC), Endothelial lipase (EL), Lecithinxholesteryl acyltransferase (LCAT).

[0419] A healthcare provider, such as a doctor, nurse, or family member, can take a family history before prescribing or administering an iRNA agent of the invention. In addition, a test may be performed to determine a geneotype or phenotype. For example, a DNA test may be performed on a sample from the patient, *e.g.*, a blood sample, to identify the PCSK9 genotype and/or phenotype before a PCSK9 dsRNA is administered to the patient. In another embodiment, a test is performed to identify a related genotype and/or phenotype, *e.g.*, a LDLR genotype. Example of genetic variants with the LDLR gene can be found in the art, *e.g.,* in the following publications which are incorporated by reference: Costanza et al (2005) Am J Epidemiol. 15;161(8):714-24; Yamada et al. (2008) J Med Genet. Jan;45(1):22-8, Epub 2007 Aug 31; and Boes et al (2009) Exp. Gerontol 44: 136-160, Epub 2008 Nov 17.

VI. Kits

[0420] The present disclosure also provides kits for using any of the iRNA agents and/or performing any of the described methods. Such kits include one or more RNAi agent(s) and instructions for use, *e.g.*, instructions for inhibiting expression of a PCSK9 in a cell by contacting the cell with the RNAi agent(s) in an amount effective to inhibit expression of the PCSK9. 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 PCSK9 (*e.g.,* means for measuring the inhibition of PCSK9 mRNA or TTR protein). Such means for measuring the inhibition of PCSK9 may comprise a means for obtaining a sample from a subject, such as, *e.g.,* a plasma sample. The kits of the invention may optionally further comprise means for administering the RNAi agent(s) to a subject or means for determining the therapeutically effective or prophylactically effective amount.

[0421] 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, suitable methods and materials are described below. 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

Materials and Methods

[0422] The following materials and methods were used in the Examples.

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

[0423] A master mix of 2μl 10X Buffer, 0.8μl 25X dNTPs, 2μl Random primers, 1μl Reverse Transcriptase, 1μl RNase inhibitor and 3.2μl of H_2O per reaction was added into 10μl total RNA. cDNA was generated using a Bio-Rad C-1000 or S-1000 thermal cycler (Hercules, CA) through the following steps: 25°C 10 min, 37°C 120 min, 85°C 5 sec, 4°C hold.

Cell culture and transfections

[0424] Hep3B, HepG2 or HeLa cells (ATCC, Manassas, VA) were grown to near confluence at 37°C in an atmosphere of 5% CO_2 in recommended media (ATCC) supplemented with 10% FBS and glutamine (ATCC) before being released from the plate by trypsinization. For duplexes screened in 96-well format, transfection was carried out by adding 44.75μl of Opti-MEM plus 0.25μl of Lipofectamine RNAiMax per well (Invitrogen, Carlsbad CA. cat # 13778-150) to 5μl of each siRNA duplex to an individual well in a 96-well plate. The mixture was then incubated at room temperature for 15 minutes. Fifty μl of complete growth media without antibiotic containing ~2 x10^4 cells were then added to the siRNA mixture. For duplexes screened in 384-well format, 5μl of Opti-MEM plus 0.1μl of Lipofectamine RNAiMax (Invitrogen, Carlsbad CA. cat # 13778-150) was mixed with 5μl of each siRNA duplex per an individual well. The mixture was then incubated at room temperature for 15 minutes followed by addition of 40μl of complete growth media without antibiotic containing ~8 x10^3 cells. Cells were incubated for 24 hours prior to RNA purification. Single dose experiments were performed at 10nM and 0.1nM final duplex concentration and dose response experiments were done using 8 X 5-fold serial dilutions starting from 2nM.

Free uptake transfection

[0425] Five μl of each GalNac conjugated siRNA in PBS was combined with $3X10^4$ freshly thawed cryopreserved *Cynomolgus* monkey hepatocytes (In Vitro Technologies- Celsis, Baltimore, MD; lot#JQD) resuspended in 95μl of In Vitro Gro CP media (In Vitro Technologies- Celsis, Baltimore, MD) in each well of a 96-well plate or 5ul siRNA and 45 μl media containing $1.2x10^3$ cells for 384 well plate format. The mixture was incubated for about 24 hours at 37°C in an atmosphere of 5% CO_2. siRNAs were tested at multiple concentrations between 500 and 0.1nM for single dose experiments and using 8 X 5-fold serial dilutions starting from 500nM for dose response experiments.

Total RNA isolation using DYNABEADS mRNA Isolation Kit (Invitrogen, part #: 610-12)

[0426] Cells were harvested and lysed in 150μl of Lysis/Binding Buffer then mixed for 5 minutes at 850rpm using an Eppendorf Thermomixer (the mixing speed was the same throughout the process). Ten microliters of magnetic beads and 80μl Lysis/Binding Buffer mixture were added to a round bottom plate and mixed for 1 minute. Magnetic beads were captured using magnetic stand and the supernatant was removed without disturbing the beads. After removing the supernatant, the lysed cells were added to the remaining beads and mixed for 5 minutes. After removing the supernatant, magnetic beads were washed 2 times with 150μl Wash Buffer A and mixed for 1 minute. Beads were captured again and the supernatant removed. Beads were then washed with 150μl Wash Buffer B, captured and the supernatant was removed. Beads were next washed with 150μl Elution Buffer, captured and the supernatant removed. Beads were allowed to dry for 2 minutes. After drying, 50μl of Elution Buffer was added and mixed for 5 minutes at 70°C. Beads were captured on a magnet for 5 minutes. Fifty μl of supernatant was removed and added to another 96-well plate.

[0427] For 384-well format, the cells were lysed for one minute by addition of 50μl Lysis/Binding buffer. Two μl of magnetic beads per well was used. The required volume of beads was aliquoted, captured on a magnetic stand, and the bead storage solution was removed. The beads were then resuspended in the required volume of Lysis/Binding buffer (25μl per well) and 25μl of bead suspension was added to the lysed cells. The lysate-bead mixture was incubated for 10 minutes on VibraTransaltor at setting #7 (UnionScientific Corp., Randallstown, MD). Subsequently beads were captured using a magnetic stand, the supernatant removed and the beads are washed once with 90μl Buffer A, followed by single washing steps with 90μl Buffer B and 100μl of Elution buffer. The beads were soaked in each washing buffer for ~1 minute (no mixing involved). After the final wash step, the beads were resuspended in 15μl of elution buffer for 5 minutes at 70°C, followed by bead capture and the rembval of the supernatant (up to 8μl) for cDNA synthesis and/or purified RNA storage (-20°C).

Real time PCR

[0428] Two μl of cDNA was added to a master mix containing 0.5μl human GAPDH TaqMan Probe (Applied Biosystems Cat #4326317E), 0.5μl human PCSK9 TaqMan probe (Applied Biosystems cat # Hs03037355_m1) for human cells or 0.5μl *Cynomolgus* GAPDH custom TaqMan Assay (150nM cyno GAP F primer-5'GCATCCTGGGCTACACTGA (SEQ ID NO: 5); 150nM cyno GAP R primer-5'-TGGGTGTCGCTGTTGAAGTC (SEQ ID NO: 6) 250nM cyno GAP probe- 5'-5HEX-CCAGGTGGTCTCCTCC-BHQ1-Q-3' (SEQ ID NO: 7)), 0.5μl *Cynomolgus* PCSK9 custom TaqMan Assay (900nM cyno PCSK9 F primer 5'-ACGTGGCTGGCATTGCA (SEQ ID NO: 8); 900nM cyno PCSK9 R primer 5'-AAGTGGATCAGTCTCTGCCTCAA (SEQ ID NO: 9); 250nM cyno PCSK9 probe 5'-6FAM-CATGATGCTGTCTGCCGAGCCG-BHQ1-Q-3' (SEQ ID NO: 10)) for *Cynomolgus* cells and 5μl Lightcycler 480 probe master mix (Roche Cat #04887301001) per well in a 384 well plate (Roche cat # 04887301001). Real time PCR was performed in a Roche LC480 Real Time PCR system (Roche) using the ΔΔCt(RQ) assay. Each duplex was tested in two independent transfections and each transfection was assayed in duplicate, unless otherwise noted.

[0429] To calculate relative fold change, real time data were analyzed using the ΔΔCt method and normalized to assays performed with cells transfected with 10nM AD-1955, or mock transfected cells. For free uptake assays the data were normalized to PBS or GalNAc-1955 (highest concentration used for experimental compounds) treated cells. IC_{50}s were calculated using a 4 parameter fit model using XLFit and normalized to cells transfected with AD-1955 over the same dose range, or to its own lowest dose.

[0430] The sense and antisense sequences of AD-1955 are: SENSE: 5'-cuuAcGcuGAGuAcuucGAdTsdT-3' (SEQ ID NO: 11); and ANTISENSE: 5'-UCGAAGuACUcAGCGuAAGdTsdT-3' (SEQ ID NO: 12).

Table B: Abbreviations of nucleotide monomers used in nucleic acid sequence representation.

Abbreviation	Nucleotide(s)
A	Adenosine-3'-phosphate

(continued)

Abbreviation	Nucleotide(s)
Ab	beta-L-adenosine-3'-phosphate
Af	2'-fluoroadenosine-3'-phosphate
Afs	2'-fluoroadenosine-3'-phosphorothioate
As	adenosine-3'-phosphorothioate
C	cytidine-3'-phosphate
Cb	beta-L-cytidine-3'-phosphate
Cf	2'-fluorocytidine-3'-phosphate
Cfs	2'-fluorocytidine-3'-phosphorothioate
Cs	cytidine-3'-phosphorothioate
G	guanosine-3'-phosphate
Gb	beta-L-guanosine-3'-phosphate
Gbs	beta-L-guanosine-3'-phosphorothioate
Gf	2'-fluoroguanosine-3'-phosphate
Gfs	2'-fluoroguanosine-3'-phosphorothioate
Gs	guanosine-3'-phosphorothioate
T	5'-methyluridine-3'-phosphate
Tf	2'-fluoro-5-methyluridine-3'-phosphate
Tfs	2'-fluoro-5-methyluridine-3'-phosphorothioate
Ts	5-methyluridine-3' -phosphorothioate
U	Uridine-3'-phosphate
Uf	2'-fluorouridine-3'-phosphate
Ufs	2'-fluorouridine -3'-phosphorothioate
Us	uridine -3'-phosphorothioate
N	any nucleotide (G, A, C, T or U)
a	2'-O-methyladenosine-3'-phosphate
as	2'-O-methyladenosine-3'-phosphorothioate
c	2'-O-methylcytidine-3'-phosphate
cs	2'-O-methylcytidine-3'-phosphorothioate
g	2'-O-methylguanosine-3'-phosphate
gs	2'-O-methylguanosine-3'-phosphorothioate
t	2'-O-methyl-5-methyluridine-3'-phosphate
ts	2'-O-methyl-5-methyluridine-3'-phosphorothioate
u	2'-O-methyluridine-3'-phosphate
us	2'-O-methyluridine-3'-phosphorothioate
dT	2'-deoxythymidine
dTs	2'-deoxythymidine-3'-phosphorothioate
dU	2'-deoxyuridine
s	phosphorothioate linkage

(continued)

Abbreviation	Nucleotide(s)
L96	N-[tris(GalNAc-alkyl)-amidodecanoyl)]-4-hydroxyprolinol Hyp-(GalNAc-alkyl)3
(Aeo)	2'-O-methoxyethyladenosine-3'-phosphate
(Aeos)	2'-O-methoxyethyladenosine-3'-phosphorothioate
(Geo)	2'-O-methoxyethylguanosine-3'-phosphate
(Geos)	2'-O-methoxyethylguanosine-3'- phosphorothioate
(Teo)	2'-O-methoxyethyl-5-methyluridine-3'-phosphate
(Teos)	2'-O-methoxyethyl-5-methyluridine-3'- phosphorothioate
(m5Ceo)	2'-O-methoxyethyl-5-methylcytidine-3'-phosphate
(m5Ceos)	2'-O-methoxyethyl-5-methylcytidine-3'- phosphorothioate
(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-methylxylouridine-2'-phosphate
(Chd)	2'-O-hexadecyl-cytidine-3'-phosphate
(pshe)	Hydroxyethylphosphorothioate
(Uhd)	2'-O-hexadecyl-uridine-3'-phosphate
(Tgn)	Thymidine-glycol nucleic acid (GNA) S-Isomer
(Cgn)	Cytidine-glycol nucleic acid (GNA)
(Chd)	2'-O-hexadecyl-cytidine-3'-phosphate
(Ggn)	2'-O-hexadecyl-cytidine-3'-phosphate
(Agn)	Adenosine-glycol nucleic acid (GNA)
P	5'-phosphate
(m5Cam)	2'-O-(N-methylacetamide)-5-methylcytidine-3'-phosphate
(m5Cams)	2'-O-(N-methylacetamide)-5-methylcytidine-3'-phosphorothioate
(Tam)	2'-O-(N-methylacetamide)thymidine-3'-phosphate
(Tams)	2'-O-(N-methylacetamide)thymidine-3'-phosphorothioate
(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
(Uyh)	2'-O-(1-hexyl-4-methylene-1,2,3-triazolyl)-uridine-3'-phosphate
(Ayh)	2'-O-(1-hexyl-4-methylene-1,2,3-triazolyl)-adenosine-3'-phosphate
(Gyh)	2'-O-(1-hexyl-4-methylene-1,2,3-triazolyl)-guanosine-3'-phosphate
(Cyh)	2'-O-(1-hexyl-4-methylene-1,2,3-triazolyl)-cytidine-3'-phosphate

Example 1. ***Synthesis of GalNAc-Conjugated Oligonucleotides***

[0431] A series of siRNA duplexes spanning the sequence of PCSK9 mRNA were designed, synthesized, and conjugated with a trivalent GalNAc at the 3-
end of the sense strand using the techniques described above. The sequences of these duplexes are shown in Table 1. These same sequences were also synthesized with various nucleotide modifications and conjugated with a trivalent GalNAc. The sequences of the modified duplexes are shown n Table 2.

Table 1. PCSK9 unmodified sequences

Duplex Name	Sense Oligo Name	Sense Trans Seq	SEQ ID NO:	Antisense Oligo Name	Antisense Trans Seq	SEQ ID NO:	Start In NM_174936.3	End In NM_174936.3
AD-53649.1	A-110542.1	CGAGGACGGCGACUACGAGGA	13	A-109239.2	UCCUCGUAGUCGCCGUCCUCGUC	234	459	481
AD-53661.1	A-110544.1	ACCGCUGCGCCAAGGAUCCGU	14	A-109243.2	ACGGAUCCUUGGCGCAGCGGUGG	235	554	576
AD-53667.1	A-110545.1	GCUGCGCCAAGGAUCCGUGGA	15	A-109245.2	UCCACGGAUCCUUGGCGCAGCGG	236	557	579
AD-53679.1	A-110547.1	CUACGUGGUGGUGCUGAAGGA	16	A-109249.2	UCCUUCAGCACCACCACGUAGGU	237	591	613
AD-53685.1	A-110548.1	CCCGCCGGGGAUACCUCACCA	17	A-109251.2	UGGUGAGGUAUCCCCGGCGGGCA	238	668	690
AD-53691.1	A-110549.1	CCGCCGGGGAUACCUCACCAA	18	A-109253.2	UUGGUGAGGUAUCCCCGGCGGGC	239	669	691
AD-53650.1	A-110550.1	GCCGGGGAUACCUCACCAAGA	19	A-109255.2	UCUUGGUGAGGUAUCCCCGGCGG	240	671	693
AD-53656.1	A-110551.1	CCGGGGAUACCUCACCAAGAU	20	A-109257.2	AUCUUGGUGAGGUAUCCCCGGCG	241	672	694
AD-53668.1	A-110553.1	AUACCUCACCAAGAUCCUGCA	21	A-109261.2	UGCAGGAUCUUGGUGAGGUAUCC	242	678	700
AD-53674.1	A-110554.1	CACCAAGAUCCUGCAUGUCUU	22	A-109263.2	AAGACAUGCAGGAUCUUGGUGAG	243	684	706
AD-53680.1	A-110555.1	CAAGAUCCUGCAUGUCUUCCA	23	A-109265.2	UGGAAGACAUGCAGGAUCUUGGU	244	687	709
AD-53692.1	A-110557.1	GUUGCCCCAUGUCGACUACAU	24	A-109269.2	AUGUAGUCGACAUGGGGCAACUU	245	768	790
AD-53651.1	A-110558.1	GCCCCAUGUCGACUACAUCGA	25	A-109271.2	UCGAUGUAGUCGACAUGGGGCAA	246	771	793
AD-53657.1	A-110559.1	CCAUGUCGACUACAUCGAGGA	26	A-109273.2	UCCUCGAUGUAGUCGACAUGGGG	247	774	796

(continued)

Duplex Name	Sense Oligo Name	Sense Trans Seq	SEQ ID NO:	Antisense Oligo Name	Antisense Trans Seq	SEQ ID NO:	Start In NM_174936.3	End In NM_174936 .3
AD-53663.1	A-110560.1	UCGACUACAUCGAGGAGGACU	27	A-109275.2	AGUCCUCCUCGAUGUAGUCGACA	248	779	801
AD-53669.1	A-110561.1	ACUACAUCGAGGAGGACUCCU	28	A-109277.2	AGGAGUCCUCCUCGAUGUAGUCG	249	782	804
AD-53675.1	A-110562.1	UACAUCGAGGAGGACUCCUCU	29	A-109279.2	AGAGGAGUCCUCCUCGAUGUAGU	250	784	806
AD-53681.1	A-110563.1	UCGAGGAGGACUCCUCUGUCU	30	A-109281.2	AGACAGAGGAGUCCUCCUCGAUG	251	788	810
AD-53687.1	A-110564.1	CGAGGAGGACUCCUCUGUCUU	31	A-109283.2	AAGACAGAGGAGUCCUCCUCGAU	252	789	811
AD-53693.1	A-110565.1	GUACCGGGCGGAUGAAUACCA	32	A-109285.2	UGGUAUUCAUCCGCCCGGUACCG	253	855	877
AD-53652.1	A-110566.1	CCUGGUGGAGGUGUAUCUCCU	33	A-109287.2	AGGAGAUACACCUCCACCAGGCU	254	894	916
AD-53658.1	A-110567.1	CUGGUGGAGGUGUAUCUCCUA	34	A-109289.2	UAGGAGAUACACCUCCACCAGGC	255	895	917
AD-53664.1	A-110568.1	GGUGGAGGUGUAUCUCCUAGA	35	A-109291.2	UCUAGGAGAUACACCUCCACCAG	256	897	919
AD-53670.1	A-110569.1	UGGAGGUGUAUCUCCUAGACA	36	A-109293.2	UGUCUAGGAGAUACACCUCCACC	257	899	921
AD-53676.1	A-110570.1	AGGUGUAUCUCCUAGACACCA	37	A-109295.2	UGGUGUCUAGGAGAUACACCUCC	258	902	924
AD-53682.1	A-110571.1	GUAUCUCCUAGACACCAGCAU	38	A-109297.2	AUGCUGGUGUCUAGGAGAUACAC	259	906	928
AD-53688.1	A-110572.1	UAUCUCCUAGACACCAGCAUA	39	A-109299.2	UAUGCUGGUGUCUAGGAGAUACA	260	907	929
AD-53694.1	A-110573.1	UCUCCUAGACACCAGCAUACA	40	A-109301.2	UGUAUGCUGGUGUCUAGGAGAUA	261	909	931

(continued)

Duplex Name	Sense Oligo Name	Sense Trans Seq	SEQ ID NO:	Antisense Oligo Name	Antisense Trans Seq	SEQ ID NO:	Start In NM_174936.3	End In NM_174936 .3
AD-53653.1	A-110574.1	UCCUAGACACCAGCAUACAGA	41	A-109303.2	UCUGUAUGCUGGUGUCUAGGAGA	262	911	933
AD-53659.1	A-110575.1	AGACACCAGCAUACAGAGUGA	42	A-109305.2	UCACUCUGUAUGCUGGUGUCUAG	263	915	937
AD-53665.1	A-110576.1	CACCAGCAUACAGAGUGACCA	43	A-109307.2	UGGUCACUCUGUAUGCUGGUGUC	264	918	940
AD-53671.1	A-110577.1	UACAGAGUGACCACCGGGAAA	44	A-109309.2	UUUCCCGGUGGUCACUCUGUAUG	265	926	948
AD-53677.1	A-110578.1	ACAGAGUGACCACCGGGAAAU	45	A-109311.2	AUUUCCCGGUGGUCACUCUGUAU	266	927	949
AD-53683.1	A-110579.1	GAGUGACCACCGGGAAAUCGA	46	A-109313.2	UCGAUUUCCCGGUGGUCACUCUG	267	930	952
AD-53689.1	A-110580.1	GGAAAUCGAGGGCAGGGUCAU	47	A-109315.2	AUGACCCUGCCCUCGAUUUCCCG	268	942	964
AD-53695.1	A-110581.1	AAUCGAGGGCAGGGUCAUGGU	48	A-109317.2	ACCAUGACCCUGCCCUCGAUUUC	269	945	967
AD-53654.1	A-110582.1	GCAGGGUCAUGGUCACCGACU	49	A-109319.2	AGUCGGUGACCAUGACCCUGCCC	270	953	975
AD-53660.1	A-110583.1	CAGGGUCAUGGUCACCGACUU	50	A-109321.2	AAGUCGGUGACCAUGACCCUGCC	271	954	976
AD-53666.1	A-110584.1	GGUCAUGGUCACCGACUUCGA	51	A-109323.2	UCGAAGUCGGUGACCAUGACCCU	272	957	979
AD-53672.1	A-110585.1	UCAUGGUCACCGACUUCGAGA	52	A-109325.2	UCUCGAAGUCGGUGACCAUGACC	273	959	981
AD-53678.1	A-110586.1	AGGACGGGACCCGCUUCCACA	53	A-109327.2	UGUGGAAGCGGGUCCCGUCCUCC	274	992	1014
AD-53684.1	A-110587.1	CGGGACCCGCUUCCACAGACA	54	A-109329.2	UGUCUGUGGAAGCGGGUCCCGUC	275	996	1018

(continued)

Duplex Name	Sense Oligo Name	Sense Trans Seq	SEQ ID NO:	Antisense Oligo Name	Antisense Trans Seq	SEQ ID NO:	Start In NM_174936.3	End In NM_174936 .3
AD-53690.1	A-110588.1	UCCACAGACAGGCCAGCAAGU	55	A-109331.2	ACUUGCUGGCCUGUCUGUGGAAG	276	1007	1029
AD-53696.1	A-110589.1	CCUGCGCGUGCUCAACUGCCA	56	A-109333.2	UGGCAG U UGAGCACGCGCAGGCU	277	1107	1129
AD-53702.1	A-110590.1	CUGCGCGUGCUCAACUGCCAA	57	A-109335.2	UUGGCAGUUGAGCACGCGCAGGC	278	1108	1130
AD-53708.1	A-110591.1	CGUGCUCAACUGCCAAGGGAA	58	A-109337.2	UUCCCUUGGCAGUUGAGCACGCG	279	1113	1135
AD-53714.1	A-110592.1	CACCCUCAUAGGCCUGGAGUU	59	A-109339.2	AACUCCAGGCCUAUGAGGGUGCC	280	1149	1171
AD-53720.1	A-110593.1	ACCCUCAUAGGCCUGGAGUUU	60	A-109341.2	AAACUCCAGGCCUAUGAGGGUGC	281	1150	1172
AD-53726.1	A-110594.1	CCCUCAUAGGCCUGGAGUUUA	61	A-109343.2	UAAACUCCAGGCCUAUGAGGGUG	282	1151	1173
AD-53732.1	A-110595.1	CCUCAUAGGCCUGGAGUUUAU	62	A-109345.2	AUAAACUCCAGGCCUAUGAGGGU	283	1152	1174
AD-53738.1	A-110596.1	CUCAUAGGCCUGGAGUUUAUU	63	A-109347.2	AAUAAACUCCAGGCCUAUGAGGG	284	1153	1175
AD-53697.1	A-110597.1	UAGGCCUGGAGUUUAUUCGGA	64	A-109349.2	UCCGAAUAAACUCCAGGCCUAUG	285	1157	1179
AD-53703.1	A-110598.1	AGGCCUGGAGUUUAUUCGGAA	65	A-109351.2	UUCCGAAUAAACUCCAGGCCUAU	286	1158	1180
AD-53709.1	A-110599.1	GGCCUGGAGUUUAUUCGGAAA	66	A-109353.2	UUUCCGAAUAAACUCCAGGCCUA	287	1159	1181
AD-53715.1	A-110600.1	GCCUGGAGUUUAUUCGGAAAA	67	A-109355.2	UUUUCCGAAUAAACUCCAGGCCU	288	1160	1182
AD-53721.1	A-110601.1	GGAGUUUAUUCGGAAAAGCCA	68	A-109357.2	UGGCUUUUCCGAAUAAACUCCAG	289	1164	1186

(continued)

Duplex Name	Sense Oligo Name	Sense Trans Seq	SEQ ID NO:	Antisense Oligo Name	Antisense Trans Seq	SEQ ID NO:	Start In NM_174936.3	End In NM_174936 .3
AD-53727.1	A-110602.1	GUUUAUUCGGAAAAGCCAGCU	69	A-109359.2	AGCUGGCUUUUCCGAAUAAACUC	290	1167	1189
AD-53733.1	A-110603.1	GGGCUGGGGUCGUGCUGGUCA	70	A-109361.2	UGACCAGCACGACCCCAGCCCUC	291	1277	1299
AD-53739.1	A-110604.1	GGUCACCGCUGCCGGCAACUU	71	A-109363.2	AAGUUGCCGGCAGCGGUGACCAG	292	1293	1315
AD-53698.1	A-110605.1	GGGACGAUGCCUGCCUCUACU	72	A-109365.2	AGUAGAGGCAGGCAUCGUCCCGG	293	1316	1338
AD-53704.1	A-110606.1	CAACUUUGGCCGCUGUGUGGA	73	A-109367.2	UCCACACAGCGGCCAAAGUUGGU	294	1419	1441
AD-53710.1	A-110607.1	UUGGCCGCUGUGUGGACCUCU	74	A-109369.2	AGAGGUCCACACAGCGGCCAAAG	295	1424	1446
AD-53716.1	A-110608.1	UGGCCGCUGUGUGGACCUCUU	75	A-109371.2	AAGAGGUCCACACAGCGGCCAAA	296	1425	1447
AD-53722.1	A-110609.1	GGCCGCUGUGUGGACCUCUUU	76	A-109373.2	AAAGAGGUCCACACAGCGGCCAA	297	1426	1448
AD-53728.1	A-110610.1	UGUGUGGACCUCUUUGCCCCA	77	A-109375.2	UGGGGCAAAGAGGUCCACACAGC	298	1432	1454
AD-53734.1	A-110611.1	GGGAGGACAUCAUUGGUGCCU	78	A-109377.2	AGGCACCAAUGAUGUCCUCCCCU	299	1454	1476
AD-53740.1	A-110612.1	ACUGCAGCACCUGCUUUGUGU	79	A-109379.2	ACACAAAGCAGGUGCUGCAGUCG	300	1481	1503
AD-53699.1	A-110613.1	GCAUUGCAGCCAUGAUGCUGU	80	A-109381.2	ACAGCAUCAUGGCUGCAAUGCCA	301	1541	1563
AD-53705.1	A-110614.1	GUUGAGGCAGAGACUGAUCCA	81	A-109383.2	UGGAUCAGUCUCUGCCUCAACUC	302	1590	1612
AD-53711.1	A-110615.1	UGAGGCAGAGACUGAUCCACU	82	A-109385.2	AG UGGAUCAG UCUCUGCCUCAAC	303	1592	1614

(continued)

Duplex Name	Sense Oligo Name	Sense Trans Seq	SEQ ID NO:	Antisense Oligo Name	Antisense Trans Seq	SEQ ID NO:	Start In NM_174936.3	End In NM_174936 .3
AD-53717.1	A-110616.1	GAGGCAGAGACUGAUCCACUU	83	A-109387.2	AAGUGGAUCAGUCUCUGCCUCAA	304	1593	1615
AD-53723.1	A-110617.1	GGCAGAGACUGAUCCACUUCU	84	A-109389.2	AGAAGUGGAUCAGUCUCUGCCUC	305	1595	1617
AD-53729.1	A-110618.1	CAGAGACUGAUCCACUUCUCU	85	A-109391.2	AGAGAAGUGGAUCAGUCUCUGCC	306	1597	1619
AD-53735.1	A-110619.1	ACUGAUCCACUUCUCUGCCAA	86	A-109393.2	UUGGCAGAGAAGUGGAUCAGUCU	307	1602	1624
AD-53741.1	A-110620.1	AUCCACUUCUCUGCCAAAGAU	87	A-109395.2	AUCUUUGGCAGAGAAGUGGAUCA	308	1606	1628
AD-53700.1	A-110621.1	GGCCUGGUUCCCUGAGGACCA	88	A-109397.2	UGGUCCUCAGGGAACCAGGCCUC	309	1638	1660
AD-53706.1	A-110622.1	GGUACUGACCCCCAACCUGGU	89	A-109399.2	ACCAGGUUGGGGGUCAGUACCCG	310	1662	1684
AD-53712.1	A-110623.1	GUUGGCAGCUGUUUUGCAGGA	90	A-109401.2	UCCUGCAAAACAGCUGCCAACCU	311	1715	1737
AD-53718.1	A-110624.1	UGGCAGCUGUUUUGCAGGACU	91	A-109403.2	AGUCCUGCAAAACAGCUGCCAAC	312	1717	1739
AD-53724.1	A-110625.1	GCAGCUGUUUUGCAGGACUGU	92	A-109405.2	ACAGUCCUGCAAAACAGCUGCCA	313	1719	1741
AD-53730.1	A-110626.1	UCUGCCGGGCCCACAACGCUU	93	A-109407.2	AAGCGUUGUGGGCCCGGCAGACC	314	1883	1905
AD-53736.1	A-110627.1	CUGCCGGGCCCACAACGCUUU	94	A-109409.2	AAAGCGUUGUGGGCCCGGCAGAC	315	1884	1906
AD-53742.1	A-110628.1	GCCCACAACGCUUUUGGGGGU	95	A-109411.2	ACCCCCAAAAGCGUUGUGGGCCC	316	1891	1913
AD-53701.1	A-110629.1	CGCUUUUGGGGGUGAGGGUGU	96	A-109413.2	ACACCCUCACCCCCAAAAGCGUU	317	1899	1921

(continued)

Duplex Name	Sense Oligo Name	Sense Trans Seq	SEQ ID NO:	Antisense Oligo Name	Antisense Trans Seq	SEQ ID NO:	Start In NM_174936.3	End In NM_174936 .3
AD-53707.1	A-110630.1	CUUUUGGGGGUGAGGGUGUCU	97	A-109415.2	AGACACCCUCACCCCCAAAAGCG	318	1901	1923
AD-53713.1	A-110631.1	UUUUGGGGGUGAGGGUGUCUA	98	A-109417.2	UAGACACCCUCACCCCCAAAAGC	319	1902	1924
AD-53719.1	A-110632.1	GGGGUGAGGGUGUCUACGCCA	99	A-109419.2	UGGCGUAGACACCCUCACCCCCA	320	1907	1929
AD-53725.1	A-110633.1	GGGUGAGGGUGUCUACGCCAU	100	A-109421.2	AUGGCGUAGACACCCUCACCCCC	321	1908	1930
AD-53731.1	A-110634.1	GGUGAGGGUGUCUACGCCAUU	101	A-109423.2	AAUGGCGUAGACACCCUCACCCC	322	1909	1931
AD-53737.1	A-110635.1	AGGGUGUCUACGCCAUUGCCA	102	A-109425.2	UGGCAAUGGCGUAGACACCCUCA	323	1913	1935
AD-53743.1	A-110636.1	GUGUCUACGCCAUUGCCAGGU	103	A-109427.2	ACCUGGCAAUGGCGUAGACACCC	324	1916	1938
AD-53749.1	A-110637.1	UGCAGCGUCCACACAGCUCCA	104	A-109429.2	UGGAGCUGUGUGGACGCUGCAGU	325	1960	1982
AD-53755.1	A-110638.1	GCAUGGGGACCCGUGUCCACU	105	A-109431.2	AGUGGACACGGGUCCCCAUGCUG	326	1994	2016
AD-53761.1	A-110639.1	CCCACAAGCCGCCUGUGCUGA	106	A-109433.2	UCAGCACAGGCGGCU UG UGGG UG	327	2078	2100
AD-53767.1	A-110640.1	GAGGCCACGAGG UCAGCCCAA	107	A-109435.2	UUGGGCUGACCUCGUGGCCUCAG	328	2097	2119
AD-53773.1	A-110641.1	CACGAGGUCAGCCCAACCAGU	108	A-109437.2	ACUGGUUGGGCUGACCUCGUGGC	329	2102	2124
AD-53779.1	A-110642.1	GGGAGGCCAGCAUCCACGCUU	109	A-109439.2	AAGCGUGGAUGCUGGCCUCCCUG	330	2135	2157
AD-53785.1	A-110643.1	AUCCACGCUUCCUGCUGCCAU	110	A-109441.2	AUGGCAGCAGGAAGCGUGGAUGC	331	2146	2168

(continued)

Duplex Name	Sense Oligo Name	Sense Trans Seq	SEQ ID NO:	Antisense Oligo Name	Antisense Trans Seq	SEQ ID NO:	Start In NM_174936.3	End In NM_174936 .3
AD-53744.1	A-110644.1	GGAAUGCAAAGUCAAGGAGCA	111	A-109443.2	UGCUCCUUGACUUUGCAUUCCAG	332	2178	2200
AD-53750.1	A-110645.1	AAUCCCGGCCCCUCAGGAGCA	112	A-109445.2	UGCUCCUGAGGGGCCGGGAUUCC	333	2202	2224
AD-53762.1	A-110647.1	GCUGGGGCUGAGCUUUAAAAU	113	A-109449.2	AUUUUAAAGCUCAGCCCCAGCCC	334	2479	2501
AD-53768.1	A-110648.1	GGAGGUGCCAGGAAGCUCCCU	114	A-109451.2	AGGGAGCUUCCUGGCACCUCCAC	335	2648	2670
AD-53774.1	A-110649.1	ACUGUGGGGCAUUUCACCAUU	115	A-109453.2	AAUGGUGAAAUGCCCCACAGUGA	336	2674	2696
AD-53780.1	A-110650.1	CCACCAAGGAGGCAGGAUUCU	116	A-109455.2	AGAAUCCUGCCUCCUUGGUGGAG	337	2811	2833
AD-53786.1	A-110651.1	CACCAAGGAGGCAGGAUUCUU	117	A-109457.2	AAGAAUCCUGCCUCCUUGGUGGA	338	2812	2834
AD-53804.1	A-110701.1	ACCAAGGAGGCAGGAUUCUUU	118	A-109557.2	AAAGAAUCCUGCCUCCUUGGUGG	339	2813	2835
AD-53810.1	A-110702.1	GGAGGCAGGAUUCUUCCCAUU	119	A-109559.2	AAUGGGAAGAAUCCUGCCUCCUU	340	2818	2840
AD-53816.1	A-110703.1	GAGGCAGGAU UCU UCCCAUGA	120	A-109561.2	UCAUGGGAAGAAUCCUGCCUCCU	341	2819	2841
AD-53745.1	A-110652.1	UGAUGGCCCUCAUCUCCAGCU	121	A-109459.2	AGCUGGAGAUGAGGGCCAUCAGC	342	2904	2926
AD-53822.1	A-110704.1	CUUUCUGGAUGGCAUCUAGCA	122	A-109563.2	UGCUAGAUGCCAUCCAGAAAGCU	343	2971	2993
AD-53751.1	A-110653.1	UUUCUGGAUGGCAUCUAGCCA	123	A-109461.2	UGGCUAGAUGCCAUCCAGAAAGC	344	2972	2994
AD-53827.1	A-110705.1	UUCUGGAUGGCAUCUAGCCAA	124	A-109565.2	UUGGCUAGAUGCCAUCCAGAAAG	345	2973	2995

(continued)

Duplex Name	Sense Oligo Name	Sense Trans Seq	SEQ ID NO:	Antisense Oligo Name	Antisense Trans Seq	SEQ ID NO:	Start In NM_174936.3	End In NM_174936 .3
AD-53757.1	A-110654.1	UCUGGAUGGCAUCUAGCCAGA	125	A-109463.2	UCUGGCUAGAUGCCAUCCAGAAA	346	2974	2996
AD-53833.1	A-110706.1	CUGGAUGGCAUCUAGCCAGAA	126	A-109567.2	UUCUGGCUAGAUGCCAUCCAGAA	347	2975	2997
AD-53793.1	A-110707.1	CUUUACUCUGCUCUAUGCCAA	127	A-109569.2	UUGGCAUAGAGCAGAGUAAAGGU	348	3053	3075
AD-53799.1	A-110708.1	UUUACUCUGCUCUAUGCCAGA	128	A-109571.2	UCUGGCAUAGAGCAGAGUAAAGG	349	3054	3076
AD-53763.1	A-110655.1	GCUCUAUGCCAGGCUGUGCUA	129	A-109465.2	UAGCACAGCCUGGCAUAGAGCAG	350	3062	3084
AD-53769.1	A-110656.1	CUCAGCCAACCCGCUCCACUA	130	A-109467.2	UAGUGGAGCGGGUUGGCUGAGAC	351	3158	3180
AD-53805.1	A-110709.1	UCAGCCAACCCGCUCCACUAA	131	A-109573.2	UUAGUGGAGCGGGUUGGCUGAGA	352	3159	3181
AD-53811.1	A-110710.1	CCUGCCAAGCUCACACAGCAA	132	A-109575.2	UUGCUGUGUGAGCUUGGCAGGCA	353	3245	3267
AD-53781.1	A-110658.1	GCCAAGCUCACACAGCAGGAA	133	A-109471.2	UUCCUGCUGUGUGAGCUUGGCAG	354	3248	3270
AD-53817.1	A-110711.1	CCAAGCUCACACAGCAGGAAA	134	A-109577.2	UUUCCUGCUGUGUGAGCUUGGCA	355	3249	3271
AD-53787.1	A-110659.1	CAAGCUCACACAGCAGGAACU	135	A-109473.2	AGUUCCUGCUGUGUGAGCUUGGC	356	3250	3272
AD-53823.1	A-110712.1	AAGCUCACACAGCAGGAACUU	136	A-109579.2	AAGUUCCUGCUGUGUGAGCUUGG	357	3251	3273
AD-53746.1	A-110660.1	CUGAAGCCAAGCCUCUUCUUA	137	A-109475.2	UAAGAAGAGGCUUGGCUUCAGAG	358	3298	3320
AD-53828.1	A-110713.1	UGAAGCCAAGCCUCUUCUUAA	138	A-109581.2	UUAAGAAGAGGCUUGGCUUCAGA	359	3299	3321

(continued)

Duplex Name	Sense Oligo Name	Sense Trans Seq	SEQ ID NO:	Antisense Oligo Name	Antisense Trans Seq	SEQ ID NO:	Start In NM_174936.3	End In NM_174936 .3
AD-53752.1	A-110661.1	GAAGCCAAGCCUCUUCUUACU	139	A-109477.2	AGUAAGAAGAGGCUUGGCUUCAG	360	3300	3322
AD-53758.1	A-110662.1	AAGCCAAGCCUCUUCUUACUU	140	A-109479.2	AAGUAAGAAGAGGCUUGGCUUCA	361	3301	3323
AD-53834.1	A-110714.1	AGUGAGGCUGGGAAGGGGAAA	141	A-109583.2	UUUCCCCUUCCCAGCCUCACUGU	362	3355	3377
AD-53764.1	A-110663.1	GUGAGGCUGGGAAGGGGAACA	142	A-109481.2	UGUUCCCCUUCCCAGCCUCACUG	363	3356	3378
AD-53770.1	A-110664.1	GGCUGGGAAGGGGAACACAGA	143	A-109483.2	UCUGUGUUCCCCUUCCCAGCCUC	364	3360	3382
AD-53776.1	A-110665.1	GAAGGGGAACACAGACCAGGA	144	A-109485.2	UCCUGGUCUGUGUUCCCCUUCCC	365	3366	3388
AD-53782.1	A-110666.1	AAGGGGAACACAGACCAGGAA	145	A-109487.2	UUCCUGGUCUGUGUUCCCCUUCC	366	3367	3389
AD-53794.1	A-110715.1	AGGGGAACACAGACCAGGAAA	146	A-109585.2	UUUCCUGGUCUGUGUUCCCCUUC	367	3368	3390
AD-53788.1	A-110667.1	GGGAACACAGACCAGGAAGCU	147	A-109489.2	AGCUUCCUGGUCUGUGUUCCCCU	368	3370	3392
AD-53747.1	A-110668.1	ACUGUCCCUCCUUGAGCACCA	148	A-109491.2	UGGUGCUCAAGGAGGGACAGUUG	369	3509	3531
AD-53753.1	A-110669.1	CCAGCCCCACCCAAGCAAGCA	149	A-109493.2	UGCUUGCUUGGGUGGGGCUGGUG	370	3527	3549
AD-53759.1	A-110670.1	CCCCACCCAAGCAAGCAGACA	150	A-109495.2	UGUCUGCUUGCUUGGGUGGGGCU	371	3531	3553
AD-53765.1	A-110671.1	CCCACCCAAGCAAGCAGACAU	151	A-109497.2	AUGUCUGCUUGCUUGGGUGGGGC	372	3532	3554
AD-53771.1	A-110672.1	CCACCCAAGCAAGCAGACAUU	152	A-109499.2	AAUGUCUGCUUGCUUGGGUGGGG	373	3533	3555

(continued)

Duplex Name	Sense Oligo Name	Sense Trans Seq	SEQ ID NO:	Antisense Oligo Name	Antisense Trans Seq	SEQ ID NO:	Start In NM_174936.3	End In NM_174936 .3
AD-53777.1	A-110673.1	CACCCAAGCAAGCAGACAU U	153	A-109501.2	AAAUGUCUGCUUGCUUGGGUGGG	374	3534	3556
AD-53783.1	A-110674.1	ACCCAAGCAAGCAGACAUUUA	154	A-109503.2	UAAAUGUCUGCUUGCUUGGGUGG	375	3535	3557
AD-53789.1	A-110675.1	CCCAAGCAAGCAGACAU U UAU	155	A-109505.2	AUAAAUGUCUGCUUGCUUGGGUG	376	3536	3558
AD-53800.1	A-110716.1	CCAAGCAAGCAGACAUUUAUU	156	A-109587.2	AAUAAAUGUCUGCUUGCUUGGGU	377	3537	3559
AD-53748.1	A-110676.1	CAAGCAAGCAGACAUUUAUCU	157	A-109507.2	AGAUAAAUGUCUGCUUGCUUGGG	378	3538	3560
AD-53754.1	A-110677.1	AAGCAAGCAGACAUUUAUCUU	158	A-109509.2	AAGAUAAAUGUCUGCUUGCUUGG	379	3539	3561
AD-53760.1	A-110678.1	AGCAAGCAGACAUUUAUCUUU	159	A-109511.2	AAAGAUAAAUGUCUGCUUGCUUG	380	3540	3562
AD-53806.1	A-110717.1	CAAGCAGACAUUUAUCUUUUU	160	A-109589.2	AAAAAGAUAAAUGUCUGCUUGCU	381	3542	3564
AD-56975.1	A-116394.4		160	A-109589.5		381		
AD-56976.1	A-116407.1		160	A-109589.11		381		
AD-56977.1	A-116406.2		160	A-109589.11		381		
AD-56978.1	A-116418.1		160	A-109589.18		381		
AD-56979.1	A-116393.1	Same	160	A-109589.6	Same	381	Same	Same
AD-56980.1	A-116408.1		160	A-109589.12		381		
AD-56981.1	A-116419.1		160	A-109589.19		381		
AD-56982.1	A-116426.1		160	A-109589.19		381		
AD-56983.1	A-116400.1		160	A-109589.7		381		
AD-56984.1	A-116409.1		160	A-109589.13		381		
AD-56985.1	A-116420.1		160	A-109589.20		381		

(continued)

Duplex Name	Sense Oligo Name	Sense Trans Seq	SEQ ID NO:	Antisense Oligo Name	Antisense Trans Seq	SEQ ID NO:	Start In NM_174936.3	End In NM_174936 .3
AD-56986.1	A-116428.1		160	A-109589.20		381		
AD-56986.2	A-116428.2		160	A-109589.17		381		
AD-56987.1	A-116410.1		160	A-109589.14		381		
AD-56988.1	A-116421.1		160	A-109589.21		381		
AD-56989.1	A-116430.1		160	A-109589.21		381		
AD-56990.1	A-116432.1		160	A-109589.9		381		
AD-56991.1	A-116415.1		160	A-109589.15		381		
AD-56992.1	A-116434.1		160	A-109589.15		381		
AD-56993.1	A-116416.1		160	A-109589.16		381		
AD-56994.1	A-116436.1		160	A-109589.22		381		
AD-56995.1	A-116417.1	Same	160	A-109589.17	Same	381	Same	Same
AD-56996.1	A-116438.1		160	A-109589.17		381		
AD-56997.1	A-116450.1		160	A-109589.17		381		
AD-56998.1	A-116471.1		160	A-109589.17		381		
AD-56999.1	A-116479.2		160	A-109589.17		381		
AD-57000.1	A-116492.3		160	A-109589.17		381		
AD-57001.1	A-116440.1		160	A-109589.17		381		
AD-57002.1	A-116452.1		160	A-109589.17		381		
AD-57003.1	A-116460.1		160	A-109589.17		381		
AD-57004.1	A-116473.1		160	A-109589.17		381		
AD-57005.1	A-116486.1		160	A-109589.17		381		
AD-57006.1	A-116494.3		160	A-109589.17		381		
AD-57007.1	A-116442.1		160	A-109589.17		381		
AD-57008.1	A-116453.1		160	A-109589.17		381		

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Duplex Name	Sense Oligo Name	Sense Trans Seq	SEQ ID NO:	Antisense Oligo Name	Antisense Trans Seq	SEQ ID NO:	Start In NM_174936.3	End In NM_174936 .3
AD-57009.1	A-116462.1		160	A-109589.17		381		
AD-57010.1	A-116475.1		160	A-109589.17		381		
AD-57011.1	A-116488.1		160	A-109589.17		381		
AD-57012.1	A-116498.1		160	A-109589.17		381		
AD-57013.1	A-116444.1		160	A-109589.17		381		
AD-57014.1	A-116454.1		160	A-109589.17		381		
AD-57015.1	A-116464.1		160	A-109589.17		381		
AD-57016.1	A-116477.1		160	A-109589.17		381		
AD-57017.1	A-116490.1		160	A-109589.17		381		
AD-57018.1	A-116500.1		160	A-109589.17		381		
AD-57019.1	A-116446.1		160	A-109589.17		381		
AD-57020.1	A-116455.1		160	A-109589.23		381		
AD-57021.1	A-116481.1		160	A-109589.23		381		
AD-57022.1	A-116448.1		160	A-109589.23		381		
AD-57023.1	A-116467.1		160	A-109589.23		381		
AD-57024.1	A-116483.1		160	A-109589.23		381		
AD-57025.1	A-116449.1		160	A-109589.23		381		
AD-57026.1	A-116457.1		160	A-109589.23		381		
AD-57027.1	A-116469.1		160	A-109589.23		381		
AD-53812.1	A-110718.1	AAGCAGACAUUUAUCUUUUGA	161	A-109591.2	UCAAAAGAUAAAUGUCUGCUUGC	382	3543	3565
AD-53818.1	A-110719.1	AGCAGACAUUUAUCUUUUGGA	162	A-109593.2	UCCAAAAGAUAAAUGUCUGCUUG	383	3544	3566
AD-53766.1	A-110679.1	GCAGACAUUUAUCUUUUGGGU	163	A-109513.2	ACCCAAAAGAUAAAUGUCUGCUU	384	3545	3567

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Duplex Name	Sense Oligo Name	Sense Trans Seq	SEQ ID NO:	Antisense Oligo Name	Antisense Trans Seq	SEQ ID NO:	Start In NM_174936.3	End In NM_174936 .3
AD-53772.1	A-110680.1	AGACAUUUAUCUUUUGGGUCU	164	A-109515.2	AGACCCAAAAGAUAAAUGUCUGC	385	3547	3569
AD-53824.1	A-110720.1	GACAUUUAUCUUUUGGGUCUU	165	A-109595.2	AAGACCCAAAAGAUAAAUGUCUG	386	3548	3570
AD-53778.1	A-110681.1	ACAUUUAUCUUUUGGGUCUGU	166	A-109517.2	ACAGACCCAAAAGAUAAAUGUCU	387	3549	3571
AD-53784.1	A-110682.1	UUUAUCUUUUGGGUCUGUCCU	167	A-109519.2	AGGACAGACCCAAAGAUAAAUG	388	3552	3574
AD-53829.1	A-110721.1	UUAUCUUUUGGGUCUGUCCUU	168	A-109597.2	AAGGACAGACCCAAAGAUAAAU	389	3553	3575
AD-53790.1	A-110683.1	UAUCUUUUGGGUCUGUCCUCU	169	A-109521.2	AGAGGACAGACCCAAAAGAUAAA	390	3554	3576
AD-53835.1	A-110722.1	AUCUUUUGGGUCUGUCCUCUU	170	A-109599.2	AAGAGGACAGACCCAAAAGAUAA	391	3555	3577
AD-53796.1	A-110684.1	UCUUUUGGGUCUGUCCUCUCU	171	A-109523.2	AGAGAGGACAGACCCAAAAGAUA	392	3556	3578
AD-53802.1	A-110685.1	UUUUGGGUCUGUCCUCUCUGU	172	A-109525.2	ACAGAGAGGACAGACCCAAAAGA	393	3558	3580
AD-53808.1	A-110686.1	UUUGGGUCUGUCCUCUCUGUU	173	A-109527.2	AACAGAGAGGACAGACCCAAAAG	394	3559	3581
AD-53795.1	A-110723.1	UUGGGUCUGUCCUCUCUGUUU	174	A-109601.2	AAACAGAGAGGACAGACCCAAAA	395	3560	3582
AD-53801.1	A-110724.1	UGGGUCUGUCCUCUCUGUUGA	175	A-109603.2	UCAACAGAGAGGACAGACCCAAA	396	3561	3583
AD-53807.1	A-110725.1	GGGUCUGUCCUCUCUGUUGCA	176	A-109605.2	UGCAACAGAGAGGACAGACCCAA	397	3562	3584
AD-53814.1	A-110687.1	GGUCUGUCCUCUCUGUUGCCU	177	A-109529.2	AGGCAACAGAGAGGACAGACCCA	398	3563	3585

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Duplex Name	Sense Oligo Name	Sense Trans Seq	SEQ ID NO:	Antisense Oligo Name	Antisense Trans Seq	SEQ ID NO:	Start In NM_174936.3	End In NM_174936 .3
AD-53820.1	A-110688.1	GUCUGUCCUCUCUGUUGCCUU	178	A-109531.2	AAGGCAACAGAGAGGACAGACCC	399	3564	3586
AD-53825.1	A-110689.1	UCUGUCCUCUCUGUUGCCUUU	179	A-109533.2	AAAGGCAACAGAGAGGACAGACC	400	3565	3587
AD-53831.1	A-110690.1	CUGUCCUCUCUGUUGCCUUUU	180	A-109535.2	AAAAGGCAACAGAGAGGACAGAC	401	3566	3588
AD-53791.1	A-110691.1	UGUCCUCUCUGUUGCCUUUUU	181	A-109537.2	AAAAAGGCAACAGAGAGGACAGA	402	3567	3589
AD-53797.1	A-110692.1	GUCCUCUCUGUUGCCUUUUUA	182	A-109539.2	UAAAAAGGCAACAGAGAGGACAG	403	3568	3590
AD-48400.1	A-98247.2	UUUUCUAGACCUGUUUUGCUU	183	A-93455.4	AAGCAAAACAGGUCUAGAAAAGU	404	3597	3619
AD-53830.1	A-110872.1			A-110873.1				
AD-53803.1	A-110693.1	UUUCUAGACCUGUUUUGCUUU	184	A-109541.2	AAAGCAAAACAGGUCUAGAAAAG	405	3598	3620
AD-53809.1	A-110694.1	UUCUAGACCUGUUUUGCUUUU	185	A-109543.2	AAAAGCAAAACAGGUCUAGAAAA	406	3599	3621
AD-53813.1	A-110726.1	UCUAGACCUGUUUUGCUUUUU	186	A-109607.2	AAAAAGCAAAACAGGUCUAGAAA	407	3600	3622
AD-53815.1	A-110695.1	CUAGACCUGUUUUGCUUUUGU	187	A-109545.2	ACAAAAGCAAAACAGGUCUAGAA	408	3601	3623
AD-56610.1	A-115523.2		187	A-115525.1		408		
AD-56611.1	A-115533.2	Same	187	A-115534.1	Same	408		Same
AD-56612.1	A-115536.2		187	A-115540.3		408		
AD-56613.1	A-115538.3		187	A-115541.5		408		
AD-56614.1	A-110695.9		187	A-115548.1		408		
AD-56615.1	A-110695.5		187	A-115519.1		408		

(continued)

Duplex Name	Sense Oligo Name	Sense Trans Seq	SEQ ID NO:	Antisense Oligo Name	Antisense Trans Seq	SEQ ID NO:	Start In NM_174936.3	End In NM_174936.3
AD-56616.1	A-115523.3		187	A-115526.1		408		
AD-56617.1	A-115535.1		187	A-109545.7		408		
AD-56618.1	A-115537.2		187	A-115540.4		408		
AD-56619.1	A-115539.3		187	A-115541.6		408		
AD-56620.1	A-115542.2		187	A-115548.2		408		
AD-56621.1	A-115520.1		187	A-115519.2		408		
AD-56622.1	A-115527.1		187	A-115526.2		408		
AD-56623.1	A-115536.1		187	A-109545.8		408		
AD-56624.1	A-115538.2		187	A-115540.5		408		
AD-56625.1	A-115542.1		187	A-109545.12		408		
AD-56626.1	A-115543.2		187	A-115548.3		408		
AD-56627.1	A-115521.1		187	A-115519.3		408		
AD-56628.1	A-115527.2		187	A-115528.1		408		
AD-56629.1	A-115537.1		187	A-109545.9		408		
AD-56630.1	A-115539.2		187	A-115540.6		408		
AD-56631.1	A-115543.1		187	A-109545.13		408		
AD-56632.1	A-115544.2		187	A-115548.4		408		
AD-56633.1	A-115520.2		187	A-109545.6		408		
AD-56634.1	A-115529.1		187	A-115530.1		408		
AD-56635.1	A-115538.1		187	A-109545.10		408		
AD-56636.1	A-110695.8		187	A-115541.1		408		
AD-56637.1	A-115544.1	Same	187	A-109545.14	Same	408		
AD-56638.1	A-115545.2		187	A-115548.5		408		
AD-56639.1	A-115520.3		187	A-115522.1		408		

(continued)

Duplex Name	Sense Oligo Name	Sense Trans Seq	SEQ ID NO:	Antisense Oligo Name	Antisense Trans Seq	SEQ ID NO:	Start In NM_174936.3	End In NM_174936 .3
AD-56640.1	A-115529.2		187	A-115531.1		408		
AD-56641.1	A-115539.1		187	A-109545.11		408		
AD-56642.1	A-115535.3		187	A-115541.2		408		
AD-56643.1	A-115545.1		187	A-109545.15		408		
AD-56644.1	A-115546.2		187	A-115548.6		408		
AD-56645.1	A-110695.6		187	A-115522.2		408		
AD-56646.1	A-115529.3		187	A-115532.1		408		
AD-56647.1	A-110695.7		187	A-115540.1		408		
AD-56648.1	A-115536.3		187	A-115541.3		408		
AD-56649.1	A-115546.1		187	A-109545.16		408		
AD-56650.1	A-115547.2		187	A-115548.7		408		
AD-56651.1	A-115523.1		187	A-115524.1		408		
AD-56652.1	A-115533.1		187	A-115532.2		408		
AD-56653.1	A-115535.2		187	A-115540.2		408		
AD-56654.1	A-115537.3		187	A-115541.4		408		
AD-56655.1	A-115547.1		187	A-109545.17		408		
AD-56656.1	A-110695.10		187	A-115549.1		408		
AD-56657.1	A-115550.1		187	A-115551.1		408		
AD-56658.1	A-115564.1		187	A-115565.1		408		
AD-56659.1	A-110695.12		187	A-115579.1		408		
AD-56662.1	A-115542.3		187	A-115549.2		408		
AD-56663.1	A-115552.1		187	A-115553.1		408		
AD-56664.1	A-115566.1		187	A-115567.1		408		

(continued)

Duplex Name	Sense Oligo Name	Sense Trans Seq	SEQ ID NO:	Antisense Oligo Name	Antisense Trans Seq	SEQ ID NO:	Start In NM_174936.3	End In NM_174936 .3
AD-56668.1	A-115543.3	Same	187	A-115549.3	Same	408		
AD-56669.1	A-115554.1		187	A-115555.1		408		
AD-56670.1	A-115568.1		187	A-115569.1		408		
AD-56673.1	A-115544.3		187	A-115549.4		408		
AD-56674.1	A-115556.1		187	A-115557.1		408		
AD-56678.1	A-115545.3		187	A-115549.5		408		
AD-56679.1	A-115558.1		187	A-115559.1		408		
AD-56680.1	A-115572.1		187	A-115573.1		408		
AD-56683.1	A-115546.3		187	A-115549.6		408		
AD-56684.1	A-115560.1		187	A-115561.1		408		
AD-56685.1	A-115574.1		187	A-115575.1		408		
AD-56688.1	A-115547.3		187	A-115549.7		408		
AD-56689.1	A-115535.4		187	A-115562.1		408		
AD-56690.1	A-115542.4		187	A-115576.1		408		
AD-56693.1	A-115520.4		187	A-115563.1		408		
AD-56694.1	A-115577.1		187	A-115578.1		408		
AD-53821.1	A-110696.1	UAGACCUGUUUUGCUUUUGUA	188	A-109547.2	UACAAAAGCAAAACAGGUCUAGA	409	3602	3624
AD-56660.1	A-115594.1	AGACCUGUUUUGCUUUUGU	189	A-115595.1	ACAAAAGCAAAACAGGUCUAG	410	3603	3623
AD-56661.1	A-115580.2	Same	189	A-115610.1	Same	410		
AD-56665.1	A-115580.1		189	A-115581.1		410		
AD-56666.1	A-115596.1		189	A-115597.1		410		
AD-56667.1	A-115611.1	GACCUGUUUUGCUUUUGU	190	A-115612.1	ACAAAAGCAAAACAGGUCAUA	411	3603	3623

(continued)

Duplex Name	Sense Oligo Name	Sense Trans Seq	SEQ ID NO:	Antisense Oligo Name	Antisense Trans Seq	SEQ ID NO:	Start In NM_174936.3	End In NM_174936.3
AD-56671.1	A-115582.1	AGACCUGUUUUGCUUUUGU	191	A-115583.1	ACAAAAGCAAAACAGGUCUAG	412	3603	3623
AD-56672.1	A-115598.1		191	A-115599.1		412		
AD-56676.1	A-115584.1	Same	191	A-115585.1	Same	412		
AD-56677.1	A-115600.1		191	A-115601.1		412	Same	Same
AD-56681.1	A-115586.1	Same	191	A-115587.1	Same	412		
AD-56682.1	A-115602.1		191	A-115603.1		412		
AD-56686.1	A-115588.1		191	A-115589.1		412		
AD-56687.1	A-115604.1		191	A-115605.1		412		
AD-56691.1	A-115590.1		191	A-115591.1		412		
AD-56692.1	A-115606.1		191	A-115607.1		412		
AD-56695.1	A-115592.1		191	A-115593.1		412		
AD-56696.1	A-115608.1		191	A-115609.1		412		
AD-53826.1	A-110697.1	UUUUGUAACUUGAAGAUAUUU	192	A-109549.2	AAAUAUCUUCAAGUUACAAAAGC	413	3616	3638
AD-53832.1	A-110698.1	UUUGUAACUUGAAGAUAUUUA	193	A-109551.2	UAAAUAUCUUCAAGUUACAAAAG	414	3617	3639
AD-53792.1	A-110699.1	UUGUAACUUGAAGAUAUUUAU	194	A-109553.2	AUAAAUAUCUUCAAGUUACAAAA	415	3618	3640
AD-53798.1	A-110700.1	UGUAACUUGAAGAUAUUUAUU	195	A-109555.2	AAUAAAUAUCUUCAAGUUACAAA	416	3619	3641
AD-53819.1	A-110727.1	GUAACUUGAAGAUAUUUAUUU	196	A-109609.2	AAAUAAAUAUCUUCAAGUUACAA	417	3620	3642
AD-53815.1		CUAGACCUGUUUUGCUUUUGU	197		ACAAAAGCAAAACAGGUCUAGAA	418	3601	

(continued)

Duplex Name	Sense Oligo Name	Sense Trans Seq	SEQ ID NO:	Antisense Oligo Name	Antisense Trans Seq	SEQ ID NO:	Start In NM_174936.3	End In NM_174936 .3
AD-57928.40		Same	197		Same	418		
AD-59182.5			197			418		
AD-59184.3			197			418		
AD-59186.3			197			418		
AD-59171.13			197			418		
AD-59176.7			197			418		
AD-59170.7			197			418		
AD-59175.7		Same	197		Same	418		
AD-59179.7			197			418		
AD-59218.1			197			418		
AD-59222.1			197			418		
AD-59226.1			197			418		
AD-59230.1			197			418		
AD-59235.1			197			418		
AD-59207.1			197			418		
AD-59211.1			197			418		
AD-59215.1			197			418		
AD-59219.1			197			418		
AD-59223.1			197			418		
AD-59181.5			197			418		
AD-59172.5			197			418		
AD-59177.5			197			418		
AD-59180.5			197			418		
AD-59183.5			197			418		

(continued)

Duplex Name	Sense Oligo Name	Sense Trans Seq	SEQ ID NO:	Antisense Oligo Name	Antisense Trans Seq	SEQ ID NO:	Start In NM_174936.3	End In NM_174936.3
AD-59185.5			197			418		
AD-59173.5			197			418		
AD-59232.1		CUAGACCUGUUUUGCUUUUGU	198		ACAAAAGCAAAACAGGUCUAGAA	419	3600	
AD-59236.1		Same	198		Same	419	Same	
AD-59216.1			198			419		
AD-59220.1			198			419		
AD-59224.1			198			419		
AD-59228.1			198			419		
AD-59233.1			198			419		
AD-59237.1			198			419		
AD-59209.1			198			419		
AD-59208.1			198			419		
AD-59212.1		CUAGACCUGUUUUGCUUUUGU	199		ACAAAAGCAAAACAGGUCUAGAA	420	3600	
AD-59210.1		CUAGACCUGUUUUGCUUUUGU	200		ACAAAAGCAAAACAGGUCUAGAA	421	3601	
AD-59214.1		AGACCUGUUUUGCUUUUGU	201		ACAAAAGCAAAACAGGUCUAG	422	3603	
AD-59227.1		Same	201		Same	422		
AD-59231.1			201			422		
AD-59198.3			201			422		
AD-59200.3			201			422		
AD-59203.3		Same	201		Same	422		
AD-59204.3			201			422		
AD-59188.3			201			422		

(continued)

Duplex Name	Sense Oligo Name	Sense Trans Seq	SEQ ID NO:	Antisense Oligo Name	Antisense Trans Seq	SEQ ID NO:	Start In NM_174936.3	End In NM_174936 .3
AD-59191.3			201			422		
AD-59213.1			201			422		
AD-59217.1			201			422		
AD-59221.1			201			422		
AD-59225.1			201			422		
AD-59229.1			201			422		
AD-59234.1			201			422		
AD-59238.1			201			422		
AD-59241.1			201			422		
AD-59245.1			201			422		
AD-59250.1			201			422		
AD-59246.1		CUAGACCUGUUUUGCUUUUGU	202		ACAAAAGCAAAACAGGUCUAGA	423	3602	
AD-59253.2		UAGACCUGUUUUGCUUUUGU	203		ACAAAAGCAAAACAGGUCUAGA	424	3602	
AD-59242.1		AGACCUGUUUUGCUUUUGU	204		ACAAAAGCAAAACAGGUCUAGA	425	3602	
AD-59253.1		UAGACCUGUUUUGCUUUUGU	205		ACAAAAGCAAAACAGGUCUAGA	426	3602	
AD-59258.1		UAGACCUGUUUUGCUUUUGU	206		ACAAAAGCAAAACAGGUCUAGA	427	3602	
AD-59251.1		CUAGACCUGUUUUGCUUUUGU	207		ACAAAAGCAAAACAGGUCUAG	428	3603	
AD-59256.1		UAGACCUGUUUUGCUUUUGU	208		ACAAAAGCAAAACAGGUCUA	429	3604	
AD-59260.1		AGACCUGUUUUGCUUUUGU	209		ACAAAAGCAAAACAGGUCU	430	3605	

(continued)

Duplex Name	Sense Oligo Name	Sense Trans Seq	SEQ ID NO:	Antisense Oligo Name	Antisense Trans Seq	SEQ ID NO:	Start In NM_174936.3	End In NM_174936 .3
AD-59248.1		GACCUGUUUUGCUUUUGU	210		ACAAAAGCAAAACAGGUCU	431	3605	
AD-59247.1		GACCUGUUUUGCUUUUGU	211		ACAAAAGCAAAACAGGUCUA	432	3604	
AD-59252.1		AGACCUGUUUUGCUUUUGU	212		ACAAAAGCAAAACAGGUCUA	433	3604	
AD-59257.1		UAGACCUGUUUUGCUUUUGU	213		ACAAAAGCAAAACAGGUCUA	434	3604	
AD-59261.1		AGACCUGUUUUGCUUUUGU	214		ACAAAAGCAAAACAGGUCUAG	435	3603	
AD-59262.1		UAGACCUGUUUUGCUUUUGU	215		ACAAAAGCAAAACAGGUCUAG	436	3603	
AD-59265.1		CUAGACCUGUUUUGCUUUUGU	216		ACAAAAGCAAAACAGGUCUAG	437	3603	
AD-59196.13		UAGACCUGUUUUGCUUUUGU	217		ACAAAAGCAAAACAGGUCUAGAA	438	3601	
AD-59189.11		AGACCUGUUUUGCUUUUGU	218		ACAAAAGCAAAACAGGUCUAGAA	439	3601	
AD-59190.3		UCUAGACCUGUUUUGCUUUUGU	219		ACAAAAGCAAAACAGGUCUAGAA	440	3601	
AD-59192.3		UUCUAGACCUGUUUUGCUUUUGU	220		ACAAAAGCAAAACAGGUCUAGAA	441	3601	
AD-59240.1			220			441		
AD-59244.1			220			441		
AD-59202.7		Same	220		Same	441	Same	
AD-59195.5			220			441		
AD-59249.1			220			441		
AD-59254.1			220			441		

(continued)

Duplex Name	Sense Oligo Name	Sense Trans Seq	SEQ ID NO:	Antisense Oligo Name	Antisense Trans Seq	SEQ ID NO:	Start In NM_174936.3	End In NM_174936 .3
AD-59259.1			220			441		
AD-59264.1			220			441		
AD-59264.2			220			441		
AD-59255.1			220			441		
AD-57928.1			220			441		
AD-58893.1			220			441		
AD-58894.1			220			441		
AD-58895.1			220			441		
AD-58896.1			220			441		
AD-58897.1			220			441		
AD-58898.1			220			441		
AD-58899.1			220			441		
AD-58900.1		CAAGCAGACAUUUAUCUUUUU	221		AAAAAGAUAAAUGUCUGCUUGCU	442	N/A	
AD-58902.1		UUUUCUAGACCUGUUUUGCUU	222		AAGCAAAACAGGUCUAGAAAAGU	443	3597	
		AGACCUGUUUUGCUUUUGU	223		ACAAAAGCAAAACAGGUCUAG	444		
		AGACCUGUUUUGCUUUUGU	224		ACAAAAGCAAAACAGGUCUAG	445		
		AGACCUGUUUUGCUUUUGU	225		ACAAAAGCAAAACAGGUCUAG	446		
		AGACCUGUUUUGCUUUUGU	226		ACAAAAGCAAAACAGGUCUAG	447		
		AGACCUGUUUUGCUUUUGU	227		ACAAAAGCAAAACAGGUCUAG	448		

(continued)

Duplex Name	Sense Oligo Name	Sense Trans Seq	SEQ ID NO:	Antisense Oligo Name	Antisense Trans Seq	SEQ ID NO:	Start In NM_174936.3	End In NM_174936 .3
		AGACCUGUUUUGCUUUUGU	228		ACAAAAGCAAAACAGGUCUAG	449		
		CUAGACCUGUUUUGCUUUUGU	229		ACAAAAGCAAAACAGGUCUAGAA	450		
		Same	229		Same	450		
			229			450		
			229			450		
			229			450		
			229			450		
			229			450		
			229			450		
			229			450		
			229			450		
			229			450		
			229			450		
			229			450		
		AGACCUGUUUUGCUUUUGU	230		ACAAAAGCAAAACAGGUCUAG	451		
		AGACCUGUUUUGCUUUUGU	231		ACAAAAGCAAAACAGGUCUAG	452		
		CUAGACCUGUUUUGCUUUUGU	232		ACAAAAGCAAAACAGGUCUAGAA	453		
		Same	232		Same	453		
			232			453		
			232			453		
			232			453		
			232			453		

(continued)

Duplex Name	Sense Oligo Name	Sense Trans Seq	SEQ ID NO:	Antisense Oligo Name	Antisense Trans Seq	SEQ ID NO:	Start In NM_174936.3	End In NM_174936 .3
		CUAGACCUGUUUUGCUUUUGU	233		ACAAAAGCAAAACAGGUCUAGAA	454		
		Same	233		Same	454		
			233			454		
			233			454		
			233			454		
			233			454		
			233			454		
			233			454		
			233			454		
			233		Same	454		
		Same	233			454		
			233			454		
			233			454		
			233			454		
			233			454		
			233			454		
			233			454		
			233			454		
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			233			454		
			233			454		
			233			454		
			233			454		
			233			454		
			233			454		
			233			454		
			233			454		
			233			454		

(continued)

Duplex Name	Sense Oligo Name	Sense Trans Seq	SEQ ID NO:	Antisense Oligo Name	Antisense Trans Seq	SEQ ID NO:	Start In NM_17 4936.3	End In NM_1 74936 .3
			233			454		
			233			454		
			233			454		
			233			454		
		Same	233		Same	454		
			233			454		
			233			454		
			233			454		
			233			454		
			233			454		
			233			454		
			233			454		
			233			454		
			233			454		
			233			454		
			233			454		
			233			454		
			233			454		
			233			454		
			233			454		
			233			454		
			233			454		
			233			454		
			233			454		

(continued)

Duplex Name	Sense Oligo Name	Sense Trans Seq	SEQ ID NO:	Antisense Oligo Name	Antisense Trans Seq	SEQ ID NO:	Start In NM_174936.3	End In NM_174936 .3
			233			454		
			233			454		
			233			454		
			233			454		
			233			454		
			233			454		
		Same	233		Same	454		
			233			454		
			233			454		
			233			454		
			233			454		
			233			454		
			233			454		
			233			454		
			233			454		
			233			454		
			233			454		
			233			454		
			233			454		

Table 2. PCSK9- modified sequences

Duplex Name	Sense Oligo Name	Sense Oligo Sequence	SEQ ID NO:	Position relative to NM_174936.3	Antisense Oligo Name	Antisense Oligo Sequence	SEQ ID NO:
AD-53649.1	A-110542.1	CfgAfgGfaCfgGfCfGfaCfuAfcGfaGfgAfL96	455	461	A-109239.2	uCfcUfcGfuAfgUfcgcCfgUfcCfuCfgsUfsc	1006
AD-53650.1	A-110550.1	GfcCfgGfgGfaUfAfCfcUfcAfcCfaAfgAfL96	456	673	A-109255.2	uCfuUfgGfuGfaGfguaUfcCfcCfgGfcsGfsg	1007
AD-53651.1	A-110558.1	GfcCfcCfaUfgUfCfGfaCfuAfcAfuCfgAfL96	457	773	A-109271.2	uCfgAfuGfuAfgUfcgaCfaUfgGfgGfcsAfsa	1008
AD-53652.1	A-110566.1	CfcUfgGfuGfgAfGfGfuGfuAfuCfuCfcUfL96	458	896	A-109287.2	aGfgAfgAfuAfcAfccuCfcAfcCfaGfgsCfsu	1009
AD-53653.1	A-110574.1	UfcCfuAfgAfcAfCfCfaGfcAfuAfcAfgAfL96	459	913	A-109303.2	uCfuGfuAfuGfcUfgguGfuCfuAfgGfasGfsa	1010
AD-53654.1	A-110582.1	GfcAfgGfgUfcAfUfGfgUfcAfcCfgAfcUfL96	460	955	A-109319.2	aGfuCfgGfuGfaCfcauGfaCfcCfuGfcsCfsc	1011
AD-53696.1	A-110589.1	CfcUfgCfgCfgUfGfCfuCfaAfcUfgCfcAfL96	461	1109	A-109333.2	uGfgCfaGfuUfgAfgcaCfgCfgCfaGfgsCfsu	1012
AD-53697.1	A-110597.1	UfaGfgCfcUfgGfAfGfuUfuAfuUfcGfgAfL96	462	1159	A-109349.2	uCfcGfaAfuAfaAfcucCfaGfgCfcUfasUfsg	1013
AD-53698.1	A-110605.1	GfgGfaCfgAfuGfCfCfuGfcCfuCfuAfcUfL96	463	1318	A-109365.2	aGfuAfgAfgGfcAfggcAfuCfgUfcCfcsGfsg	1014
AD-53699.1	A-110613.1	GfcAfuUfgCfaGfCfCfaUfgAfuGfcUfgUfL96	464	1543	A-109381.2	aCfaGfcAfuCfaUfggcUfgCfaAfuGfcsCfsa	1015
AD-53700.1	A-110621.1	GfgCfcUfgGfuUfCfCfcUfgAfgGfaCfcAfL96	465	1640	A-109397.2	uGfgUfcCfuCfaGfggaAfcCfaGfgCfcsUfsc	1016
AD-53701.1	A-110629.1	CfgCfuUfuUfgGfGfGfgUfgAfgGfgUfgUfL96	466	1901	A-109413.2	aCfaCfcCfuCfaCfcccCfaAfaAfgCfgsUfsu	1017
AD-48400.1	A-98247.2	UfuUfuCfuAfgAfcCfuGfuUfuUfgCfuUfL96	467		A-93455.4	aAfgCfaAfaAfcAfgGfuCfuAfgAfaAfasGfsu	1018
AD-53656.1	A-110551.1	CfcGfgGfgAfuAfCfCfuCfaCfcAfaGfaUfL96	468	674	A-109257.2	aUfcUfuGfgUfgAfgguAfuCfcCfcGfgsCfsg	1019
AD-53657.1	A-110559.1	CfcAfuGfuCfgAfCfUfaCfaUfcGfaGfgAfL96	469	776	A-109273.2	uCfcUfcGfaUfgUfaguCfgAfcAfuGfgsGfsg	1020
AD-53658.1	A-110567.1	CfuGfgUfgGfaGfGfUfgUfaUfcUfcCfuAfL96	470	897	A-109289.2	uAfgGfaGfaUfaCfaccUfcCfaCfcAfgsGfsc	1021
AD-53659.1	A-110575.1	AfgAfcAfcCfaGfCfAfuAfcAfgAfgUfgAfL96	471	917	A-109305.2	uCfaCfuCfuGfuAfugcUfgGfuGfuCfusAfsg	1022
AD-53660.1	A-110583.1	CfaGfgGfuCfaUfGfGfuCfaCfcGfaCfuUfL96	472	956	A-109321.2	aAfgUfcGfgUfgAfccaUfgAfcCfcUfgsCfsc	1023
AD-53702.1	A-110590.1	CfuGfcGfcGfuGfCfUfcAfaCfuGfcCfaAfL96	473	1110	A-109335.2	uUfgGfcAfgUfuGfagcAfcGfcGfcAfgsGfsc	1024
AD-53703.1	A-110598.1	AfgGfcCfuGfgAfGfUfuUfaUfuCfgGfaAfL96	474	1160	A-109351.2	uUfcCfgtAfaUfaAfacuCfcAfgGfcCfusAfsu	1025
AD-53704.1	A-110606.1	CfaAfcUfuUfgGfCfCfgCfuGfuGfuGfgAfL96	475	1421	A-109367.2	uCfcAfcAfcAfgCfggcCfaAfaGfuUfgsGfsu	1026
AD-53705.1	A-110614.1	GfuUfgAfgGfcAfGfAfgAfcUfgAfuCfcAfL96	476	1592	A-109383.2	uGfgAfuCfaGfuCfucuGfcCfuCfaAfcsUfsc	1027

(continued)

Duplex Name	Sense Oligo Name	Sense Oligo Sequence	SEQ ID NO:	Position relative to NM_174936.3	Antisense Oligo Name	Antisense Oligo Sequence	SEQ ID NO:
AD-53706.1	A-110622.1	GfgUfaCfuGfaCfCfCfcCfaAfcCfuGfgUfL96	477	1664	A-109399.2	aCfcAfgGfuUfgGfgggUfcAfgUfaCfcsCfsg	1028
AD-53707.1	A-110630.1	CfuUfuUfgGfgGfGfUfgAfgGfgUfgUfcUfL96	478	1903	A-109415.2	aGfaCfaCfcCfuCfaccCfcCfaAfaAfgsCfsg	1029
AD-53661.1	A-110544.1	AfcCfgCfuGfcGfCfCfaAfgGfaUfcCfgUfL96	479	556	A-109243.2	aCfgGfaUfcCfuUfggcGfcAfgCfgGfusGfsg	1030
AD-53663.1	A-110560.1	UfcGfaCfuAfcAfUfCfgAfgGfaGfgAfcUfL96	480	781	A-109275.2	aGfuCfcUfcCfuCfgauGfuAfgUfcGfasCfsa	1031
AD-53664.1	A-110568.1	GfgUfgGfaGfgUfGfUfaUfcUfcCfuAfgAfL96	481	899	A-109291.2	uCfuAfgGfaGfaUfacaCfcUfcCfaCfcsAfsg	1032
AD-53665.1	A-110576.1	CfaCfcAfgCfaUfAfCfaGfaGfuGfaCfcAfL96	482	920	A-109307.2	uGfgUfcAfcUfcUfguaUfgCfuGfgUfgsUfsc	1033
AD-53666.1	A-110584.1	GfgUfcAfuGfgUfCfAfcCfgAfcUfuCfgAfL96	483	959	A-109323.2	uCfgAfaGfuCfgGfugaCfcAfuGfaCfcsCfsu	1034
AD-53708.1	A-110591.1	CfgUfgCfuCfaAfCfUfgCfcAfaGfgGfaAfL96	484	1115	A-109337.2	uUfcCfcUfuGfgCfaguUfgAfgCfaCfgsCfsg	1035
AD-53709.1	A-110599.1	GfgCfcUfgGfaGfUfUfuAfuUfcGfgAfaAfL96	485	1161	A-109353.2	uUfuCfcGfaAfuAfaacUfcCfaGfgCfcsUfsa	1036
AD-53710.1	A-110607.1	UfuGfgCfcGfcUfGfUfgUfgGfaCfcUfcUfL96	486	1426	A-109369.2	aGfaGfgUfcCfaCfacaGfcGfgCfcAfasAfsg	1037
AD-53711.1	A-110615.1	UfgAfgGfcAfgAfGfAfcUfgAfuCfcAfcUfL96	487	1594	A-109385.2	aGfuGfgAfuCfaGfucuCfuGfcCfuCfasAfsc	1038
AD-53712.1	A-110623.1	GfuUfgGfcAfgCfUfGfuUfuUfgCfaGfgAfL96	488	1717	A-109401.2	uCfcUfgCfaAfaAfcagCfuGfcCfaAfcsCfsu	1039
AD-53713.1	A-110631.1	UfuUfuGfgGfgGfUfGfaGfgGfuGfuCfuAfL96	489	1904	A-109417.2	uAfgAfcAfcCfcUfcacCfcCfcAfaAfasGfsc	1040
AD-53667.1	A-110545.1	GfcUfgCfgCfcAfAfGfgAfuCfcGfuGfgAfL96	490	559	A-109245.2	uCfcAfcGfgAfuCfcuuGfgCfgCfaGfcsGfsg	1041
AD-53668.1	A-110553.1	AfuAfcCfuCfaCfCfAfaGfaUfcCfuGfcAfL96	491	680	A-109261.2	uGfcAfgGfaUfcUfuggUfgAfgGfuAfusCfsc	1042
AD-53669.1	A-110561.1	AfcUfaCfaUfcGfAfGfgAfgGfaCfuCfcUfL96	492	784	A-109277.2	aGfgAfgUfcCfuCfcucGfaUfgUfaGfusCfsg	1043
AD-53670.1	A-110569.1	UfgGfaGfgUfgUfAfUfcUfcCfuAfgAfcAfL96	493	901	A-109293.2	uGfuCfuAfgGfaGfauaCfaCfcUfcCfasCfsc	1044
AD-53671.1	A-110577.1	UfaCfaGfaGfuGfAfCfcAfcCfgGfgAfaAfL96	494	928	A-109309.2	uUfuCfcCfgGfuGfgucAfcUfcUfgUfasUfsg	1045
AD-53672.1	A-110585.1	UfcAfuGfgUfcAfCfCfgAfcUfuCfgAfgAfL96	495	961	A-109325.2	uCfuCfgAfaGfuCfgguGfaCfcAfuGfasCfsc	1046
AD-53714.1	A-110592.1	CfaCfcCfuCfaUfAfGfgCfcUfgGfaGfuUfL96	496	1151	A-109339.2	aAfcUfcCfaGfgCfcuaUfgAfgGfgUfgsCfsc	1047
AD-53715.1	A-110600.1	GfcCfuGfgAfgUfUfUfaUfuCfgGfaAfaAfL96	497	1162	A-109355.2	uUfuUfcCfgAfaUfaaaCfuCfcAfgGfcsCfsu	1048
AD-53716.1	A-110608.1	UfgGfcCfgCfuGfUfGfuGfgAfcCfuCfuUfL96	498	1427	A-109371.2	aAfgAfgGfuCfcAfcacAfgCfgGfcCfasAfsa	1049

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Duplex Name	Sense Oligo Name	Sense Oligo Sequence	SEQ ID NO:	Position relative to NM_174936.3	Antisense Oligo Name	Antisense Oligo Sequence	SEQ ID NO:
AD-53717.1	A-110616.1	GfaGfgCfaGfaGfAfCfuGfaUfcCfaCfuUfL96	499	1595	A-109387.2	aAfgUfgGfaUfcAfgucUfcUfgCfcUfcsAfsa	1050
AD-53718.1	A-110624.1	UfgGfcAfgCfuGfUfUfuUfgCfaGfgAfcUfL96	500	1719	A-109403.2	aGfuCfcUfgCfaAfaacAfgCfuGfcCfasAfsc	1051
AD-53719.1	A-110632.1	GfgGfgUfgAfgGfGfUfgUfcUfaCfgCfcAfL96	501	1909	A-109419.2	uGfgCfgUfaGfaCfaccCfuCfaCfcCfcsCfsa	1052
AD-53674.1	A-110554.1	CfaCfcAfaGfaUfCfCfuGfcAfuGfuCfuUfL96	502	686	A-109263.2	aAfgAfcAfuGfcAfggaUfcUfuGfgUfgsAfsg	1053
AD-53675.1	A-110562.1	UfaCfaUfcGfaGfGfAfgGfaCfuCfcUfcUfL96	503	786	A-109279.2	aGfaGfgAfgUfcCfuccUfcGfaUfgUfasGfsu	1054
AD-53676.1	A-110570.1	AfgGfuGfuAfuCfUfCfcUfaGfaCfaCfcAfL96	504	904	A-109295.2	uGfgUfgUfcUfaGfgagAfuAfcAfcCfusCfsc	1055
AD-53677.1	A-110578.1	AfcAfgAfgUfgAfCfCfa CfcGfgGfaAfaUfL96	505	929	A-109311.2	aUfuUfcCfcGfgUfgguCfaCfuCfuGfusAfsu	1056
AD-53678.1	A-110586.1	AfgGfaCfgGfgAfCfCfcGfcUfuCfcAfcAfL96	506	994	A-109327.2	uGfuGfgAfaGfcGfgguCfcCfgUfcCfusCfsc	1057
AD-53720.1	A-110593.1	AfcCfcUfcAfuAfGfGfcCfuGfgAfgUfuUfL96	507	1152	A-109341.2	aAfaCfuCfcAfgGfccuAfuGfaGfgGfusGfsc	1058
AD-53721.1	A-110601.1	GfgAfgUfuUfaUfUfCfgGfaAfaAfgCfcAfL96	508	1166	A-109357.2	uGfgCfuUfuUfcCfgaaUfaAfaCfuCfcsAfsg	1059
AD-53722.1	A-110609.1	GfgCfcGfcUfgUfGfUfgGfaCfcUfcUfuUfL96	509	1428	A-109373.2	aAfaGfaGfgUfcCfacaCfaGfcGfgCfcsAfsa	1060
AD-53723.1	A-110617.1	GfgCfaGfaGfaCfUfGfaUfcCfaCfuUfcUfL96	510	1597	A-109389.2	aGfaAfgUfgGfaUfcagUfcUfcUfgCfcsUfsc	1061
AD-53724.1	A-110625.1	GfcAfgCfuGfu UfUfUfgCfaGfgAfcUfgUfL96	511	1721	A-109405.2	aCfaGfuCfcUfgCfaaaAfcAfgCfuGfcsCfsa	1062
AD-53725.1	A-110633.1	GfgGfuGfaGfgGfUfGfuCfuAfcGfcCfaUfL96	512	1910	A-109421.2	aUfgGfcGfuAfgAfcacCfcUfcAfcCfcsCfsc	1063
AD-53679.1	A-110547.1	CfuAfcGfuGfgUfGfGfuGfcUfgAfaGfgAfL96	513	593	A-109249.2	uCfcUfuCfaGfcAfccaCfcAfcGfuAfgsGfsu	1064
AD-53680.1	A-110555.1	CfaAfgAfuCfcUfGfCfaUfgUfcUfuCfcAfL96	514	689	A-109265.2	uGfgAfaGfaCfaUfgcaGfgAfuCfuUfgsGfsu	1065
AD-53681.1	A-110563.1	UfcGfaGfgAfgGfAfCfuCfcUfcUfgUfcUfL96	515	790	A-109281.2	aGfaCfaGfaGfgAfgucCfuCfcUfcGfasUfsg	1066
AD-53682.1	A-110571.1	GfuAfuCfuCfcUfAfGfaCfaCfcAfgCfaUfL96	516	908	A-109297.2	aUfgCfuGfgUfgUfcuaGfgAfgAfuAfcsAfsc	1067
AD-53683.1	A-110579.1	GfaGfuGfaCfcAfCfCfgGfgAfaAfuCfgAfL96	517	932	A-109313.2	uCfgAfuUfuCfcCfgguGfgUfcAfcUfcsUfsg	1068
AD-53684.1	A-110587.1	CfgGfgAfcCfcGfCfUfuCfcAfcAfgAfcAfL96	518	998	A-109329.2	uGfuCfuGfuGfgAfagcGfgGfuCfcCfgsUfsc	1069
AD-53726.1	A-110594.1	CfcCfuCfaUfaGfGfCfcUfgGfaGfuUfuAfL96	519	1153	A-109343.2	uAfaAfcUfcCfaGfgccUfaUfgAfgGfgsUfsg	1070
AD-53727.1	A-110602.1	GfuUfuAfuUfcGfGfAfaAfaGfcCfaGfcUfL96	520	1169	A-109359.2	aGfcUfgGfcUfuUfuccGfaAfuAfaAfcsUfsc	1071

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Duplex Name	Sense Oligo Name	Sense Oligo Sequence	SEQ ID NO:	Position relative to NM_174936.3	Antisense Oligo Name	Antisense Oligo Sequence	SEQ ID NO:
AD-53728.1	A-110610.1	UfgUfgUfgGfaCfCfUfcUfuUfgCfcCfcAfL96	521	1434	A-109375.2	uGfgGfgCfaAfaGfaggUfcCfaCfaCfasGfsc	1072
AD-53729.1	A-110618.1	CfaGfaGfaCfuGfAfUfcCfaCfuUfcUfcUfL96	522	1599	A-109391.2	aGfaGfaAfgUfgGfaucAfgUfcUfcUfgsCfsc	1073
AD-53730.1	A-110626.1	UfcUfgCfcGfgGfCfCfcAfcAfaCfgCfuUfL96	523	1885	A-109407.2	aAfgCfgUfuGfuGfggcCfcGfgCfaGfasCfsc	1074
AD-53731.1	A-110634.1	GfgUfgAfgGfgUfGfUfcUfaCfgCfcAfuUfL96	524	1911	A-109423.2	aAfuGfgCfgUfaGfacaCfcCfuCfaCfcsCfsc	1075
AD-53685.1	A-110548.1	CfcCfgCfcGfgGfGfAfuAfcCfuCfaCfcAfL96	525	670	A-109251.2	uGfgUfgAfgGfuAfuccCfcGfgCfgGfgsCfsa	1076
AD-53687.1	A-110564.1	CfgAfgGfaGfgAfCfUfcCfuCfuGfuCfuUfL96	526	791	A-109283.2	aAfgAfcAfgAfgGfaguCfcUfcCfuCfgsAfsu	1077
AD-53688.1	A-110572.1	UfaUfcUfcCfuAfGfAfcAfcCfaGfcAfuAfL96	527	909	A-109299.2	uAfuGfcUfgGfuGfucuAfgGfaGfaUfasCfsa	1078
AD-53689.1	A-110580.1	GfgAfaAfuCfgAfGfGfgCfaGfgGfuCfaUfL96	528	944	A-109315.2	aUfgAfcCfcUfgCfccuCfgAfuUfuCfcsCfsg	1079
AD-53690.1	A-110588.1	UfcCfaCfaGfaCfAfGfgCfcAfgCfaAfgUfL96	529	1009	A-109331.2	aCfuUfgCfuGfgCfcugUfcUfgUfgGfasAfsg	1080
AD-53732.1	A-110595.1	CfcUfcAfuAfgGfCfCfuGfgAfgUfuUfaUfL96	530	1154	A-109345.2	aUfaAfaCfuCfcAfggcCfuAfuGfaGfgsGfsu	1081
AD-53733.1	A-110603.1	GfgGfcUfgGfgGfUfCfgUfgCfuGfgUfcAfL96	531	1279	A-109361.2	uGfaCfcAfgCfaCfgacCfcCfaGfcCfcsUfsc	1082
AD-53734.1	A-110611.1	GfgGfaGfgAfcAfUfCfaUfuGfgUfgCfcUfL96	532	1456	A-109377.2	aGfgCfaCfcAfaUfgauGfuCfcUfcCfcsCfsu	1083
AD-53735.1	A-110619.1	AfcUfgAfuCfcAfCfUfuCfuCfuGfcCfaAfL96	533	1604	A-109393.2	uUfgGfcAfgAfgAfaguGfgAfuCfaGfusCfsu	1084
AD-53736.1	A-110627.1	CfuGfcCfgGfgCfCfCfaCfaAfcGfcUfuUfL96	534	1886	A-109409.2	aAfaGfcGfuUfgUfgggCfcCfgGfcAfgsAfsc	1085
AD-53737.1	A-110635.1	AfgGfgUfg Ufc UfAfCfgCfcAfu U fgCfcAfL96	535	1915	A-109425.2	uGfgCfaAfuGfgCfguaGfaCfaCfcCfusCfsa	1086
AD-53691.1	A-110549.1	CfcGfcCfgGfgGfAfUfaCfcUfcAfcCfaAfL96	536	671	A-109253.2	uUfgGfuGfaGfgUfaucCfcCfgGfcGfgsGfsc	1087
AD-53692.1	A-110557.1	GfuUfgCfcCfcAfUfGfuCfgAfcUfaCfaUfL96	537	770	A-109269.2	aUfgUfaGfuCfgAfcauGfgGfgCfaAfcsUfsu	1088
AD-53693.1	A-110565.1	GfuAfcCfgGfgCfGfGfaUfgAfaUfaCfcAfL96	538	857	A-109285.2	uGfgUfaUfuCfaUfccgCfcCfgGfuAfcsCfsg	1089
AD-53694.1	A-110573.1	UfcUfcCfuAfgAfCfAfcCfaGfcAfuAfcAfL96	539	911	A-109301.2	uGfuAfuGfcUfgGfuguCfuAfgGfaGfasUfsa	1090
AD-53695.1	A-110581.1	AfaUfcGfaGfgGfCfAfgGfgUfcAfuGfgUfL96	540	947	A-109317.2	aCfcAfuGfaCfcCfugcCfcUfcGfaUfusUfsc	1091
AD-53738.1	A-110596.1	CfuCfaUfaGfgCfCfUfgGfaGfuUfuAfuUfL96	541	1155	A-109347.2	aAfuAfaAfcUfcCfaggCfcUfaUfgAfgsGfsg	1092
AD-53739.1	A-110604.1	GfgUfcAfcCfgCfUfGfcCfgGfcAfaCfuUfL96	542	1295	A-109363.2	aAfgUfuGfcCfgGfcagCfgGfuGfaCfcsAfsg	1093

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Duplex Name	Sense Oligo Name	Sense Oligo Sequence	SEQ ID NO:	Position relative to NM_174936.3	Antisense Oligo Name	Antisense Oligo Sequence	SEQ ID NO:
AD-53740.1	A-110612.1	AfcUfgCfaGfcAfCfCfuGfcUfuUfgUfgUfL96	543	1483	A-109379.2	aCfaCfaAfaGfcAfgguGfcUfgCfaGfusCfsg	1094
AD-53741.1	A-110620.1	AfuCfcAfcUfuCfUfCfuGfcCfaAfaGfaUfL96	544	1608	A-109395.2	aUfcUfuUfgGfcAfgagAfaGfuGfgAfusCfsa	1095
AD-53742.1	A-110628.1	GfcCfcAfcAfaCfGfCfuUfuUfgGfgGfgUfL96	545	1893	A-109411.2	aCfcCfcCfaAfaAfgcgUfuGfuGfgGfcsCfsc	1096
AD-53743.1	A-110636.1	GfuGfuCfuAfcGfCfCfaUfuGfcCfaGfgUfL96	546	1918	A-109427.2	aCfcUfgGfcAfaUfggcGfuAfgAfcAfcsCfsc	1097
AD-53744.1	A-110644.1	GfgAfaUfgCfaAfAfGfuCfaAfgGfaGfcAfL96	547	2180	A-109443.2	uGfcUfcCfuUfgAfcuuUfgCfaUfuCfcsAfsg	1098
AD-53745.1	A-110652.1	UfgAfuGfgCfcCfUfCfaUfcUfcCfaGfcUfL96	548	2906	A-109459.2	aGfcUfgGfaGfaUfgagGfgCfcAfuCfasGfsc	1099
AD-53746.1	A-110660.1	CfuGfaAfgCfcAfAfGfcCfuCfuUfcUfuAfL96	549	3300	A-109475.2	uAfaGfaAfgAfgGfcu u GfgCfu UfcAfgsAfsg	1100
AD-53747.1	A-110668.1	AfcUfgUfcCfcUfCfCfuUfgAfgCfaCfcAfL96	550	3511	A-109491.2	uGfgUfgCfuCfaAfggaGfgGfaCfaGfusUfsg	1101
AD-53748.1	A-110676.1	CfaAfgCfaAfgCfAfGfaCfaUfuUfaUfcUfL96	551	3540	A-109507.2	aGfaUfaAfaUfgUfcugCfuUfgCfuUfgsGfsg	1102
AD-53790.1	A-110683.1	UfaUfcUfuUfuGfGfGfuCfuGfuCfcUfcUfL96	552	3556	A-109521.2	aGfaGfgAfcAfgAfcccAfaAfaGfaUfasAfsa	1103
AD-53791.1	A-110691.1	UfgUfcCfuCfuCfUfGfuUfgCfcUfuUfuUfL96	553	3569	A-109537.2	aAfaAfaGfgCfaAfcagAfgAfgGfaCfasGfsa	1104
AD-53792.1	A-110699.1	UfuGfuAfaCfuUfGfAfaGfaUfaUfuUfaUfL96	554	3620	A-109553.2	aUfaAfaUfaUfcUfucaAfgUfuAfcAfasAfsa	1105
AD-53793.1	A-110707.1	CfuUfuAfcUfcUfGfCfuCfuAfuGfcCfaAfL96	555	3055	A-109569.2	uUfgGfcAfuAfgAfgcaGfaGfuAfaAgsGfsu	1106
AD-53794.1	A-110715.1	AfgGfgGfaAfcAfCfAfgAfcCfaGfgAfaAfL96	556	3370	A-109585.2	uUfuCfcUfgGfuCfuguGfuUfcCfcCfusUfsc	1107
AD-53795.1	A-110723.1	UfuGfgGfuCfuGfUfCfcUfcUfcUfgUfuUfL96	557	3562	A-109601.2	aAfaCfaGfaGfaGfgacAfgAfcCfcAfasAfsa	1108
AD-53749.1	A-110637.1	UfgCfaGfcGfuCfCfAfcAfcAfgCfuCfcAfL96	558	1962	A-109429.2	uGfgAfgCfuGfuGfuggAfcGfcUfgCfasGfsu	1109
AD-53750.1	A-110645.1	AfaUfcCfcGfgCfCfCfcUfcAfgGfaGfcAfL96	559	2204	A-109445.2	uGfcUfcCfuGfaGfgggCfcGfgGfaUfusCfsc	1110
AD-53751.1	A-110653.1	UfuUfcUfgGfaUfGfGfcAfuCfuAfgCfcAfL96	560	2974	A-109461.2	uGfgCfuAfgAfuGfccaUfcCfaGfaAfasGfsc	1111
AD-53752.1	A-110661.1	GfaAfgCfcAfaGfCfCfuCfuUfcUfuAfcUfL96	561	3302	A-109477.2	aGfuAfaGfaAfgAfggcUfuGfgCfuUfcsAfsg	1112
AD-53753.1	A-110669.1	CfcAfgCfcCfcAfCfCfcAfaGfcAfaGfcAfL96	562	3529	A-109493.2	uGfcUfuGfcUfuGfgguGfgGfgCfuGfgsUfsg	1113
AD-53754.1	A-110677.1	AfaGfcAfaGfcAfGfAfcAfuUfuAfuCfuUfL96	563	3541	A-109509.2	aAfgAfuAfaAfuGfucuGfcUfuGfcUfusGfsg	1114
AD-53796.1	A-110684.1	UfcUfuUfuGfgGfUfCfuGfuCfcUfcUfcUfL96	564	3558	A-109523.2	aGfaGfaGfgAfcAfgacCfcAfaAfaGfasUfsa	1115

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Duplex Name	Sense Oligo Name	Sense Oligo Sequence	SEQ ID NO:	Position relative to NM_174936.3	Antisense Oligo Name	Antisense Oligo Sequence	SEQ ID NO:
AD-53797.1	A-110692.1	GfuCfcUfcUfcUfGfUfuGfcCfuUfuUfuAfL96	565	3570	A-109539.2	uAfaAfaAfgGfcAfacaGfaGfaGfgAfcsAfsg	1116
AD-53798.1	A-110700.1	UfgUfaAfcUfuGfAfAfgAfuAfuUfuAfuUfL96	566	3621	A-109555.2	aAfuAfaAfuAfuCfuucAfaGfuUfaCfasAfsa	1117
AD-53799.1	A-110708.1	UfuUfaCfuCfuGfCfUfcUfaUfgCfcAfgAfL96	567	3056	A-109571.2	uCfuGfgCfaUfaGfagcAfgAfgUfaAfasGfsg	1118
AD-53800.1	A-110716.1	CfcAfaGfcAfaGfCfAfgAfcAfuUfuAfuUfL96	568	3539	A-109587.2	aAfuAfaAfuGfuCfugcUfuGfcUfuGfgsGfsu	1119
AD-53801.1	A-110724.1	UfgGfgUfcUfgUfCfCfuCfuCfuGfuUfgAfL96	569	3563	A-109603.2	uCfaAfcAfgAfgAfggaCfaGfaCfcCfasAfsa	1120
AD-53755.1	A-110638.1	GfcAfuGfgGfgAfCfCfcGfuGfuCfcAfcUfL96	570	1996	A-109431.2	aGfuGfgAfcAfcGfgguCfcCfcAfuGfcsUfsg	1121
AD-53757.1	A-110654.1	UfcUfgGfaUfgGfCfAfuCfuAfgCfcAfgAfL96	571	2976	A-109463.2	uCfuGfgCfuAfgAfugcCfaUfcCfaGfasAfsa	1122
AD-53758.1	A-110662.1	AfaGfcCfaAfgCfCfUfcUfuCfuUfaCfuUfL96	572	3303	A-109479.2	aAfgUfaAfgAfaGfaggCfuUfgGfcUfusCfsa	1123
AD-53759.1	A-110670.1	CfcCfcAfcCfcAfAfGfcAfaGfcAfgAfcAfL96	573	3533	A-109495.2	uGfuCfuGfcUfuGfcuuGfgGfuGfgGfgsCfsu	1124
AD-53760.1	A-110678.1	AfgCfaAfgCfaGfAfCfaUfuUfaUfcUfuUfL96	574	3542	A-109511.2	aAfaGfaUfaAfaUfgucUfgCfuUfgCfusUfsg	1125
AD-53802.1	A-110685.1	UfuUfuGfgGfuCfUfGfuCfcUfcUfgUfL96	575	3560	A-109525.2	aCfaGfaGfaGfgAfcagAfcCfcAfaAfasGfsa	1126
AD-53803.1	A-110693.1	UfuUfcUfaGfaCfCfUfgUfuUfuGfcUfuUfL96	576	3600	A-109541.2	aAfaGfcAfaAfaCfaggUfcUfaGfaAfasAfsg	1127
AD-53804.1	A-110701.1	AfcCfaAfgGfaGfGfCfaGfgAfuUfcUfuUfL96	577	2815	A-109557.2	aAfaGfaAfuCfcUfgccUfcCfuUfgGfusGfsg	1128
AD-53805.1	A-110709.1	UfcAfgCfcAfaCfCfCfgCfuCfcAfcUfaAfL96	578	3161	A-109573.2	uUfaGfuGfgAfgCfgggUfuGfgCfuGfasGfsa	1129
AD-53806.1	A-110717.1	CfaAfgCfaGfaCfAfUfuUfaUfcUfuUfuUfL96	579	3544	A-109589.2	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1130
AD-53807.1	A-110725.1	GfgGfuCfuGfuCfCfUfcUfcUfgUfuGfcAfL96	580	3564	A-109605.2	uGfcAfaCfaGfaGfaggAfcAfgAfcCfcsAfsa	1131
AD-53761.1	A-110639.1	CfcCfaCfaAfgCfCfGfcCfuGfuGfcUfgAfL96	581	2080	A-109433.2	uCfaGfcAfcAfgGfcggCfuUfgUfgGfgsUfsg	1132
AD-53762.1	A-110647.1	GfcUfgGfgGfcUfGfAfgCfuUfuAfaAfaUfL96	582	2481	A-109449.2	aUfuUfuAfaAfgCfucaGfcCfcCfaGfcsCfsc	1133
AD-53763.1	A-110655.1	GfcUfcUfaUfgCfCfAfgGfcUfgUfgCfuAfL96	583	3064	A-109465.2	uAfgCfaCfaGfcCfuggCfaUfaGfaGfcsAfsg	1134
AD-53764.1	A-110663.1	GfuGfaGfgCfuGfGfGfaAfgGfgGfaAfcAfL96	584	3358	A-109481.2	uGfuUfcCfcCfuUfcccAfgCfcUfcAfcsUfsg	1135
AD-53765.1	A-110671.1	CfcCfaCfcCfaAfGfCfaAfgCfaGfaCfaUfL96	585	3534	A-109497.2	aUfgUfcUfgCfuUfgcuUfgGfgUfgGfgsGfsc	1136
AD-53766.1	A-110679.1	GfcAfgAfcAfuUfUfAfuCfuUfuUfgGfgUfL96	586	3547	A-109513.2	aCfcCfaAfaAfgAfuaaAfuGfuCfuGfcsUfsu	1137

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Duplex Name	Sense Oligo Name	Sense Oligo Sequence	SEQ ID NO:	Position relative to NM_174936.3	Antisense Oligo Name	Antisense Oligo Sequence	SEQ ID NO:
AD-53808.1	A-110686.1	UfuUfgGfgUfcUfGfUfcCfuCfuCfuGfuUfL96	587	3561	A-109527.2	aAfcAfgAfgAfgGfacaGfaCfcCfaAfasAfsg	1138
AD-53809.1	A-110694.1	UfuCfuAfgAfcCfUfGfuUfuUfgCfuUfuUfL96	588	3601	A-109543.2	aAfaAfgCfaAfaAfcagGfuCfuAfgAfasAfsa	1139
AD-53810.1	A-110702.1	GfgAfgGfcAfgGfAfUfuCfuUfcCfcAfuUfL96	589	2820	A-109559.2	aAfuGfgGfaAfgAfaucCfuGfcCfuCfcsUfsu	1140
AD-53811.1	A-110710.1	CfcUfgCfcAfaGfCfUfcAfcAfcAfgCfaAfL96	590	3247	A-109575.2	uUfgCfuGfuGfuGfagcUfuGfgCfaGfgsCfsa	1141
AD-53812.1	A-110718.1	AfaGfcAfgAfcAfUfUfuAfuCfuUfuUfgAfL96	591	3545	A-109591.2	uCfaAfaAfgAfuAfaauGfuCfuGfcUfusGfsc	1142
AD-53813.1	A-110726.1	UfcUfaGfaCfcUfGfUfuUfuGfcUfuUfuUfL96	592	3602	A-109607.2	aAfaAfaGfcAfaAfacaGfgUfcUfaGfasAfsa	1143
AD-53767.1	A-110640.1	GfaGfgCfcAfcGfAfGfgUfcAfgCfcCfaAfL96	593	2099	A-109435.2	uUfgGfgCfuGfaCfcucGfuGfgCfcUfcsAfsg	1144
AD-53768.1	A-110648.1	GfgAfgGfuGfcCfAfGfgAfaGfcUfcCfcUfL96	594	2650	A-109451.2	aGfgGfaGfcUfuCfcugGfcAfcCfuCfcsAfsc	1145
AD-53769.1	A-110656.1	CfuCfaGfcCfaAfCfCfcGfcUfcCfaCfuAfL96	595	3160	A-109467.2	uAfgUfgGfaGfcGfgguUfgGfcUfgAfgsAfsc	1146
AD-53770.1	A-110664.1	GfgCfuGfgGfaAfGfGfgGfaAfcAfcAfgAfL96	596	3362	A-109483.2	uCfuGfuGfuUfcCfccuUfcCfcAfgCfcsUfsc	1147
AD-53771.1	A-110672.1	CfcAfcCfcAfaGfCfAfaGfcAfgAfcAfuUfL96	597	3535	A-109499.2	aAfuGfuCfuGfcUfugcUfuGfgGfuGfgsGfsg	1148
AD-53772.1	A-110680.1	AfgAfcAfuUfuAfUfCfuUfuUfgGfgUfcUfL96	598	3549	A-109515.2	aGfaCfcCfaAfaAfgauAfaAfuGfuCfusGfsc	1149
AD-53814.1	A-110687.1	GfgUfcUfgUfcCfUfCfuCfuGfuUfgCfcUfL96	599	3565	A-109529.2	aGfgCfaAfcAfgAfgagGfaCfaGfaCfcsCfsa	1150
AD-53815.1	A-110695.1	CfuAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	600	3603	A-109545.2	aCfaAfaAfgCfaAfaacAfgGfuCfuAfgsAfsa	1151
AD-53816.1	A-110703.1	GfaGfgCfaGfgAfUfUfcUfuCfcCfaUfgAfL96	601	2821	A-109561.2	uCfaUfgGfgAfaGfaauCfcUfgCfcUfcsCfsu	1152
AD-53817.1	A-110711.1	CfcAfaGfcUfcAfCfAfcAfgCfaGfgAfaAfL96	602	3251	A-109577.2	uUfuCfcUfgCfuGfuguGfaGfcUfuGfgsCfsa	1153
AD-53818.1	A-110719.1	AfgCfaGfaCfaUfUfUfaUfcUfuUfuGfgAfL96	603	3546	A-109593.2	uCfcAfaAfaGfaUfaaaUfgUfcUfgCfusUfsg	1154
AD-53819.1	A-110727.1	GfuAfaCfuUfgAfAfGfaUfaUfuUfaUfuUfL96	604	3622	A-109609.2	aAfaUfaAfaUfaUfcuuCfaAfgUfuAfcsAfsa	1155
AD-53773.1	A-110641.1	CfaCfgAfgGfuCfAfGfcCfcAfaCfcAfgUfL96	605	2104	A-109437.2	aCfuGfgUfuGfgGfcugAfcCfuCfgUfgsGfsc	1156
AD-53774.1	A-110649.1	AfcUfgUfgGfgGfCfAfuUfuCfaCfcAfuUfL96	606	2676	A-109453.2	aAfuGfgUfgAfaAfugcCfcCfaCfaGfusGfsa	1157
AD-53776.1	A-110665.1	GfaAfgGfgGfaAfCfAfcAfgAfcCfaGfgAfL96	607	3368	A-109485.2	uCfcUfgGfuCfuGfuguUfcCfcCfuUfcsCfsc	1158
AD-53777.1	A-110673.1	CfaCfcCfaAfgCfAfAfgCfaGfaCfaUfuUfL96	608	3536	A-109501.2	aAfaUfgUfcUfgCfuugCfuUfgGfgUfgsGfsg	1159

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Duplex Name	Sense Oligo Name	Sense Oligo Sequence	SEQ ID NO:	Position relative to NM_174936.3	Antisense Oligo Name	Antisense Oligo Sequence	SEQ ID NO:
AD-53778.1	A-110681.1	AfcAfuUfuAfuCfUfUfuUfgGfgUfcUfgUfL96	609	3551	A-109517.2	aCfaGfaCfcCfaAfaagAfuAfaAfuGfusCfsu	1160
AD-53820.1	A-110688.1	GfuCfuGfuCfcUfCfUfcUfgUfuGfcCfuUfL96	610	3566	A-109531.2	aAfgGfcAfaCfaGfagaGfgAfcAfgAfcsCfsc	1161
AD-53821.1	A-110696.1	UfaGfaCfcUfgUfUfUfuGfcUfuUfuGfuAfL96	611	3604	A-109547.2	uAfcAfaAfaGfcAfaaaCfaGfgUfcUfasGfsa	1162
AD-53822.1	A-110704.1	CfuUfuCfuGfgAfUfGfgCfaUfcUfaGfcAfL96	612	2973	A-109563.2	uGfcUfaGfaUfgCfcauCfcAfgAfaAfgsCfsu	1163
AD-53823.1	A-110712.1	AfaGfcUfcAfcAfCfAfgCfaGfgAfaCfuUfL96	613	3253	A-109579.2	aAfgUfuCfcUfgCfuguGfuGfaGfcUfusGfsg	1164
AD-53824.1	A-110720.1	GfaCfaUfuUfaUfCfUfuUfuGfgGfuCfuUfL96	614	3550	A-109595.2	aAfgAfcCfcAfaAfagaUfaAfaUfgUfcsUfsg	1165
AD-48400.4	A-98247.3	UfuUfuCfuAfgAfcCfuGfuUfuUfgCfuUfL96	615		A-93455.5	aAfgCfaAfaAfcAfgGfuCfuAfgAfaAfasGfsu	1166
AD-53779.1	A-110642.1	GfgGfaGfgCfcAfGfCfaUfcCfaCfgCfuUfL96	616	2137	A-109439.2	aAfgCfgUfgGfaUfgcuGfgCfcUfcCfcsUfsg	1167
AD-53780.1	A-110650.1	CfcAfcCfaAfgGfAfGfgCfaGfgAfuUfcUfL96	617	2813	A-109455.2	aGfaAfuCfcUfgCfcucCfuUfgGfuGfgsAfsg	1168
AD-53781.1	A-110658.1	GfcCfaAfgCfuCfAfCfaCfaGfcAfgGfaAfL96	618	3250	A-109471.2	uUfcCfuGfcUfgUfgugAfgCfuUfgGfcsAfsg	1169
AD-53782.1	A-110666.1	AfaGfgGfgAfaCfAfCfaGfaCfcAfgGfaAfL96	619	3369	A-109487.2	uUfcCfuGfgUfcUfgugUfuCfcCfcUfusCfsc	1170
AD-53783.1	A-110674.1	AfcCfcAfaGfcAfAfGfcAfgAfcAfuUfuAfL96	620	3537	A-109503.2	uAfaAfuGfuCfuGfcuuGfcUfuGfgGfusGfsg	1171
AD-53784.1	A-110682.1	UfuUfaUfcUfuUfUfGfgGfuCfuGfuCfcUfL96	621	3554	A-109519.2	aGfgAfcAfgAfcCfcaaAfaGfaUfaAfasUfsg	1172
AD-53825.1	A-110689.1	UfcUfgUfcCfuCfUfCfuGfuUfgCfcUfuUfL96	622	3567	A-109533.2	aAfaGfgCfaAfcAfgagAfgGfaCfaGfasCfsc	1173
AD-53826.1	A-110697.1	UfuUfuGfuAfaCfUfUfgAfaGfaUfaUfuUfL96	623	3618	A-109549.2	aAfaUfaUfcUfuCfaagUfuAfcAfaAfasGfsc	1174
AD-53827.1	A-110705.1	UfuCfuGfgAfuGfGfCfaUfcUfaGfcCfaAfL96	624	2975	A-109565.2	uUfgGfcUfaGfaUfgccAfuCfcAfgAfasAfsg	1175
AD-53828.1	A-110713.1	UfgAfaGfcCfaAfGfCfcUfcUfuCfuUfaAfL96	625	3301	A-109581.2	uUfaAfgAfaGfaGfgcuUfgGfcUfuCfasGfsa	1176
AD-53829.1	A-110721.1	UfuAfuCfuUfuUfGfGfgUfcUfgUfcCfuUfL96	626	3555	A-109597.2	aAfgGfaCfaGfaCfccaAfaAfgAfuAfasAfsu	1177
AD-53830.1	A-110872.1	UfuUfuCfuAfgAfCfCfuGfuUfuUfgCfuUfL96	627		A-110873.1	aAfgCfaAfaAfcAfgguCfuAfgAfaAfasGfsu	1178
AD-53785.1	A-110643.1	AfuCfcAfcGfcUfUfCfcUfgCfuGfcCfaUfL96	628	2148	A-109441.2	aUfgGfcAfgCfaGfgaaGfcGfuGfgAfusGfsc	1179
AD-53786.1	A-110651.1	CfaCfcAfaGfgAfGfGfcAfgGfaUfuCfuUfL96	629	2814	A-109457.2	aAfgAfaUfcCfuGfccuCfcUfuGfgUfgsGfsa	1180
AD-53787.1	A-110659.1	CfaAfgCfuCfaCfAfCfaGfcAfgGfaAfcUfL96	630	3252	A-109473.2	aGfuUfcCfuGfcUfgugUfgAfgCfuUfgsGfsc	1181

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Duplex Name	Sense Oligo Name	Sense Oligo Sequence	SEQ ID NO:	Position relative to NM_174936.3	Antisense Oligo Name	Antisense Oligo Sequence	SEQ ID NO:
AD-53788.1	A-110667.1	GfgGfaAfcAfcAfGfAfcCfaGfgAfaGfcUfL96	631	3372	A-109489.2	aGfcUfuCfcUfgGfucuGfuGfuUfcCfcsCfsu	1182
AD-53789.1	A-110675.1	CfcCfaAfgCfaAfGfCfaGfaCfaUfuUfaUfL96	632	3538	A-109505.2	aUfaAfaUfgUfcUfgcuUfgCfuUfgGfgsUfsg	1183
AD-53831.1	A-110690.1	CfuGfuCfcUfcUfCfUfgUfuGfcCfuUfuUfL96	633	3568	A-109535.2	aAfaAfgGfcAfaCfagaGfaGfgAfcAfgsAfsc	1184
AD-53832.1	A-110698.1	UfuUfgUfaAfcUfUfGfaAfgAfuAfuUfuAfL96	634	3619	A-109551.2	uAfaAfuAfuCfuUfcaaGfuUfaCfaAfasAfsg	1185
AD-53833.1	A-110706.1	CfuGfgAfuGfgCfAfUfcUfaGfcCfaGfaAfL96	635	2977	A-109567.2	uUfcUfgGfcUfaGfaugCfcAfuCfcAfgsAfsa	1186
AD-53834.1	A-110714.1	AfgUfgAfgGfcUfGfGfgAfaGfgGfgAfaAfL96	636	3357	A-109583.2	uUfuCfcCfcUfuCfccaGfcCfuCfaCfusGfsu	1187
AD-53835.1	A-110722.1	AfuCfuUfuUfgGfGfUfcUfgUfcCfuCfuUfL96	637	3557	A-109599.2	aAfgAfgGfaCfaGfaccCfaAfaAfgAfusAfsa	1188
AD-48399.1	A-100981.1	CfaCfuUfaCfgCfuGfaGfuAfcUfuCfgAfL96	638		A-100982.1	uCfgAfaGfuAfcUfcAfgCfgUfaAfgUfgsAfsu	1189
AD-53815.5	A-110695.11	CfuAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	639	3603	A-109545.18	aCfaAfaAfgCfaAfaacAfgGfuCfuAfgsAfsa	1190
AD-53815.4	A-110695.4	CfuAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	640	3603	A-109545.5	aCfaAfaAfgCfaAfaacAfgGfuCfuAfgsAfsa	1191
AD-56633.1	A-115520.2	cuAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	641	3603	A-109545.6	aCfaAfaAfgCfaAfaacAfgGfuCfuAfgsAfsa	1192
AD-56617.1	A-115535.1	CfuagAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	642	3603	A-109545.7	aCfaAfaAfgCfaAfaacAfgGfuCfuAfgsAfsa	1193
AD-56623.1	A-115536.1	CfuagAfcCfuGfUfUfuUfgcuUfuUfguL96	643	3603	A-109545.8	aCfaAfaAfgCfaAfaacAfgGfuCfuAfgsAfsa	1194
AD-56629.1	A-115537.1	CfuagAfccuGfUfUfuUfgcuUfuUfguL96	644	3603	A-109545.9	aCfaAfaAfgCfaAfaacAfgGfuCfuAfgsAfsa	1195
AD-56635.1	A-115538.1	CfuagAfccuGfUfUfuugcuUfuuguL96	645	3603	A-109545.10	aCfaAfaAfgCfaAfaacAfgGfuCfuAfgsAfsa	1196
AD-56641.1	A-115539.1	CfuagaccuGfUfUfuugcuuuuguL96	646	3603	A-109545.11	aCfaAfaAfgCfaAfaacAfgGfuCfuAfgsAfsa	1197
AD-56625.1	A-115542.1	CfuAfGfAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	647	3603	A-109545.12	aCfaAfaAfgCfaAfaacAfgGfuCfuAfgsAfsa	1198
AD-56631.1	A-115543.1	CfuAfGfAfcCfuGfUfUfuUfGfCfuUfuUfgUfL96	648	3603	A-109545.13	aCfaAfaAfgCfaAfaacAfgGfuCfuAfgsAfsa	1199
AD-56637.1	A-115544.1	CfuAfGfAfcCfuGfUfUfuUfGfCfuUfUfUfgUfL96	649	3603	A-109545.14	aCfaAfaAfgCfaAfaacAfgGfuCfuAfgsAfsa	1200
AD-56643.1	A-115545.1	CfuAfGfAfCfCfuGfUfUfuUfGfCfuUfUfUfGfUfL96	650	3603	A-109545.15	aCfaAfaAfgCfaAfaacAfgGfuCfuAfgsAfsa	1201
AD-56649.1	A-115546.1	CfUfAfGfAfCfCfuGfUfUfuUfGfCfUfUfUfUfGfUfL96	651	3603	A-109545.16	aCfaAfaAfgCfaAfaacAfgGfuCfuAfgsAfsa	1202

(continued)

Duplex Name	Sense Oligo Name	Sense Oligo Sequence	SEQ ID NO:	Position relative to NM_174936.3	Antisense Oligo Name	Antisense Oligo Sequence	SEQ ID NO:
AD-56655.1	A-115547.1	CfUfAfGfAfCfCfUfGfUfUfUfUfGfCfUfUfUfUfGfUf L96	652	3603	A-109545.17	aCfaAfaAfgCfaAfaacAfgGfuCfuAfgsAfsa	1203
AD-56615.1	A-110695.5	CfuAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	653	3603	A-115519.1	acaAfaAfgcaAfaacAfgGfuCfuAfgsAfsa	1204
AD-56621.1	A-115520.1	cuAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	654	3603	A-115519.2	acaAfaAfgcaAfaacAfgGfuCfuAfgsAfsa	1205
AD-56627.1	A-115521.1	cuAfgAfcCfuGfUfUfuugCfuUfuugUfL96	655	3603	A-115519.3	acaAfaAfgcaAfaacAfgGfuCfuAfgsAfsa	1206
AD-56639.1	A-115520.3	cuAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	656	3603	A-115522.1	ACfaAfaAfgCfaAfaacAfgGfuCfuAfgsAfsa	1207
AD-56645.1	A-110695.6	CfuAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	657	3603	A-115522.2	ACfaAfaAfgCfaAfaacAfgGfuCfuAfgsAfsa	1208
AD-56651.1	A-115523.1	(iC)uAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	658	3603	A-115524.1	(iA)CfaAfaAfgCfaAfaacAfgGfuCfuAfgsAfs(iA)	1209
AD-56610.1	A-115523.2	(iC)uAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	659	3603	A-115525.1	aCfaAfaAfgCfaAfaacAfgGfuCfuAfgsAfs(iA)	1210
AD-56616.1	A-115523.3	(iC)uAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	660	3603	A-115526.1	acaAfaAfgcaAfaacAfgGfuCfuAfgsAfs(iA)	1211
AD-56622.1	A-115527.1	(iC)uAfgAfcCfuGfUfUfuUfgCfuUfuugUfL96	661	3603	A-115526.2	acaAfaAfgcaAfaacAfgGfuCfuAfgsAfs(iA)	1212
AD-56628.1	A-115527.2	(iC)uAfgAfcCfuGfUfUfuUfgCfuUfuugUfL96	662	3603	A-115528.1	(iA)caAfaAfgcaAfaacAfgGfuCfuAfgsAfs(iA)	1213
AD-56634.1	A-115529.1	CbuAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	663	3603	A-115530.1	AbCfaAfaAfgCfaAfaacAfgGfuCfuAfgsAfsAb	1214
AD-56640.1	A-115529.2	CbuAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	664	3603	A-115531.1	aCfaAfaAfgCfaAfaacAfgGfuCfuAfgsAfsAb	1215
AD-56646.1	A-115529.3	CbuAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	665	3603	A-115532.1	acaAfaAfgcaAfaacAfgGfuCfuAfgsAfsAb	1216
AD-56652.1	A-115533.1	CbuAfgAfcCfuGfUfUfuUfgCfuUfuugUfL96	666	3603	A-115532.2	acaAfaAfgcaAfaacAfgGfuCfuAfgsAfsAb	1217
AD-56611.1	A-115533.2	CbuAfgAfcCfuGfUfUfuUfgCfuUfuugUfL96	667	3603	A-115534.1	(iA)caAfaAfgcaAfaacAfgGfuCfuAfgsAfsAb	1218
AD-56647.1	A-110695.7	CfuAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	668	3603	A-115540.1	aCfaaaAfgCfaAfaacAfgGfuCfuAfgsasa	1219
AD-56653.1	A-115535.2	CfuagAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	669	3603	A-115540.2	aCfaaaAfgCfaAfaacAfgGfuCfuAfgsasa	1220
AD-56612.1	A-115536.2	CfuagAfcCfuGfUfUfuUfgcuUfuUfguL96	670	3603	A-115540.3	aCfaaaAfgCfaAfaacAfgGfuCfuAfgsasa	1221
AD-56618.1	A-115537.2	CfuagAfccuGfUfUfuUfgcuUfuUfguL96	671	3603	A-115540.4	aCfaaaAfgCfaAfaacAfgGfuCfuAfgsasa	1222
AD-56624.1	A-115538.2	CfuagAfccuGfUfUfuugcuUfuuguL96	672	3603	A-115540.5	aCfaaaAfgCfaAfaacAfgGfuCfuAfgsasa	1223

(continued)

Duplex Name	Sense Oligo Name	Sense Oligo Sequence	SEQ ID NO:	Position relative to NM_174936.3	Antisense Oligo Name	Antisense Oligo Sequence	SEQ ID NO:
AD-56630.1	A-115539.2	CfuagaccuGfUfUfuugcuuuuguL96	673	3603	A-115540.6	aCfaaaAfgCfaAfaacAfgGfuCfuAfgsasa	1224
AD-56636.1	A-110695.8	CfuAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	674	3603	A-115541.1	aCfaaaAfgCfaAfaacAfgguCfuAfgsasa	1225
AD-56642.1	A-115535.3	CfuagAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	675	3603	A-115541.2	aCfaaaAfgCfaAfaacAfgguCfuAfgsasa	1226
AD-56648.1	A-115536.3	CfuagAfcCfuGfUfUfuUfgcuUfuUfguL96	676	3603	A-115541.3	aCfaaaAfgCfaAfaacAfgguCfuAfgsasa	1227
AD-56654.1	A-115537.3	CfuagAfccuGfUfUfuUfgcuUfuUfguL96	677	3603	A-115541.4	aCfaaaAfgCfaAfaacAfgguCfuAfgsasa	1228
AD-56613.1	A-115538.3	CfuagAfccuGfUfUfuugcuUfuuguL96	678	3603	A-115541.5	aCfaaaAfgCfaAfaacAfgguCfuAfgsasa	1229
AD-56619.1	A-115539.3	CfuagaccuGfUfUfuugcuuuuguL96	679	3603	A-115541.6	aCfaaaAfgCfaAfaacAfgguCfuAfgsasa	1230
AD-56614.1	A-110695.9	CfuAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	680	3603	A-115548.1	aCfaAfAfAfgCfaAfaacAfgGfUfCfuAfgsAfsa	1231
AD-56620.1	A-115542.2	CfuAfGfAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	681	3603	A-115548.2	aCfaAfAfAfgCfaAfaacAfgGfUfCfuAfgsAfsa	1232
AD-56626.1	A-115543.2	CfuAfGfAfcCfuGfUfUfuUfGfCfuUfuUfgUfL96	682	3603	A-115548.3	aCfaAfAfAfgCfaAfaacAfgGfUfCfuAfgsAfsa	1233
AD-56632.1	A-115544.2	CfuAfGfAfcCfuGfUfUfuUfGfCfuUfUfUfgUfL96	683	3603	A-115548.4	aCfaAfAfAfgCfaAfaacAfgGfUfCfuAfgsAfsa	1234
AD-56638.1	A-115545.2	CfuAfGfAfCfCfuGfUfUfuUfGfCfuUfUfUfGfUfL96	684	3603	A-115548.5	aCfaAfAfAfgCfaAfaacAfgGfUfCfuAfgsAfsa	1235
AD-56644.1	A-115546.2	CfUfAfGfAfCfCfuGfUfUfuUfGfCfUfUfUfUfGfUfL96	685	3603	A-115548.6	aCfaAfAfAfgCfaAfaacAfgGfUfCfuAfgsAfsa	1236
AD-56650.1	A-115547.2	CfUfAfGfAfCfCfUfGfUfUfUfUfGfCfUfUfUfUfGfUf L96	686	3603	A-115548.7	aCfaAfAfAfgCfaAfaacAfgGfUfCfuAfgsAfsa	1237
AD-56656.1	A-110695.10	CfuAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	687	3603	A-115549.1	aCfaAfAfAfGfCfaAfaacAfgGfUfCfuAfgsAfsa	1238
AD-56662.1	A-115542.3	CfuAfGfAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	688	3603	A-115549.2	aCfaAfAfAfGfCfaAfaacAfgGfUfCfuAfgsAfsa	1239
AD-56668.1	A-115543.3	CfuAfGfAfcCfuGfUfUfuUfGfCfuUfuUfgUfL96	689	3603	A-115549.3	aCfaAfAfAfGfCfaAfaacAfgGfUfCfuAfgsAfsa	1240
AD-56673.1	A-115544.3	CfuAfGfAfcCfuGfUfUfuUfGfCfuUfUfUfgUfL96	690	3603	A-115549.4	aCfaAfAfAfGfCfaAfaacAfgGfUfCfuAfgsAfsa	1241
AD-56678.1	A-115545.3	CfuAfGfAfCfCfuGfUfUfuUfGfCfuUfUfUfGfUfL96	691	3603	A-115549.5	aCfaAfAfAfGfCfaAfaacAfgGfUfCfuAfgsAfsa	1242

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Duplex Name	Sense Oligo Name	Sense Oligo Sequence	SEQ ID NO:	Position relative to NM_174936.3	Antisense Oligo Name	Antisense Oligo Sequence	SEQ ID NO:
AD-56683.1	A-115546.3	cfUfAfGfAfCfCfuGfUfUfuUfGfCfUfUfUfUfGfUfL 96	692	3603	A-115549.6	aCfaAfAfAfGfCfaAfaacAfgGfUfCfuAfgsAfsa	1243
AD-56688.1	A-115547.3	cfUfAfGfAfCfCfUfGfUfUfUfUfGfCfUfUfUfUfGfUf L96	693	3603	A-115549.7	aCfaAfAfAfGfCfaAfaacAfgGfUfCfuAfgsAfsa	1244
AD-56657.1	A-115550.1	CfuAfgAfcCfuGfUfUfUfgCfuUfuugUfL96	694	3603	A-115551.1	aCfAfAfaAfgCfaAfaacAfgGfuCfuAfgsAfsa	1245
AD-56663.1	A-115552.1	CfuAfgAfcCfuGfUfUfUfgCfuuuUfgUfL96	695	3603	A-115553.1	aCfaAfAfAfgCfaAfaacAfgGfuCfuAfgsAfsa	1246
AD-56669.1	A-115554.1	CfuAfgAfcCfuGfUfUfUfgcuUfuUfgUfL96	696	3603	A-115555.1	aCfaAfaAfGfCfaAfaacAfgGfuCfuAfgsAfsa	1247
AD-56674.1	A-115556.1	CfuAfgAfcCfuGfUfUfuugCfuUfuUfgUfL96	697	3603	A-115557.1	aCfaAfaAfgCfAfAfaacAfgGfuCfuAfgsAfsa	1248
AD-56679.1	A-115558.1	CfuAfgAfccuGfUfUfUfgCfuUfuUfgUfL96	698	3603	A-115559.1	aCfaAfaAfgCfaAfaacAfGfGfuCfuAfgsAfsa	1249
AD-56684.1	A-115560.1	CfuAfgacCfuGfUfUfUfgCfuUfuUfgUfL96	699	3603	A-115561.1	aCfaAfaAfgCfaAfaacAfgGfUfCfuAfgsAfsa	1250
AD-56689.1	A-115535.4	CfuagAfcCfuGfUfUfUfgCfuUfuUfgUfL96	700	3603	A-115562.1	aCfaAfaAfgCfaAfaacAfgGfuCfUfAfgsAfsa	1251
AD-56693.1	A-115520.4	cuAfgAfcCfuGfUfUfUfgCfuUfuUfgUfL96	701	3603	A-115563.1	aCfaAfaAfgCfaAfaacAfgGfuCfuAfGfsAfsa	1252
AD-56658.1	A-115564.1	CfuAfgAfcCfuGfUfUfUfgCfuUfUfUfgUfL96	702	3603	A-115565.1	aCfaaaAfgCfaAfaacAfgGfuCfuAfgsAfsa	1253
AD-56664.1	A-115566.1	CfuAfgAfcCfuGfUfUfUfgCfUfUfuUfgUfL96	703	3603	A-115567.1	aCfaAfaagCfaAfaacAfgGfuCfuAfgsAfsa	1254
AD-56670.1	A-115568.1	CfuAfgAfcCfuGfUfUfUfGfCfuUfuUfgUfL96	704	3603	A-115569.1	aCfaAfaAfgcaAfaacAfgGfuCfuAfgsAfsa	1255
AD-56680.1	A-115572.1	CfuAfgAfcCfUfGfUfUfuUfgCfuUfuUfgUfL96	705	3603	A-115573.1	aCfaAfaAfgCfaAfaacagGfuCfuAfgsAfsa	1256
AD-56685.1	A-115574.1	CfuAfgAfCfcCfuGfUfUfuUfgCfuUfuUfgUfL96	706	3603	A-115575.1	aCfaAfaAfgCfaAfaacAfgguCfuAfgsAfsa	1257
AD-56690.1	A-115542.4	CfuAfGfAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	707	3603	A-115576.1	aCfaAfaAfgCfaAfaacAfgGfucuAfgsAfsa	1258
AD-56694.1	A-115577.1	CfUfAfgAfcCfuGfUfUfu UfgCfu Ufu UfgUfL96	708	3603	A-115578.1	aCfaAfaAfgCfaAfaacAfgGfuCfuagsAfsa	1259
AD-56659.1	A-110695.12	CfuAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	709	3603	A-115579.1	aCfaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1260
AD-56665.1	A-115580.1	AfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	710	3605	A-115581.1	aCfaAfaAfgCfaAfaacAfgGfuCfusAfsg	1261
AD-56671.1	A-115582.1	AfgAfcCfuGfUfUfuUfgCfuUfuugUfL96	711	3605	A-115583.1	aCfAfAfaAfgCfaAfaacAfgGfuCfusAfsg	1262

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Duplex Name	Sense Oligo Name	Sense Oligo Sequence	SEQ ID NO:	Position relative to NM_174936.3	Antisense Oligo Name	Antisense Oligo Sequence	SEQ ID NO:
AD-56676.1	A-115584.1	AfgAfcCfuGfUfUfuUfgCfuuuUfgUfL96	712	3605	A-115585.1	aCfaAfAfAfgCfaAfaacAfgGfuCfusAfsg	1263
AD-56681.1	A-115586.1	AfgAfcCfuGfUfUfuUfgcuUfuUfgUfL96	713	3605	A-115587.1	aCfaAfaAfGfCfaAfaacAfgGfuCfusAfsg	1264
AD-56686.1	A-115588.1	AfgAfcCfuGfUfUfuugCfuUfuUfgUfL96	714	3605	A-115589.1	aCfaAfaAfgCfAfAfaacAfgGfuCfusAfsg	1265
AD-56691.1	A-115590.1	AfgAfccuGfUfUfuUfgCfuUfuUfgUfL96	715	3605	A-115591.1	aCfaAfaAfgCfaAfaacAfGfGfuCfusAfsg	1266
AD-56695.1	A-115592.1	AfgacCfuGfUfUfuUfgCfuUfuUfgUfL96	716	3605	A-115593.1	aCfaAfaAfgCfaAfaacAfgGfUfCfusAfsg	1267
AD-56660.1	A-115594.1	agAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	717	3605	A-115595.1	aCfaAfaAfgCfaAfaacAfgGfuCfUfsAfsg	1268
AD-56666.1	A-115596.1	AfgAfcCfuGfUfUfuUfgCfuUfUfUfgUfL96	718	3605	A-115597.1	aCfaaaAfgCfaAfaacAfgGfuCfusAfsg	1269
AD-56672.1	A-115598.1	AfgAfcCfuGfUfUfuUfgCfUfUfuUfgUfL96	719	3605	A-115599.1	aCfaAfaagCfaAfaacAfgGfuCfusAfsg	1270
AD-56677.1	A-115600.1	AfgAfcCfuGfUfUfuUfGfCfuUfuUfgUfL96	720	3605	A-115601.1	aCfaAfaAfgcaAfaacAfgGfuCfusAfsg	1271
AD-56682.1	A-115602.1	AfgAfcCfuGfUfUfUfUfgCfuUfuUfgUfL96	721	3605	A-115603.1	aCfaAfaAfgCfaaaacAfgGfuCfusAfsg	1272
AD-56687.1	A-115604.1	AfgAfcCfUfGfUfUfuUfgCfuUfuUfgUfL96	722	3605	A-115605.1	aCfaAfaAfgCfaAfaacagGfuCfusAfsg	1273
AD-56692.1	A-115606.1	AfgAfCfCfuGfUfUfuUfgCfuUfuUfgUfL96	723	3605	A-115607.1	aCfaAfaAfgCfaAfaacAfgguCfusAfsg	1274
AD-56696.1	A-115608.1	AfGfAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	724	3605	A-115609.1	aCfaAfaAfgCfaAfaacAfgGfucusAfsg	1275
AD-56661.1	A-115580.2	AfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	725	3605	A-115610.1	aCfaAfaAfgCfaAfaacAfgGfuCfusasg	1276
AD-56667.1	A-115611.1	gAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	726	3605	A-115612.1	aCfaAfaAfgCfaAfaacAfgGfuCfausa	1277
AD-53806.11	A-110717.10	CfaAfgCfaGfaCfAfUfuUfaUfcUfuUfuUfL96	727	3544	A-109589.15	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1278
AD-53806.13	A-110717.11	CfaAfgCfaGfaCfAfUfuUfaUfcUfuUfuUfL96	728	3544	A-109589.10	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1279
AD-53806.12	A-110717.12	CfaAfgCfaGfaCfAfUfuUfaUfcUfuUfuUfL96	729	3544	A-109589.22	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1280
AD-53806.5	A-110717.4	CfaAfgCfaGfaCfAfUfuUfaUfcUfuUfuUfL96	730	3544	A-109589.5	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1281
AD-53806.6	A-110717.5	CfaAfgCfaGfaCfAfUfuUfaUfcUfuUfuUfL96	731	3544	A-109589.7	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1282
AD-53806.7	A-110717.6	CfaAfgCfaGfaCfAfUfuUfaUfcUfuUfuUfL96	732	3544	A-109589.8	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1283
AD-53806.8	A-110717.7	CfaAfgCfaGfaCfAfUfuUfaUfcUfuUfuUfL96	733	3544	A-109589.9	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1284

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Duplex Name	Sense Oligo Name	Sense Oligo Sequence	SEQ ID NO:	Position relative to NM_174936.3	Antisense Oligo Name	Antisense Oligo Sequence	SEQ ID NO:
AD-53806.9	A-110717.8	CfaAfgCfaGfaCfAfUfuUfaUfcUfuUfuUfL96	734	3544	A-109589.9	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1285
AD-53806.10	A-110717.9	CfaAfgCfaGfaCfAfUfuUfaUfcUfuUfuUfL96	735	3544	A-109589.9	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1286
AD-56979.1	A-116393.1	caAfgCfaGfaCfAfUfuUfaUfcUfuUfuUfL96	736	3544	A-109589.6	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1287
AD-56979.2	A-116393.2	caAfgCfaGfaCfAfUfuUfaUfcUfuUfuUfL96	737	3544	A-109589.17	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1288
AD-56975.3	A-116394.1	(iC)aAfgCfaGfaCfAfUfuUfaUfcUfuUfuUfL96	738	3544	A-109589.9	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1289
AD-56975.4	A-116394.2	(iC)aAfgCfaGfaCfAfUfuUfaUfcUfuUfuUfL96	739	3544	A-109589.15	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1290
AD-56975.5	A-116394.3	(iC)aAfgCfaGfaCfAfUfuUfaUfcUfuUfuUfL96	740	3544	A-109589.22	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1291
AD-56975.1	A-116394.4	(iC)aAfgCfaGfaCfAfUfuUfaUfcUfuUfuUfL96	741	3544	A-109589.5	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1292
AD-56975.2	A-116394.5	(iC)aAfgCfaGfaCfAfUfuUfaUfcUfuUfuUfL96	742	3544	A-109589.6	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1293
AD-56983.1	A-116400.1	CbaAfgCfaGfaCfAfUfuUfaUfcUfuUfuUfL96	743	3544	A-109589.7	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1294
AD-56983.2	A-116400.2	CbaAfgCfaGfaCfAfUfuUfaUfcUfuUfuUfL96	744	3544	A-109589.8	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1295
AD-56983.3	A-116400.3	CbaAfgCfaGfaCfAfUfuUfaUfcUfuUfuUfL96	745	3544	A-109589.9	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1296
AD-56983.4	A-116400.4	CbaAfgCfaGfaCfAfUfuUfaUfcUfuUfuUfL96	746	3544	A-109589.9	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1297
AD-56983.5	A-116400.5	CbaAfgCfaGfaCfAfUfuUfaUfcUfuUfuUfL96	747	3544	A-109589.15	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1298
AD-56977.3	A-116406.1	CfaagCfaGfaCfAfUfuUfaUfcUfuUfuUfL96	748	3544	A-109589.10	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1299
AD-56977.1	A-116406.2	CfaagCfaGfaCfAfUfuUfaUfcUfuUfuUfL96	749	3544	A-109589.11	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1300
AD-56977.2	A-116406.3	CfaagCfaGfaCfAfUfuUfaUfcUfuUfuUfL96	750	3544	A-109589.18	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1301
AD-56976.1	A-116407.1	CfaagCfaGfaCfAfUfuUfaucUfuUfuUfL96	751	3544	A-109589.11	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1302
AD-56976.2	A-116407.2	CfaagCfaGfaCfAfUfuUfaucUfuUfuUfL96	752	3544	A-109589.12	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1303
AD-56980.1	A-116408.1	CfaagCfagaCfAfUfuUfaucUfuUfuUfL96	753	3544	A-109589.12	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1304
AD-56980.2	A-116408.2	CfaagCfagaCfAfUfuUfaucUfuUfuUfL96	754	3544	A-109589.13	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1305
AD-56984.1	A-116409.1	CfaagCfagaCfAfUfuUfaucUfuuuUfL96	755	3544	A-109589.13	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1306

(continued)

Duplex Name	Sense Oligo Name	Sense Oligo Sequence	SEQ ID NO:	Position relative to NM_174936.3	Antisense Oligo Name	Antisense Oligo Sequence	SEQ ID NO:
AD-56984.2	A-116409.2	CfaagCfagaCfAfUfuUfaucUfuuuUfL96	756	3544	A-109589.14	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1307
AD-56987.1	A-116410.1	CfaagCfagaCfAfUfuUfaucUfuuuuL96	757	3544	A-109589.14	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1308
AD-56987.2	A-116410.2	CfaagCfagaCfAfUfuUfaucUfuuuuL96	758	3544	A-109589.9	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1309
AD-56991.1	A-116415.1	CfaagCfagaCfAfUfuUfaucuuuuuL96	759	3544	A-109589.15	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1310
AD-56993.1	A-116416.1	CfaagcagaCfAfUfuUfaucuuuuuL96	760	3544	A-109589.16	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1311
AD-56995.1	A-116417.1	CfaagcagaCfAfUfuuaucuuuuuL96	761	3544	A-109589.17	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1312
AD-56978.1	A-116418.1	CfaAfGfCfaGfaCfAfUfuUfaUfcUfuUfuUfL96	762	3544	A-109589.18	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1313
AD-56978.2	A-116418.2	CfaAfGfCfaGfaCfAfUfuUfaUfcUfuUfuUfL96	763	3544	A-109589.17	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1314
AD-56981.1	A-116419.1	CfaAfGfCfaGfaCfAfUfuUfAfUfcUfuUfuUfL96	764	3544	A-109589.19	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1315
AD-56985.1	A-116420.1	CfaAfGfCfaGfaCfAfUfuUfAfUfCfUfuUfuUfL96	765	3544	A-109589.20	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1316
AD-56988.1	A-116421.1	CfaAfGfCfAfGfaCfAfUfuUfAfUfCfUfuUfuUfL96	766	3544	A-109589.21	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1317
AD-56988.2	A-116421.2	CfaAfGfCfAfGfaCfAfUfuUfAfUfCfUfuUfuUfL96	767	3544	A-109589.9	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1318
AD-56988.3	A-116421.3	CfaAfGfCfAfGfaCfAfUfuUfAfUfCfUfuUfuUfL96	768	3544	A-109589.15	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1319
AD-56982.1	A-116426.1	CfaAfgcaGfaCfAfUfuUfaUfcUfuUfuUfL96	769	3544	A-109589.19	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1320
AD-56982.2	A-116426.2	CfaAfgcaGfaCfAfUfuUfaUfcUfuUfuUfL96	770	3544	A-109589.23	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1321
AD-56986.1	A-116428.1	CfaAfgCfagaCfAfUfuUfaUfcUfuUfuUfL96	771	3544	A-109589.20	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1322
AD-56986.2	A-116428.2	CfaAfgCfagaCfAfUfuUfaUfcUfuUfuUfL96	772	3544	A-109589.17	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1323
AD-56989.1	A-116430.1	CfaAfgCfaGfacAfUfuUfaUfcUfuUfuUfL96	773	3544	A-109589.21	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1324
AD-56990.1	A-116432.1	CfaAfgCfaGfaCfAfuuUfaUfcUfuUfuUfL96	774	3544	A-109589.9	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1325
AD-56992.1	A-116434.1	CfaAfgCfaGfaCfAfUfuUfaucUfuUfuUfL96	775	3544	A-109589.15	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1326
AD-56992.2	A-116434.2	CfaAfgCfaGfaCfAfUfuUfaucUfuUfuUfL96	776	3544	A-109589.17	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1327
AD-56994.1	A-116436.1	CfaAfgCfaGfaCfAfUfuUfaUfcUfuuuUfL96	777	3544	A-109589.22	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1328

(continued)

Duplex Name	Sense Oligo Name	Sense Oligo Sequence	SEQ ID NO:	Position relative to NM_174936.3	Antisense Oligo Name	Antisense Oligo Sequence	SEQ ID NO:
AD-56994.2	A-116436.2	CfaAfgCfaGfaCfAfUfuUfaUfcUfuuuUfL96	778	3544	A-109589.23	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1329
AD-56996.1	A-116438.1	caagCfaGfaCfAfUfuUfaUfcUfuUfuUfL96	779	3544	A-109589.17	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1330
AD-57001.1	A-116440.1	CfaAfgcagaCfAfUfuUfaUfcUfuUfuUfL96	780	3544	A-109589.17	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1331
AD-57007.1	A-116442.1	CfaAfgCfaGfaCfAfuuuaUfcUfuUfuUfL96	781	3544	A-109589.17	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1332
AD-57013.1	A-116444.1	CfaAfgCfaGfaCfAfUfuUfaucuuUfuUfL96	782	3544	A-109589.17	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1333
AD-57019.1	A-116446.1	CfaAfgCfaGfaCfAfUfuUfaUfcUfuuuuL96	783	3544	A-109589.17	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1334
AD-57022.1	A-116448.1	CfaAfgCfaGfaCfAfUfuUfaUfcUfUfUfuUfL96	784	3544	A-109589.23	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1335
AD-57025.1	A-116449.1	CfaAfgCfaGfaCfAfUfuUfaUfCfUfuUfuUfL96	785	3544	A-109589.23	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1336
AD-56997.1	A-116450.1	CfaAfgCfaGfaCfAfUfuUfAfUfcUfuUfuUfL96	786	3544	A-109589.17	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1337
AD-57002.1	A-116452.1	CfaAfgCfaGfaCfAfUfUfUfaUfcUfuUfuUfL96	787	3544	A-109589.17	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1338
AD-57008.1	A-116453.1	CfaAfgCfaGfAfCfAfUfuUfaUfcUfuUfuUfL96	788	3544	A-109589.17	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1339
AD-57014.1	A-116454.1	CfaAfgCfAfGfAfCfAfUfuUfaUfcUfuUfuUfL96	789	3544	A-109589.17	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1340
AD-57020.1	A-116455.1	CfAfAfgCfaGfaCfAfUfuUfaUfcUfuUfuUfL96	790	3544	A-109589.23	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1341
AD-57020.2	A-116455.2	CfAfAfgCfaGfaCfAfUfuUfaUfcUfuUfuUfL96	791	3544	A-109589.23	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1342
AD-57026.1	A-116457.1	CfaAfgCfaGfaCfAfUfuUfaUfcuuUfuUfL96	792	3544	A-109589.23	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1343
AD-57003.1	A-116460.1	CfaAfgCfaGfaCfAfUfuuaUfcUfuUfuUfL96	793	3544	A-109589.17	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1344
AD-57009.1	A-116462.1	CfaAfgCfaGfaCfauuUfaUfcUfuUfuUfL96	794	3544	A-109589.17	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1345
AD-57015.1	A-116464.1	CfaAfgCfaGfacaUfuUfaUfcUfuUfuUfL96	795	3544	A-109589.17	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1346
AD-57023.1	A-116467.1	CfaAfgCfaGfaCfAfUfuUfaucUfUfUfuUfL96	796	3544	A-109589.23	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1347
AD-57027.1	A-116469.1	CfaAfgCfaGfaCfAfUfuuaUfcUfUfUfuUfL96	797	3544	A-109589.23	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1348
AD-56998.1	A-116471.1	CfaAfgCfagaCfAfUfuUfaUfcUfUfUfuUfL96	798	3544	A-109589.17	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1349
AD-57004.1	A-116473.1	CfaAfgcaGfaCfAfUfuUfaUfcUfUfUfuUfL96	799	3544	A-109589.17	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1350

(continued)

Duplex Name	Sense Oligo Name	Sense Oligo Sequence	SEQ ID NO:	Position relative to NM_174936.3	Antisense Oligo Name	Antisense Oligo Sequence	SEQ ID NO:
AD-57010.1	A-116475.1	CfaagCfaGfaCfAfUfuUfaUfcUfUfUfuUfL96	800	3544	A-109589.17	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1351
AD-57016.1	A-116477.1	caAfgCfaGfaCfAfUfuUfaUfcUfUfUfuUfL96	801	3544	A-109589.17	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1352
AD-56999.2	A-116479.1	CfaAfgCfaGfaCfAfUfuUfAfUfcUfUfUfuUfL96	802	3544	A-109589.17	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1353
AD-56999.1	A-116479.2	CfaAfgCfaGfaCfAfUfuUfAfUfcUfUfUfuUfL96	803	3544	A-109589.17	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1354
AD-57021.1	A-116481.1	CfaAfgCfAfGfaCfAfUfuUfaUfcUfUfUfuUfL96	804	3544	A-109589.23	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1355
AD-57024.1	A-116483.1	CfaAfGfCfaGfaCfAfUfuUfaUfcUfUfUfuUfL96	805	3544	A-109589.23	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1356
AD-57005.1	A-116486.1	CfaAfgCfaGfaCfAfUfuUfaUfCfUfuuuUfL96	806	3544	A-109589.17	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1357
AD-57011.1	A-116488.1	CfaAfgCfaGfaCfAfUfuuaUfCfUfuUfuUfL96	807	3544	A-109589.17	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1358
AD-57017.1	A-116490.1	CfaAfGfCfagaCfAfUfuUfaUfcUfuUfuUfL96	808	3544	A-109589.17	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1359
AD-57000.2	A-116492.1	Cf(Aeo)Af(Geo)CfaGfaCfAfUfuUfaUfcUf(Teo)Uf(Teo)UfL96	809	3544	A-109589.17	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1360
AD-57000.3	A-116492.2	Cf(Aeo)Af(Geo)CfaGfaCfAfUfuUfaUfcUf(Teo)Uf(Teo)UfL96	810	3544	A-109589.23	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1361
AD-57000.1	A-116492.3	Cf(Aeo)Af(Geo)CfaGfaCfAfUfuUfaUfcUf(Teo)Uf(Teo)UfL96	811	3544	A-109589.17	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1362
AD-57006.2	A-116494.1	Cf(Aeo)Af(Geo)CfaGfaCfAfUfuUf(Aeo)Uf(m5Ceo)Uf(Teo)Uf(Teo)UfL96	812	3544	A-109589.23	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1363
AD-57006.3	A-116494.2	Cf(Aeo)Af(Geo)CfaGfaCfAfUfuUf(Aeo)Uf(m5Ceo)Uf(Teo)Uf(Teo)UfL96	813	3544	A-109589.23	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1364
AD-57006.1	A-116494.3	Cf(Aeo)Af(Geo)CfaGfaCfAfUfuUf(Aeo)Uf(m5Ceo)Uf(Teo)Uf(Teo)UfL96	814	3544	A-109589.17	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1365

(continued)

Duplex Name	Sense Oligo Name	Sense Oligo Sequence	SEQ ID NO:	Position relative to NM_174936.3	Antisense Oligo Name	Antisense Oligo Sequence	SEQ ID NO:
AD-57012.1	A-116498.1	Cf(Aeo)Af(Geo)CfaGfaCfAfUfuUfaUfcUf(Teo)Uf(Teo)UbL96	815	3544	A-109589.17	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1366
AD-57018.1	A-116500.1	Cf(Aeo)Af(Geo)CfaGfaCfAfUfuUf(Aeo)Uf(m5Ceo)Uf(Teo)Uf(Teo)UbL96	816	3544	A-109589.17	aAfaAfaGfaUfaAfaugUfcUfgCfuUfgsCfsu	1367
AD-53815.1		CfuAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	817	3601		aCfaAfaAfgCfaAfaacAfgGfuCfuAfgsAfsa	1368
AD-57928.40		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	818	3601		asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1369
AD-59182.5		CfsusAfgAfcCfuGfUfUfuugCfuuuuguL96	819	3601		asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1370
AD-59184.3		CfsusAfgAfcCfuGfuUfuugCfuuuuguL96	820	3601		asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1371
AD-59186.3		CfsusAfgAfcCfuGfUfuugCfuuuuguL96	821	3601		asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1372
AD-59171.13		CfsusAfgAfcCfuGfuuuugCfuuuuguL96	822	3601		asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1373
AD-59176.7		CfsusAfgAfcCfuGfuuuugcuuuuguL96	823	3601		asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1374
AD-59170.7		CfsusagacCfuGfuuuugCfuuuuguL96	824	3601		asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1375
AD-59175.7		CfsusagacCfuGfuuuugcuuuuguL96	825	3601		asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1376
AD-59179.7		csusagacCfuGfuuuugcuuuuguL96	826	3601		asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1377
AD-59218.1		CfsusAfgAfcCfuGfuuuugCfuuuuguL96	827	3601		asCfsaAfaAfgCfaAfAfAfcAfgGfuCfuAfgsasa	1378
AD-59222.1		CfsusAfgAfcCfuGfuuuugcuuuuguL96	828	3601		asCfsaAfaAfgCfaAfAfAfcAfgGfuCfuAfgsasa	1379
AD-59226.1		CfsusagacCfuGfuuuugCfuuuuguL96	829	3601		asCfsaAfaAfgCfaAfAfAfcAfgGfuCfuAfgsasa	1380
AD-59230.1		CfsusagacCfuGfuuuugcuuuuguL96	830	3601		asCfsaAfaAfgCfaAfAfAfcAfgGfuCfuAfgsasa	1381
AD-59235.1		csusagacCfuGfuuuugcuuuuguL96	831	3601		asCfsaAfaAfgCfaAfAfAfcAfgGfuCfuAfgsasa	1382
AD-59207.1		CfsusAfgAfcCfuGfuuuugCfuuuuguL96	832	3601		asCfsaAfAfAfgCfaAfaAfcAfgGfuCfuagsasa	1383
AD-59211.1		CfsusAfgAfcCfuGfuuuugcuuuuguL96	833	3601		asCfsaAfAfAfgCfaAfaAfcAfgGfuCfuagsasa	1384
AD-59215.1		CfsusagacCfuGfuuuugCfuuuuguL96	834	3601		asCfsaAfAfAfgCfaAfaAfcAfgGfuCfuagsasa	1385

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Duplex Name	Sense Oligo Name	Sense Oligo Sequence	SEQ ID NO:	Position relative to NM_174936.3	Antisense Oligo Name	Antisense Oligo Sequence	SEQ ID NO:
AD-59219.1		CfsusagacCfuGfuuuugcuuuuguL96	835	3601		asCfsaAfAfAfgCfaAfaAfcAfgGfuCfuagsasa	1386
AD-59223.1		csusagacCfuGfuuuugcuuuuguL96	836	3601		asCfsaAfAfAfgCfaAfaAfcAfgGfuCfuagsasa	1387
AD-59181.5		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgsUfL96	837	3601		asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1388
AD-59172.5		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgsgsUfL96	838	3601		asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1389
AD-59177.5		CfsusAfgAfcCfuGfUfUfuUfgCfsuUfsuUfsgsUfL96	839	3601		asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1390
AD-59180.5		CfsusAfgAfcCfuGfUfUfuUfgCfsuUfsuUfsgsUfsL96	840	3601		asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1391
AD-59183.5		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfsgsUfsL96	841	3601		asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1392
AD-59185.5		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfsL96	842	3601		asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1393
AD-59173.5		CfsusAfgAfcCfuGfUfUfuugCfuuuugsuL96	843	3601		asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1394
AD-59232.1		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	844	3600		PasCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1395
AD-59236.1		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	845	3601		asCfsaAfaAfsgCfaAfaacAfgGfuCfsuAfgsasa	1396
AD-59216.1		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgsUfL96	846	3601		asCfsaAfaAfsgCfaAfaacAfgGfuCfsuAfgsasa	1397
AD-59220.1		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgsgUfL96	847	3601		asCfsaAfaAfsgCfaAfaacAfgGfuCfsuAfgsasa	1398
AD-59224.1		CfsusAfgAfcCfuGfUfUfuUfgCfsuUfsuUfsgsUfL9 6	848	3601		asCfsaAfaAfsgCfaAfaacAfgGfuCfsuAfgsasa	1399
AD-59228.1		CfsusAfgAfcCfuGfUfUfuUfgCfsuUfsuUfsgsUfsL 96	849	3601		asCfsaAfaAfsgCfaAfaacAfgGfuCfsuAfgsasa	1400
AD-59233.1		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfsgsUfsL96	850	3601		asCfsaAfaAfsgCfaAfaacAfgGfuCfsuAfgsasa	1401
AD-59237.1		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfsL96	851	3601		asCfsaAfaAfsgCfaAfaacAfgGfuCfsuAfgsasa	1402

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Duplex Name	Sense Oligo Name	Sense Oligo Sequence	SEQ ID NO:	Position relative to NM_174936.3	Antisense Oligo Name	Antisense Oligo Sequence	SEQ ID NO:
AD-59209.1		CfsusAfgAfcCfuGfUfUfuugCfuuuugsuL96	852	3601		asCfsaAfaAfsgCfaAfaacAfgGfuCfsuAfgsasa	1403
AD-59208.1		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	853	3601		asCfsaAfaAfsgCfaAfaacAfgGfuCfsusAfgsasa	1404
AD-59212.1		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	854	3600		PasCfsaAfaAfsgCfaAfaacAfgGfuCfsuAfgsasa	1405
AD-59210.1		csusAGAccuGuuuuGcuuuuGuL96	855	3601		AscsAAAAGcAAAAcAGGucuAGsasa	1406
AD-59214.1		AsGsAccuGuuuuGcuuuuGuL96	856	3603		AscsAAAAGcAAAAcAGGucusAsG	1407
AD-59227.1		CfsusAfGfAfccuGfuuuuGfcuuuuGfuL96	857	3601		asCfsAfAfAfAfGfcAfAfAfAfcAfGfGfucuAfGfsasa	1408
AD-59231.1		CfsusAfGfAfccuGfuuuuGfcuuuuGfuL96	858	3601		asCfsAfAfAfAfGfcAfAfaacAfGfGfucuAfGfsasa	1409
AD-59198.3		(C3m)usAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	859	3601		asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1410
AD-59200.3		(C3m)(U3m)AfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	860	3601		asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1411
AD-59203.3		(m5Cam)usAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	861	3601		asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1412
AD-59204.3		(m5Cam)(Tam)AfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	862	3601		asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1413
AD-59188.3		(m5Cams)(Tams)AfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	863	3601		asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1414
AD-59191.3		(m5Cams)usAfgAfcCfuGfUfUfuUfgCfuUfuUfgU	864	3601		asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1415

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Duplex Name	Sense Oligo Name	Sense Oligo Sequence	SEQ ID NO:	Position relative to NM_174936.3	Antisense Oligo Name	Antisense Oligo Sequence	SEQ ID NO:
		fL96					
AD-59213.1		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	865	3601		asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgs(A3m)a	1416
AD-59217.1		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	866	3601		asCfsaAfaAfgCfaAfaacAfgGfuCfuAf(G3m)(A3m)a	1417
AD-59221.1		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	867	3601		asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgs(Aam)a	1418
AD-59225.1		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	868	3601		asCfsaAfaAfgCfaAfaacAfgGfuCfuAf(Gam)(Aam)a	1419
AD-59229.1		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	869	3601		asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgs(Aams)a	1420
AD-59234.1		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	870	3601		asCfsaAfaAfgCfaAfaacAfgGfuCfuAf(Gams)(Aams)a	1421
AD-59238.1		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	871	3601		(A3m)CfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1422
AD-59241.1		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	872	3601		as(C3m)aAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1423
AD-59245.1		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	873	3601		(Aam)CfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1424
AD-59250.1		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	874	3601		as(m5Cam)aAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1425

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Duplex Name	Sense Oligo Name	Sense Oligo Sequence	SEQ ID NO:	Position relative to NM_174936.3	Antisense Oligo Name	Antisense Oligo Sequence	SEQ ID NO:
AD-59246.1		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	875	3602		asCfsaAfaAfgCfaAfaacAfgGfuCfuAfsgsa	1426
AD-59253.2		usAfsgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	876	3602		asCfsaAfaAfgCfaAfaacAfgGfuCfuAfsgsa	1427
AD-59242.1		AfsgsAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	877	3602		asCfsaAfaAfgCfaAfaacAfgGfuCfuAfsgsa	1428
AD-59253.1		usAfsgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	878	3602		asCfsaAfaAfgCfaAfaacAfgGfuCfuAfsgsa	1429
AD-59258.1		usasgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	879	3602		asCfsaAfaAfgCfaAfaacAfgGfuCfuAfsgsa	1430
AD-59251.1		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	880	3603		asCfsaAfaAfgCfaAfaacAfgGfuCfusAfsg	1431
AD-59256.1		usAfsgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	881	3604		asCfsaAfaAfgCfaAfaacAfgGfuCfsusAf	1432
AD-59260.1		AfsgsAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	882	3605		asCfsaAfaAfgCfaAfaacAfgGfusCfsu	1433
AD-59248.1		gsAfscCfuGfUfUfuUfgCfuUfuUfgUfL96	883	3605		asCfsaAfaAfgCfaAfaacAfgGfusCfsu	1434
AD-59247.1		gsAfscCfuGfUfUfuUfgCfuUfuUfgUfL96	884	3604		asCfsaAfaAfgCfaAfaacAfgGfuCfsusa	1435
AD-59252.1		AfsgsAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	885	3604		asCfsaAfaAfgCfaAfaacAfgGfuCfsusa	1436
AD-59257.1		usAfsgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	886	3604		asCfsaAfaAfgCfaAfaacAfgGfuCfsusa	1437
AD-59261.1		AfsgsAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	887	3603		asCfsaAfaAfgCfaAfaacAfgGfuCfusasg	1438
AD-59262.1		usAfsgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	888	3603		asCfsaAfaAfgCfaAfaacAfgGfuCfusasg	1439
AD-59265.1		csusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	889	3603		asCfsaAfaAfgCfaAfaacAfgGfuCfusasg	1440
AD-59196.13		usAfsgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	890	3601		asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1441
AD-59189.11		AfsgsAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	891	3601		asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1442
AD-59190.3		usCfsuAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	892	3601		asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1443
AD-59192.3		UfsusCfuAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	893	3601		asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1444
AD-59240.1		CfsusAfgAfcCfuGfuuuugCfuuuuguL96	894	3601		asCfsaAfaAfsgCfaAfaacAfgGfuCfuAfgs(A3m)a	1445

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Duplex Name	Sense Oligo Name	Sense Oligo Sequence	SEQ ID NO:	Position relative to NM_174936.3	Antisense Oligo Name	Antisense Oligo Sequence	SEQ ID NO:
AD-59244.1		CfsusAfgAfcCfuGfuuuugCfuuuuguL96	895	3601		asCfsaAfaAfsgCfaAfaacAfgGfuCfuAfgsasa	1446
AD-59202.7		(C3m)usagaccuguuuugcuuuuguL96	896	3601		asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1447
AD-59195.5		(C3m)usAfgAfcCfuGfuuuugCfuuuuguL96	897	3601		asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1448
AD-59249.1		CfsusAfgAfcCfuGfUfUfuugCfuuuuguL96	898	3601		asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgs(A3m)a	1449
AD-59254.1		CfsusAfgAfcCfuGfuuuugCfuuuuguL96	899	3601		asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgs(A3m)a	1450
AD-59259.1		(C3 m)usAfgAfcCfuGfuuuugCfuuu uguL96	900	3601		asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgs(A3m)a	1451
AD-59264.1		(C3m)usagaccuguuuugcuuuuguL96	901	3601		asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgs(A3m)a	1452
AD-59264.2		(C3m)usagaccuguuuugcuuuuguL96	902	3601		asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgs(A3m)a	1453
AD-59255.1		CsusagaccuGfUfUfuugcuuuuguL96	903	3601		asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgs(A3m)a	1454
AD-57928.1		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	904	3601		asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1455
AD-58893.1		CfsuAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	905	3601		asCfaAfaAfgCfaAfaacAfgGfuCfuAfgasa	1456
AD-58894.1		CfusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	906	3601		aCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsaa	1457
AD-58895.1		CfuAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	907	3601		asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1458
AD-58896.1		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	908	3601		aCfaAfaAfgCfaAfaacAfgGfuCfuAfgaa	1459
AD-58897.1		CfsusAfsgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	909	3601		asCfsasAfaAfgCfaAfaacAfgGfuCfuAfsgsasa	1460

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Duplex Name	Sense Oligo Name	Sense Oligo Sequence	SEQ ID NO:	Position relative to NM_174936.3	Antisense Oligo Name	Antisense Oligo Sequence	SEQ ID NO:
AD-58898.1		CfsusAfsgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	910	3601		asCfsaAfaAfgCfsaAfaacAfsgGfuCfuAfsgsasa	1461
AD-58899.1		CfsusAfsgAfcCfuGfUfUfuUfgCfuUfuUfsgUfL96	911	3601		asCfsaAfaAfgCfsaAfaacAfsgGfuCfuAfsgsasa	1462
AD-58900.1		CfsasAfgCfaGfaCfAfUfuUfaUfcUfuUfuUfL96	912	NA		asAfsaAfaGfaUfaAfaugUfcUfgCfuUfgscsu	1463
AD-58902.1		UfsusUfuCfuAfgAfCfCfuGfuUfuUfgCfuUfL96	913	3597		asAfsgCfaAfaAfcAfgguCfuAfgAfaAfasgsu	1464
		(A3mx)(G3mx)AfcCfuGfUfUfuUfgCfuUfuUfgUfL96	914			asCfsaAfaAfgCfaAfaacAfgGfuCfusasg	1465
		(A3mx)(G3mx)AfcCfuGfUfUfuUfgCfuUfuUfgUfL96	915			(A3mx)CfaAfaAfgCfaAfaacAfgGfuCfusasg	1466
		(A3mx)(G3mx)AfcCfuGfUfUfuUfgCfuUfuUfgUfL96	916			(A3mx)CfaAfaAfgCfaAfaacAfgGfuCfu(A3mx)g	1467
		(A3mx)gAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	917			asCfsaAfaAfgCfaAfaacAfgGfuCfusasg	1468
		(A3mx)gAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	918			(A3mx)CfaAfaAfgCfaAfaacAfgGfuCfusasg	1469
		(A3mx)gAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	919			(A3mx)CfaAfaAfgCfaAfaacAfgGfuCfu(A3mx)g	1470
		(C3mx)(U3mx)AfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	920			asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1471
		(C3mx)(U3mx)AfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	921			(A3mx)CfaAfaAfgCfaAfaacAfgGfuCfuAf(G3mx)(A3mx)a	1472
		(C3mx)uAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	922			asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1473
		(C3mx)uAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	923			(A3mx)CfaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1474

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Duplex Name	Sense Oligo Name	Sense Oligo Sequence	SEQ ID NO:	Position relative to NM_174936.3	Antisense Oligo Name	Antisense Oligo Sequence	SEQ ID NO:
		(C3mx)uAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	924			(A3mx)CfaAfaAfgCfaAfaacAfgGfuCfuAfg(A3mx)a	1475
		(C3mx)uAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	925			(A3mx)CfaAfaAfgCfaAfaacAfgGfuCfuAf(G3mx)(A3mx)a	1476
		(C3mx)usAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	926			asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1477
		(Chd)susAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	927			asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1478
		(phe)CfsuAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	928			asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1479
		(phe)CfuAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	929			asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1480
		(pshe)CfsuAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	930			asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1481
		(pshe)CfuAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	931			asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1482
		AfsgsAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	932			(A3mx)CfaAfaAfgCfaAfaacAfgGfuCfusasg	1483
		AfsgsAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	933			(A3mx)CfaAfaAfgCfaAfaacAfgGfuCfu(A3mx)g	1484
		Cfs(Uhd)sAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	934			asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1485
		CfsusAfgAf(Chd)CfuGfUfUfuUfgCfuUfuUfgUfL96	935			asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1486
		CfsusAfgAfc(Chd)uGfUfUfuUfgCfuUfuUfgUfL96	936			asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1487

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Duplex Name	Sense Oligo Name	Sense Oligo Sequence	SEQ ID NO:	Position relative to NM_174936.3	Antisense Oligo Name	Antisense Oligo Sequence	SEQ ID NO:
		CfsusAfgAfcCf(Uhd)GfUfUfuUfgCfuUfuUfgUfL96	937			asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1488
		CfsusAfgAfcCfuGfUfUf(Uhd)UfgCfuUfuUfgUfL96	938			asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1489
		CfsusAfgAfcCfuGfUfUfuUf(Ggn)CfuUfuUfgUfL96	939			asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1490
		CfsusAfgAfcCfuGfUfUfuUfg(Cgn)uUfuUfgUfL96	940			asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1491
		CfsusAfgAfcCfuGfUfUfuUfg(Chd)uUfuUfgUfL96	941			asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1492
		CfsusAfgAfcCfuGfUfUfuUfgCf(Tgn)UfuUfgUfL96	942			asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1493
		CfsusAfgAfcCfuGfUfUfuUfgCf(Uhd)UfuUfgUfL96	943			asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1494
		CfsusAfgAfcCfuGfUfUfuUfgCfu(Tgn)uUfgUfL96	944			asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1495
		CfsusAfgAfcCfuGfUfUfuUfgCfuUf(Tgn)UfgUfL96	945			asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1496
		CfsusAfgAfcCfuGfUfUfuUfgCfuUf(Uhd)UfgUfL96	946			asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1497
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfu(Tgn)gUfL96	947			asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1498
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfu(Uhd)gUfL96	948			asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1499
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUf(Ggn)UfL96	949			asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1500
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfg(Tgn)L96	950			asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1501
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfg(Uhd)L96	951			asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1502

(continued)

Duplex Name	Sense Oligo Name	Sense Oligo Sequence	SEQ ID NO:	Position relative to NM_174936.3	Antisense Oligo Name	Antisense Oligo Sequence	SEQ ID NO:
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfUL96	952			asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1503
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfUL96	953			(Agn)CfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1504
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfUL96	954			(Agn)CfaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1505
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfUL96	955			P(Agn)CfaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1506
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfUL96	956			as(Cgn)aAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1507
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfUL96	957			asCfs(Agn)AfaAfgCfaAfaacAfgGfuCfuAfgsas a	1508
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfUL96	958			asCfsa(Agn)aAfgCfaAfaacAfgGfuCfuAfgsasa	1509
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfUL96	959			asCfsaAf(Agn)AfgCfaAfaacAfgGfuCfuAfgsas a	1510
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfUL96	960			asCfsaAfa(Agn)gCfaAfaacAfgGfuCfuAfgsasa	1511
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfUL96	961			asCfsaAfaAf(Ggn)CfaAfaacAfgGfuCfuAfgsas a	1512
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfUL96	962			asCfsaAfaAfg(Cgn)aAfaacAfgGfuCfuAfgsasa	1513
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfUL96	963			asCfsaAfaAfgCf(Agn)AfaacAfgGfuCfuAfgsas a	1514
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfUL96	964			asCfsaAfaAfgCfa(Agn)aacAfgGfuCfuAfgsasa	1515
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfUL96	965			asCfsaAfaAfgCfaAf(Agn)acAfgGfuCfuAfgsas a	1516
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfUL96	966			asCfsaAfaAfgCfaAfa(Agn)cAfgGfuCfuAfgsas a	1517

(continued)

Duplex Name	Sense Oligo Name	Sense Oligo Sequence	SEQ ID NO:	Position relative to NM_174936.3	Antisense Oligo Name	Antisense Oligo Sequence	SEQ ID NO:
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	967			asCfsaAfaAfgCfaAfaa(Cgn)AfgGfuCfuAfgsas a	1518
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	968			asCfsaAfaAfiCfaAfaacAfiGfuCfuAfisasa	1519
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	969			asCfsaAfaAfgCfaAfaacAfgGfuCfuAfg(A3mx) a	1520
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	970			asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgs(A3mx) a	1521
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	971			asCfsaAfaAfgCfaAfaacAfgGfuCfuAf(G3mx)(A 3mx)a	1522
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	972			(A3mx)CfaAfaAfgCfaAfaacAfgGfuCfuAfgsas a	1523
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	973			(A3mx)CfsaAfaAfgCfaAfaacAfgGfuCfuAfgsas a	1524
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	974			P(A3mx)CfaAfaAfgCfaAfaacAfgGfuCfuAfgsa sa	1525
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	975			a(C3mx)aAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1526
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	976			as(C3mx)aAfaAfgCfaAfaacAfgGfuCfuAfgsas a	1527
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	977			(A3mx)(C3mx)aAfaAfgCfaAfaacAfgGfuCfuAf gsasa	1528

(continued)

Duplex Name	Sense Oligo Name	Sense Oligo Sequence	SEQ ID NO:	Position relative to NM_174936.3	Antisense Oligo Name	Antisense Oligo Sequence	SEQ ID NO:
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	978			(A3mx)CfaAfaAfgCfaAfaacAfgGfuCfuAfg(A3mx)a	1529
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	979			(A3mx)CfsaAfaAfgCfaAfaacAfgGfuCfuAfgs(A3mx)a	1530
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	980			(A3mx)CfaAfaAfgCfaAfaacAfgGfuCfuAf(G3mx)(A3mx)a	1531
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	981			asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgasas(phe)	1532
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	982			asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgaas(phe)	1533
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	983			sCfsaAfaAfgCfaAfaacAfgGfuCfuAfgaa(phe)	1534
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	984			asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsas(phe)	1535
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	985			asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgas(phe)	1536
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	986			asCfsaAfaAfgCfaAfaacAfgGfuCfuAfga(phe)	1537
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	987			asCfsaAfaAfgCfaAfaacAfgGf(Uhd)CfuAfgsas	1538
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	988			asCfsaAfaAfgCfaAfaacAfgGfuCf(Uhd)Afgsas	1539
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	989			asCfsaAfaAfg(Chd)aAfaacAfgGfuCfuAfgsasa	1540
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	990			asCfsaAfaagCfaAfaacAfgGfucuAfgsasa	1541

(continued)

Duplex Name	Sense Oligo Name	Sense Oligo Sequence	SEQ ID NO:	Position relative to NM_174936.3	Antisense Oligo Name	Antisense Oligo Sequence	SEQ ID NO:
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfguL96	991			asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1542
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfguL96	992			asCfsaAfaagCfaAfaacAfgGfucuAfgsasa	1543
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuugUfL96	993			asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1544
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuugUfL96	994			asCfsaAfaagCfaAfaacAfgGfucuAfgsasa	1545
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuuguL96	995			asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1546
		CfsusAfgAfcCfuGfUfUfuUfgCfuUfuuguL96	996			asCfsaAfaagCfaAfaacAfgGfucuAfgsasa	1547
		CfsusAfgAfcCfuGfUfUfuUfgcuuuugUfL96	997			asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1548
		CfsusAfgAfcCfuGfUfUfuUfgcuuuugUfL96	998			asCfsaAfaagCfaAfaacAfgGfucuAfgsasa	1549
		CfsusAfgAfcCfuGfUfUfuUfgcuuuuguL96	999			asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1550
		CfsusAfgAfcCfuGfUfUfuUfgcuuuuguL96	1000			asCfsaAfaagCfaAfaacAfgGfucuAfgsasa	1551
		CfsusAfgAfcCfuGfUfUfuUfgUfuUfuUfgUfL96	1001			asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1552
		CfsusAfgAfcCfuGfUfUfuUfiCfuUfuUfiUfL96	1002			asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1553
		CfsusAfgAfcCfuGfUfUfuUfiCfuUfuUfiUfL96	1003			asCfsaAfaAfiCfaAfaacAfgGfuCfuAfgsasa	1554
		CfsusAfgAfcCfuGfUfUfuUfiCfuUfuUfiUfL96	1004			asCfsaAfaAfiCfaAfaacAfiGfuCfuAfisasa	1555
		CfsusAfiAfcCfuGfUfUfuUfiCfuUfuUfiUfL96	1005			asCfsaAfaAfiCfaAfaacAfiGfuCfuAfisasa	1556

Example 2. *In vitro and in vivo* screening.

[0432] A subset of these duplexes was evaluated for efficacy in single dose free uptake assays in *Cynomolgus* monkey hepatocytes. Briefly, primary *Cynomolgus* monkey hepatocytes (PCH) were treated with the conjugated modified siRNA duplexes at three concentrations, 500nM, 100nM and 10nM. The 100nM and 10nM free uptake assays were performed twice and the data are represented as average message remaining relative to control +/- the standard deviation (SD). The 500nM screen was performed a single time. Table 3 shows the results of these assays.

Table 3. PCSK9 efficacy screen by free uptake in primary *Cynomolgous* monkey hepatocytes.

DUPLEX ID	PCH 500 nM	PCH 100nM Avg	PCH 10nM Avg	PCH 100nM SD	PCH 10nM SD
AD-48399	1.08	1.03	0.98	0.09	0.02
AD-48399	0.97	0.95	1.10	0.03	0.09
AD-48399	0.89	0.98	1.02	0.06	0.06
AD-48399	1.04	1.00	1.01	0.02	0.08
AD-48399	0.92	1.03	0.96	0.02	0.09
AD-48399	1.13	1.03	0.96	0.05	0.01
AD-48400	0.48	0.63	0.90	0.04	0.00
AD-48400.4	0.65	0.78	0.89	0.14	0.13
AD-53649.1	0.96	0.96	1.14	0.02	0.07
AD-53650.1	0.97	0.92	1.15	0.01	0.06
AD-53651.1	1.02	0.98	1.15	0.13	0.10
AD-53652.1	0.83	0.89	1.14	0.20	0.05
AD-53653.1	0.85	0.95	1.26	0.04	0.07
AD-53654.1	0.84	0.93	1.19	0.02	0.13
AD-53656.1	0.92	0.92	1.07	0.05	0.03
AD-53657.1	0.92	0.89	1.02	0.05	0.03
AD-53658.1	0.89	0.83	0.97	0.04	0.14
AD-53659.1	0.79	0.82	1.05	0.06	0.13
AD-53660.1	0.89	0.86	0.98	0.07	0.07
AD-53661.1	0.92	1.03	1.07	0.02	0.04
AD-53663.1	0.88	0.90	1.08	0.03	0.02
AD-53664.1	0.95	0.86	1.00	0.09	0.13
AD-53665.1	0.92	0.91	1.05	0.01	0.13
AD-53666.1	0.73	0.80	0.95	0.08	0.02
AD-53667.1	0.95	0.96	1.12	0.06	0.03
AD-53668.1	1.03	0.89	1.17	0.03	0.12
AD-53669.1	1.12	0.90	1.05	0.01	0.15
AD-53670.1	0.85	0.88	1.00	0.06	0.06
AD-53671.1	0.87	0.90	0.93	0.02	0.04
AD-53672.1	0.87	0.86	0.95	0.04	0.16
AD-53674.1	0.69	0.75	0.92	0.08	0.02
AD-53675.1	0.99	0.92	1.17	0.11	0.06

(continued)

DUPLEX ID	PCH 500 nM	PCH 100nM Avg	PCH 10nM Avg	PCH 100nM SD	PCH 10nM SD
AD-53676.1	0.90	0.87	1.10	0.03	0.08
AD-53677.1	1.22	0.86	1.12	0.10	0.04
AD-53678.1	1.01	0.98	1.03	0.03	0.12
AD-53679.1	0.96	0.85	1.02	0.04	0.11
AD-53680.1	1.21	0.94	0.99	0.03	0.01
AD-53681.1	1.02	0.94	1.01	0.01	0.11
AD-53682.1	0.98	0.90	1.01	0.06	0.11
AD-53683.1	0.95	0.90	1.01	0.02	0.08
AD-53684.1	1.14	1.01	1.01	0.09	0.07
AD-53685.1	0.96	0.92	1.03	0.00	0.07
AD-53687.1	1.31	0.91	1.02	0.02	0.11
AD-53688.1	0.90	0.95	0.96	0.03	0.03
AD-53689.1	0.97	0.95	1.05	0.04	0.07
AD-53690.1	0.82	0.97	0.99	0.13	0.08
AD-53691.1	0.99	1.01	0.97	0.01	0.12
AD-53692.1	1.11	0.91	1.00	0.04	0.03
AD-53693.1	1.02	0.96	1.02	0.04	0.10
AD-53694.1	1.12	0.98	0.97	0.07	0.06
AD-53695.1	0.97	1.04	0.94	0.11	0.08
AD-53696.1	0.85	0.91	1.23	0.10	0.01
AD-53697.1	0.89	0.91	1.06	0.03	0.00
AD-53698.1	0.90	0.86	1.15	0.06	0.01
AD-53699.1	0.84	0.85	1.07	0.00	0.03
AD-53700.1	0.93	1.02	1.21	0.02	0.15
AD-53701.1	1.01	0.96	1.12	0.00	0.17
AD-53702.1	0.95	0.94	1.06	0.05	0.15
AD-53703.1	0.82	0.85	1.04	0.07	0.13
AD-53704.1	0.92	0.97	0.94	0.04	0.02
AD-53705.1	0.96	0.98	1.00	0.11	0.15
AD-53706.1	0.90	0.97	1.03	0.01	0.20
AD-53707.1	0.86	0.98	1.11	0.14	0.24
AD-53708.1	1.10	0.94	1.05	0.02	0.15
AD-53709.1	0.79	0.84	1.08	0.01	0.18
AD-53710.1	1.03	0.91	1.06	0.01	0.09
AD-53711.1	0.90	0.90	0.99	0.00	0.28
AD-53712.1	0.97	0.92	0.97	0.00	0.12
AD-53713.1	0.98	0.93	1.07	0.01	0.16
AD-53714.1	1.09	0.86	0.99	0.03	0.09

(continued)

DUPLEX ID	PCH 500 nM	PCH 100nM Avg	PCH 10nM Avg	PCH 100nM SD	PCH 10nM SD
AD-53715.1	1.04	0.83	0.94	0.06	0.06
AD-53716.1	0.82	0.85	1.02	0.05	0.14
AD-53717.1	0.98	0.94	0.98	0.11	0.12
AD-53718.1	0.89	1.04	1.01	0.18	0.01
AD-53719.1	0.98	1.05	1.05	0.06	0.17
AD-53720.1	1.02	0.88	1.08	0.01	0.15
AD-53721.1	0.88	0.95	1.03	0.07	0.11
AD-53722.1	0.98	0.95	1.01	0.06	0.12
AD-53723.1	0.89	0.89	1.02	0.10	0.06
AD-53724.1	0.98	0.93	1.00	0.13	0.01
AD-53725.1	1.04	1.05	1.09	0.19	0.11
AD-53726.1	0.87	0.88	0.88	0.00	0.02
AD-53727.1	0.82	0.92	1.02	0.05	0.13
AD-53728.1	0.86	0.93	1.06	0.03	0.08
AD-53729.1	0.86	0.81	1.02	0.12	0.03
AD-53730.1	1.01	0.95	1.02	0.07	0.01
AD-53731.1	0.99	0.98	1.00	0.08	0.07
AD-53732.1	0.93	0.86	1.01	0.12	0.11
AD-53733.1	1.06	1.02	1.08	0.05	0.06
AD-53734.1	0.95	0.93	1.04	0.12	0.05
AD-53735.1	1.00	0.93	1.01	0.02	0.06
AD-53736.1	0.90	1.09	1.16	0.05	0.01
AD-53737.1	0.94	0.93	1.00	0.02	0.09
AD-53738.1	0.93	0.79	0.93	0.03	0.01
AD-53739.1	1.11	0.90	0.90	0.05	0.00
AD-53740.1	0.86	0.92	0.97	0.08	0.01
AD-53741.1	0.96	0.84	0.92	0.00	0.07
AD-53742.1	1.03	0.93	1.03	0.04	0.06
AD-53743.1	0.92	0.98	1.05	0.08	0.14
AD-53744.1	0.95	1.02	1.03	0.08	0.12
AD-53745.1	0.81	0.99	1.11	0.10	0.18
AD-53746.1	0.65	0.83	1.04	0.07	0.16
AD-53747.1	0.82	0.88	1.02	0.05	0.13
AD-53748.1	0.46	0.59	0.72	0.06	0.07
AD-53749.1	0.93	0.90	1.04	0.12	0.16
AD-53750.1	0.90	1.02	0.97	0.02	0.10
AD-53751.1	0.92	0.87	1.02	0.19	0.16
AD-53752.1	0.73	0.88	0.99	0.06	0.18

(continued)

DUPLEX ID	PCH 500 nM	PCH 100nM Avg	PCH 10nM Avg	PCH 100nM SD	PCH 10nM SD
AD-53753.1	0.87	0.97	1.06	0.07	0.19
AD-53754.1	0.43	0.58	0.72	0.10	0.05
AD-53755.1	1.01	0.99	1.03	0.03	0.02
AD-53757.1	0.98	0.91	1.07	0.05	0.13
AD-53758.1	0.63	0.73	0.92	0.05	0.00
AD-53759.1	0.91	0.92	0.99	0.02	0.08
AD-53760.1	0.51	0.67	0.80	0.03	0.12
AD-53761.1	0.89	1.07	1.10	0.11	0.18
AD-53762.1	1.06	1.00	0.96	0.12	0.10
AD-53763.1	0.95	1.10	1.00	0.07	0.09
AD-53764.1	0.99	0.94	0.99	0.05	0.16
AD-53765.1	0.92	0.87	0.86	0.09	0.11
AD-53766.1	0.75	0.78	0.86	0.09	0.14
AD-53767.1	1.01	1.02	0.97	0.05	0.18
AD-53768.1	0.89	1.07	0.97	0.09	0.15
AD-53769.1	0.89	1.11	0.95	0.05	0.11
AD-53770.1	0.76	1.01	0.98	0.01	0.12
AD-53771.1	0.70	0.74	0.84	0.06	0.12
AD-53772.1	0.72	0.83	0.85	0.04	0.11
AD-53773.1	0.96	1.00	0.98	0.05	0.07
AD-53774.1	0.75	0.92	1.01	0.06	0.14
AD-53776.1	0.78	0.94	0.97	0.11	0.08
AD-53777.1	0.67	0.68	0.74	0.11	0.01
AD-53778.1	0.74	0.73	0.92	0.13	0.14
AD-53779.1	1.00	0.98	0.95	0.14	0.04
AD-53780.1	0.90	0.92	0.98	0.12	0.05
AD-53781.1	0.84	0.95	1.00	0.17	0.06
AD-53782.1	0.87	0.92	0.90	0.11	0.02
AD-53783.1	0.71	0.79	0.78	0.14	0.03
AD-53784.1	0.68	0.82	0.86	0.10	0.10
AD-53785.1	1.10	0.96	0.96	0.09	0.07
AD-53786.1	0.98	0.89	0.95	0.20	0.14
AD-53787.1	1.23	0.93	1.00	0.11	0.21
AD-53788.1	0.95	0.90	0.94	0.17	0.08
AD-53789.1	0.55	0.60	0.78	0.09	0.08
AD-53790.1	0.70	0.91	1.04	0.08	0.16
AD-53791.1	0.47	0.67	0.92	0.12	0.09
AD-53792.1	0.52	0.75	0.89	0.06	0.04

(continued)

DUPLEX ID	PCH 500 nM	PCH 100nM Avg	PCH 10nM Avg	PCH 100nM SD	PCH 10nM SD
AD-53793.1	0.88	1.03	1.07	0.20	0.09
AD-53794.1	0.85	1.00	1.09	0.17	0.22
AD-53795.1	0.58	0.71	1.00	0.10	0.12
AD-53796.1	0.62	0.78	0.96	0.07	0.12
AD-53797.1	0.72	0.78	0.93	0.12	0.10
AD-53798.1	0.50	0.55	0.76	0.08	0.03
AD-53799.1	0.98	0.92	1.10	0.11	0.21
AD-53800.1	0.59	0.65	0.87	0.15	0.14
AD-53801.1	0.81	0.84	1.05	0.14	0.18
AD-53802.1	0.68	0.79	1.03	0.13	0.13
AD-53803.1	0.51	0.53	0.77	0.09	0.05
AD-53804.1	0.94	0.86	1.05	0.15	0.15
AD-53805.1	0.95	0.93	1.03	0.12	0.19
AD-53806.1	0.38	0.45	0.78	0.05	0.12
AD-53807.1	0.85	0.95	1.15	0.09	0.24
AD-53808.1	0.81	0.85	0.93	0.08	0.11
AD-53809.1	0.50	0.62	0.77	0.00	0.12
AD-53810.1	0.84	0.82	0.98	0.16	0.22
AD-53811.1	0.94	0.95	1.00	0.10	0.11
AD-53812.1	0.61	0.76	0.97	0.14	0.22
AD-53813.1	0.67	0.76	0.94	0.01	0.15
AD-53814.1	0.58	0.67	0.84	0.11	0.19
AD-53815.1	0.49	0.50	0.72	0.09	0.17
AD-53816.1	0.82	0.91	0.93	0.08	0.10
AD-53817.1	0.92	0.94	1.07	0.13	0.36
AD-53818.1	0.83	0.99	0.99	0.07	0.41
AD-53819.1	0.61	0.75	0.88	0.24	0.16
AD-53820.1	0.71	0.81	0.92	0.17	0.04
AD-53821.1	0.56	0.54	0.68	0.13	0.05
AD-53822.1	1.24	0.88	1.05	0.12	0.17
AD-53823.1	1.03	0.86	0.99	0.11	0.18
AD-53824.1	0.76	0.73	0.93	0.16	0.11
AD-53825.1	0.57	0.63	0.82	0.18	0.04
AD-53826.1	0.54	0.51	0.78	0.08	0.07
AD-53827.1	0.99	0.91	1.05	0.12	0.08
AD-53828.1	0.69	0.77	0.87	0.09	0.16
AD-53829.1	0.72	0.91	0.95	0.11	0.16
AD-53830.1	0.48	0.73	0.76	0.11	0.01

(continued)

DUPLEX ID	PCH 500 nM	PCH 100nM Avg	PCH 10nM Avg	PCH 100nM SD	PCH 10nM SD
AD-53831.1	0.97	0.92	1.00	0.22	0.25
AD-53832.1	0.68	0.63	0.81	0.15	0.02
AD-53833.1	0.92	0.90	0.84	0.20	0.03
AD-53834.1	1.15	0.93	0.86	0.16	0.02
AD-53835.1	0.88	0.79	0.81	0.18	0.03
PBS	0.90	1.02	0.99	0.04	0.15

[0433] The modified and conjugated PCSK9 siRNA duplexes were also evaluated for efficacy by transfection assays in three human cell lines. PCSK9 siRNAs were transfected in three different cell lines, HeLa, Hep3B and HepG2 at two doses, 10nM and 0.1nM. The results of these assays are shown in Table 4 and the data are expressed as a fraction of the message remaining relative to control.

[0434] Figure 1 shows that there is a general reproducibility in the silencing activity of the PCSK9 duplexes between the free uptake assays and the transfection assays.

[0435] The IC_{50} values for selected duplexes by free-uptake in *Cynomologous* cells and by transfection in Hep3B cells are shown in Table 5.

Table 4. PCSK9 efficacy screen by transfection in human cell lines.

DUPLEX ID	Hela, 10nM	Hela, 0.1nM	Hep3b, 10nM	Hep3b, 0.1nM	HepG2, 10nM	HepG2, 0.1nM
AD-48399	0.94	0.90	1.18	1.03	1.34	1.05
AD-48399	0.90	1.03	0.87	0.88	0.84	0.91
AD-48399	0.88	1.14	0.90	0.99	0.92	1.04
AD-48399	1.22	0.97	0.95	0.98	0.81	0.92
AD-48399	1.04	0.81	1.01	1.10	1.03	1.09
AD-48399	1.06	1.20	1.14	1.04	1.16	1.01
AD-48400	0.05	0.63	0.10	0.51	0.17	0.69
AD-48400.4	0.06	0.28	0.14	0.31	0.13	0.32
AD-53649.1	0.84	1.05	1.07	0.94	0.97	1.11
AD-53650.1	0.16	0.87	0.41	0.87	0.52	1.12
AD-53651.1	0.47	0.86	0.49	0.92	0.71	1.08
AD-53652.1	0.34	0.93	0.50	0.96	0.40	1.21
AD-53653.1	0.36	0.99	0.43	1.01	0.52	1.13
AD-53654.1	0.85	1.06	0.99	0.92	0.95	1.06
AD-53656.1	0.46	0.92	0.78	0.98	0.80	0.74
AD-53657.1	0.71	0.97	0.75	1.01	0.81	0.94
AD-53658.1	0.32	0.97	0.50	0.91	0.58	1.05
AD-53659.1	0.11	0.86	0.24	0.93	0.22	0.94
AD-53660.1	0.35	1.12	0.43	0.99	0.44	1.31
AD-53661.1	0.94	1.07	0.85	0.95	0.88	0.92
AD-53663.1	0.82	1.03	0.74	1.06	1.04	1.04
AD-53664.1	0.60	0.94	0.61	1.06	0.85	1.28
AD-53665.1	0.33	1.00	0.55	1.01	0.45	1.12

(continued)

DUPLEX ID	Hela, 10nM	Hela, 0.1nM	Hep3b, 10nM	Hep3b, 0.1nM	HepG2, 10nM	HepG2, 0.1nM
AD-53666.1	0.09	0.98	0.22	0.97	0.21	1.08
AD-53667.1	0.94	1.07	0.95	0.96	0.95	1.02
AD-53668.1	0.27	0.88	0.36	1.07	0.35	1.13
AD-53669.1	0.81	1.02	0.93	1.08	1.35	1.24
AD-53670.1	0.55	0.94	0.52	0.48	0.45	1.13
AD-53671.1	0.68	1.07	0.78	1.02	0.82	1.27
AD-53672.1	0.22	1.04	0.38	1.06	0.34	1.15
AD-53674.1	0.08	0.67	0.15	0.85	0.15	0.80
AD-53675.1	0.25	1.04	0.43	0.95	0.38	1.04
AD-53676.1	0.81	0.94	0.90	1.14	0.98	1.06
AD-53677.1	0.45	0.90	0.70	0.98	0.70	1.14
AD-53678.1	0.41	1.02	0.72	1.04	0.70	1.15
AD-53679.1	0.44	0.93	0.58	0.88	0.50	0.95
AD-53680.1	0.36	0.99	0.55	0.98	0.52	0.96
AD-53681.1	0.33	0.93	0.57	1.12	0.54	1.11
AD-53682.1	0.84	0.94	0.85	1.06	0.93	1.13
AD-53683.1	0.65	0.78	0.95	1.05	0.73	1.06
AD-53684.1	0.57	0.98	0.79	0.92	0.62	1.08
AD-53685.1	0.85	0.90	0.94	0.95	0.69	0.98
AD-53687.1	0.15	0.83	0.39	1.09	0.34	1.23
AD-53688.1	0.45	0.89	0.72	1.01	0.57	1.19
AD-53689.1	0.56	0.93	1.04	1.14	0.59	1.24
AD-53690.1	0.45	0.79	0.53	1.26	0.41	1.22
AD-53691.1	0.82	1.03	0.91	1.22	0.57	1.05
AD-53692.1	0.68	0.81	0.81	0.89	0.82	1.05
AD-53693.1	0.61	0.92	0.85	0.81	0.53	1.03
AD-53694.1	0.59	0.87	0.58	1.01	0.53	0.82
AD-53695.1	0.91	0.78	1.02	1.23	1.14	1.11
AD-53696.1	0.57	0.98	0.82	1.01	0.68	1.05
AD-53697.1	0.31	1.04	0.40	0.95	0.24	0.90
AD-53698.1	0.17	0.97	0.31	0.92	0.32	0.84
AD-53699.1	0.29	1.00	0.47	0.90	0.47	1.23
AD-53700.1	0.81	1.07	0.94	0.99	0.97	1.08
AD-53701.1	0.89	1.07	0.96	0.84	0.65	0.93
AD-53702.1	0.45	1.03	0.84	1.08	0.72	0.99
AD-53703.1	0.18	0.79	0.28	0.97	0.29	0.90
AD-53704.1	0.77	0.80	0.88	1.06	0.91	0.95
AD-53705.1	0.63	0.89	0.81	1.06	0.76	0.97

(continued)

DUPLEX ID	Hela, 10nM	Hela, 0.1nM	Hep3b, 10nM	Hep3b, 0.1nM	HepG2, 10nM	HepG2, 0.1nM
AD-53706.1	0.39	0.82	0.41	1.00	0.48	0.88
AD-53707.1	0.42	0.97	0.60	0.83	0.54	0.80
AD-53708.1	0.49	0.95	0.82	0.96	1.07	1.09
AD-53709.1	0.19	0.90	0.43	0.85	0.38	1.05
AD-53710.1	0.66	1.00	0.82	0.85	0.69	1.08
AD-53711.1	0.40	0.90	0.45	0.95	0.23	1.03
AD-53712.1	0.47	0.99	0.51	0.94	0.62	0.97
AD-53713.1	0.52	1.05	0.69	0.83	0.79	0.94
AD-53714.1	0.43	1.01	0.71	1.11	0.75	1.12
AD-53715.1	0.23	0.99	0.58	1.24	0.58	1.09
AD-53716.1	0.39	1.00	0.52	0.98	0.51	0.80
AD-53717.1	0.20	0.84	0.33	1.02	0.41	1.09
AD-53718.1	0.35	1.08	0.33	1.02	0.45	0.97
AD-53719.1	0.58	0.96	0.74	0.84	0.79	1.01
AD-53720.1	0.31	1.00	0.55	1.09	0.48	1.24
AD-53721.1	0.26	1.02	0.62	0.92	0.49	0.94
AD-53722.1	0.50	0.99	0.86	0.99	0.87	1.26
AD-53723.1	0.28	0.86	0.37	0.92	0.54	1.11
AD-53724.1	0.18	1.11	0.20	0.98	0.36	1.05
AD-53725.1	0.47	1.00	0.63	0.95	0.60	1.04
AD-53726.1	0.19	1.01	0.42	0.96	0.41	1.21
AD-53727.1	0.55	0.82	0.77	1.08	0.68	1.35
AD-53728.1	0.44	0.92	0.65	1.11	0.68	1.44
AD-53729.1	0.11	0.92	0.25	0.94	0.11	1.01
AD-53730.1	0.31	0.91	0.51	1.05	0.59	1.34
AD-53731.1	0.26	0.63	0.42	0.95	0.44	1.07
AD-53732.1	0.17	0.87	0.29	0.99	0.36	0.98
AD-53733.1	1.06	0.72	1.21	1.14	1.07	1.28
AD-53734.1	0.79	0.92	0.93	0.98	0.90	1.33
AD-53735.1	0.54	0.87	0.83	1.12	0.66	1.24
AD-53736.1	0.40	0.69	0.76	1.09	0.76	1.11
AD-53737.1	0.29	0.82	0.41	1.04	0.39	0.96
AD-53738.1	0.19	0.70	0.24	1.09	0.28	1.10
AD-53739.1	0.91	0.94	0.72	1.07	0.78	1.09
AD-53740.1	0.17	1.06	0.42	1.07	0.32	1.05
AD-53741.1	0.17	0.91	0.32	0.99	0.41	1.05
AD-53742.1	0.55	1.07	0.69	0.97	0.72	1.08
AD-53743.1	0.71	0.99	0.75	0.76	0.58	1.08

(continued)

DUPLEX ID	Hela, 10nM	Hela, 0.1nM	Hep3b, 10nM	Hep3b, 0.1nM	HepG2, 10nM	HepG2, 0.1nM
AD-53744.1	0.13	0.86	0.50	0.69	0.36	0.87
AD-53745.1	0.46	0.91	0.78	0.72	0.87	0.94
AD-53746.1	0.13	0.82	0.23	0.50	0.28	0.90
AD-53747.1	0.29	1.08	0.54	0.77	0.50	1.07
AD-53748.1	0.04	0.22	0.12	0.21	0.20	0.32
AD-53749.1	0.56	0.76	0.48	0.81	0.53	0.85
AD-53750.1	0.61	0.75	0.69	0.81	0.81	1.07
AD-53751.1	0.25	0.69	0.37	0.72	0.26	0.77
AD-53752.1	0.11	0.43	0.13	0.40	0.16	0.61
AD-53753.1	0.70	0.76	0.75	0.92	0.63	1.09
AD-53754.1	0.06	0.31	0.10	0.34	0.12	0.40
AD-53755.1	0.46	0.91	0.66	0.84	0.56	0.79
AD-53757.1	0.61	0.90	0.50	0.89	0.44	0.91
AD-53758.1	0.11	0.31	0.11	0.29	0.11	0.60
AD-53759.1	0.61	0.87	0.57	0.84	0.56	0.98
AD-53760.1	0.05	0.36	0.14	0.42	0.12	0.53
AD-53761.1	0.95	0.99	0.76	0.72	0.55	0.61
AD-53762.1	0.58	1.18	0.74	0.88	0.69	0.88
AD-53763.1	0.16	0.86	0.19	0.64	0.21	0.75
AD-53764.1	0.70	0.91	0.54	0.85	0.59	0.94
AD-53765.1	0.16	0.63	0.38	0.64	0.30	0.87
AD-53766.1	0.09	0.72	0.16	0.67	0.18	0.63
AD-53767.1	0.30	1.14	0.69	0.83	0.71	0.83
AD-53768.1	0.50	0.98	0.75	0.98	0.52	1.06
AD-53769.1	0.36	1.07	0.26	0.62	0.39	0.83
AD-53770.1	0.27	1.08	0.45	1.00	0.44	1.25
AD-53771.1	0.18	0.62	0.19	0.44	0.21	0.65
AD-53772.1	0.12	0.75	0.30	0.66	0.18	0.85
AD-53773.1	0.39	0.98	0.60	0.84	0.19	1.00
AD-53774.1	0.07	0.54	0.25	0.40	0.20	0.71
AD-53776.1	0.33	0.97	0.45	0.94	0.34	0.95
AD-53777.1	0.06	0.39	0.18	0.30	0.11	0.41
AD-53778.1	0.09	0.72	0.24	0.69	0.23	0.78
AD-53779.1	0.47	0.66	0.68	0.67	0.57	0.81
AD-53780.1	0.29	0.93	0.61	0.71	0.42	0.92
AD-53781.1	0.41	0.99	0.38	0.87	0.28	1.09
AD-53782.1	0.56	0.47	0.56	0.89	0.41	1.16
AD-53783.1	0.16	0.68	0.32	0.46	0.34	0.61

(continued)

DUPLEX ID	Hela, 10nM	Hela, 0.1nM	Hep3b, 10nM	Hep3b, 0.1nM	HepG2, 10nM	HepG2, 0.1nM
AD-53784.1	0.15	0.71	0.27	0.72	0.25	0.80
AD-53785.1	0.17	0.90	0.57	0.71	0.29	0.64
AD-53786.1	0.11	0.78	0.28	0.48	0.24	0.74
AD-53787.1	0.34	0.72	0.56	1.04	0.46	0.81
AD-53788.1	0.36	0.83	0.46	0.95	0.32	0.65
AD-53789.1	0.09	0.43	0.18	0.42	0.12	0.47
AD-53790.1	0.10	0.74	0.30	0.65	0.31	0.81
AD-53791.1	0.07	0.51	0.20	0.30	0.16	0.58
AD-53792.1	0.05	0.40	0.11	0.30	0.17	0.64
AD-53793.1	0.23	1.19	0.42	0.84	0.45	1.12
AD-53794.1	0.43	1.15	0.65	0.67	0.42	0.95
AD-53795.1	0.08	0.37	0.15	0.34	0.12	0.48
AD-53796.1	0.07	0.33	0.19	0.49	0.15	0.58
AD-53797.1	0.10	0.43	0.16	0.39	0.20	0.62
AD-53798.1	0.04	0.31	0.09	0.29	0.16	0.60
AD-53799.1	0.22	0.71	0.30	0.85	0.27	0.85
AD-53800.1	0.09	0.34	0.16	0.35	0.14	0.51
AD-53801.1	0.09	0.28	0.25	0.55	0.20	0.54
AD-53802.1	0.10	0.31	0.20	0.40	0.15	0.72
AD-53803.1	0.07	0.27	0.08	0.21	0.14	0.29
AD-53804.1	0.18	0.57	0.29	0.47	0.27	0.79
AD-53805.1	0.69	0.85	0.68	0.85	0.48	1.01
AD-53806.1	0.07	0.38	0.18	0.43	0.13	0.50
AD-53807.1	0.29	0.61	0.26	0.71	0.28	0.68
AD-53808.1	0.15	0.68	0.26	0.50	0.28	0.72
AD-53809.1	0.04	0.23	0.17	0.22	0.12	0.31
AD-53810.1	0.31	0.88	0.30	0.55	0.36	0.85
AD-53811.1	0.28	0.77	0.33	0.57	0.39	0.87
AD-53812.1	0.12	0.69	0.16	0.62	0.22	0.79
AD-53813.1	0.11	0.33	0.18	0.26	0.17	0.40
AD-53814.1	0.12	0.59	0.57	0.60	0.29	0.57
AD-53815.1	0.03	0.27	0.11	0.18	0.18	0.33
AD-53816.1	0.16	0.89	0.24	0.62	0.32	0.75
AD-53817.1	0.26	0.98	0.44	0.69	0.44	1.18
AD-53818.1	0.12	0.71	0.21	0.55	0.21	0.70
AD-53819.1	0.09	0.52	0.12	0.45	0.12	0.46
AD-53820.1	0.20	0.96	0.27	0.67	0.34	0.74
AD-53821.1	0.04	0.29	0.10	0.23	0.13	0.29

(continued)

DUPLEX ID	Hela, 10nM	Hela, 0.1nM	Hep3b, 10nM	Hep3b, 0.1nM	HepG2, 10nM	HepG2, 0.1nM
AD-53822.1	0.54	1.05	0.60	0.91	0.48	0.96
AD-53823.1	0.21	0.76	0.41	0.59	0.33	0.85
AD-53824.1	0.16	0.78	0.40	0.51	0.36	0.70
AD-53825.1	0.05	0.40	0.12	0.31	0.24	0.73
AD-53826.1	0.04	0.34	0.10	0.21	0.20	0.34
AD-53827.1	0.40	1.11	0.40	0.84	0.31	1.15
AD-53828.1	0.17	0.51	0.23	0.55	0.17	1.14
AD-53829.1	0.06	0.71	0.21	0.58	0.24	1.21
AD-53830.1	0.07	0.27	0.06	0.30	0.15	0.43
AD-53831.1	0.09	0.56	0.21	0.39	0.16	0.95
AD-53832.1	0.08	0.52	0.26	0.31	0.11	0.76
AD-53833.1	1.04	1.05	0.74	1.24	0.60	1.58
AD-53834.1	0.70	1.14	0.71	0.85	0.38	1.47
AD-53835.1	0.11	0.43	0.33	0.35	0.09	0.53
PBS	0.67	1.13	0.90	0.90	0.99	0.99

Table 5. PCSK9 IC_{50} values for selected duplexes by free uptake in *Cynomologous* monkey cells and by transfection in the Hep3B human cell line.

	Transfection	Free uptake
Duplex	IC50, nM	IC50, nM
AD-53806.1	0.07	18.00
AD-53748.1	0.06	16.88
AD-53815.1	0.05	39.21
AD-53809.1	0.05	571.00
AD-53821.1	0.05	55.41
AD-53830.1	0.08	ND
AD-53754.1	0.25	67.42
AD-53800.1	0.30	ND
AD-53798.1	0.04	ND
AD-53789.1	0.37	ND
AD-48400.4	0.23	ND

[0436] AD-48400 was also assayed for *in vivo* efficacy in female mice carrying a human PCSK9 transgene randomly inserted into the genome without disruption of the endogenous PCSK9 gene. Briefly, mice were injected subcutaneously with a single 20 mg/kg dose at Day 0, a single 100 mg/kg dose at Day 0, and five 20 mg/kg doses at Days 0, 1, 2, 3, 4, and 5. Serum was collected at Days -6, -3, 0, 1, 2, 3, 4, and 7 and the amount of PCSK9 protein was determined by ELISA assay. The results of these analyses are depicted in Figure 2 and show that there is a dose response effect with AD-48400 conjugated to GalNAc at all three dosages tested.

[0437] The six most efficacious duplexes ideintified by the *in vitro* screens described above, were evaluated for *in vivo* efficacy and duration of response. Transgenic PCSK9 mice were injected at Days 0, 1, 2, 3, and 4 with either 5 mg/kg or 25 mg/kg of AD-48400, AD-53830, AD-53806, AD-53815, AD-53748, or AD-53798. Serum PCSK9 protein levels were determined by ELISA on Days -3, 0, 1, 2, 3, 4, 8, 11. 15. 18, 22, 26, 31, and 36. The results are depicted in Figures 3A and 3B.

Example 3. Lead Optimization.

[0438] Based on the efficacy assays described in Example 2 above, PCSK9 siRNAs based on the parent sequences of AD-53815 and AD-53806 with a variety of chemical modifications were evaluated for efficacy in free uptake assays in primary *Cynomolgous* monkey hepatocytes (PCH) at 200nM, 20nM, 2nM, and 0.2nM. For all doses other than 0.2nM dose, assays were performed twice and data are expressed as the average fraction message remaining relative to control. The 0.2nM dose was assayed a single time. The results of these assays are shown in Table 6.

Table 6. Efficacy screens for lead optimization of AD-53815 and AD-53806 by free uptake in *Cynomolgous* monkey hepatocytes.

Parent duplex	Duplex ID	200nM Avg	20nM Avg	2nM Avg	0.2nM-384	200nM SD	20nM SD	2nM SD
AD-53815	AD-53815.5	0.45	0.48	0.74	0.95	0.05	0.00	0.05
AD-53815	AD-53815.4	0.43	0.54	0.84	0.83	0.00	0.04	0.10
AD-53815	AD-56633.1	0.33	0.52	0.82	0.88	0.04	0.01	0.10
AD-53815	AD-56617.1	0.40	0.65	0.91	1.06	0.03	0.02	0.03
AD-53815	AD-56623.1	0.52	0.61	0.87	1.05	0.03	0.04	0.21
AD-53815	AD-56629.1	0.50	0.62	0.87	1.05	0.04	0.13	0.17
AD-53815	AD-56635.1	0.45	0.71	0.92	1.03	0.03	0.02	0.03
AD-53815	AD-56641.1	0.47	0.73	0.84	1.04	0.04	0.00	0.17
AD-53815	AD-56625.1	0.49	0.55	0.82	1.12	0.01	0.16	0.16
AD-53815	AD-56631.1	0.48	0.57	0.82	1.05	0.04	0.11	0.06
AD-53815	AD-56637.1	0.48	0.58	0.76	1.01	0.01	0.14	0.13
AD-53815	AD-56643.1	0.59	0.77	0.93	1.04	0.05	0.01	0.04
AD-53815	AD-56649.1	0.76	0.87	0.95	1.06	0.02	0.07	0.14
AD-53815	AD-56655.1	0.73	0.86	0.85	0.96	0.01	0.04	0.11
AD-53815	AD-56615.1	0.58	0.70	0.92	0.98	0.00	0.02	0.03
AD-53815	AD-56621.1	0.71	0.76	0.93	0.95	0.18	0.07	0.07
AD-53815	AD-56627.1	0.58	0.72	0.93	0.94	0.01	0.08	0.02
AD-53815	AD-56639.1	0.52	0.57	0.72	0.94	0.16	0.00	0.04
AD-53815	AD-56645.1	0.32	0.49	0.74	0.88	0.03	0.03	0.14
AD-53815	AD-56651.1	0.71	0.94	0.88	0.88	0.08	0.29	0.12
AD-53815	AD-56610.1	0.31	0.57	0.82	0.93	0.02	0.01	0.04
AD-53815	AD-56616.1	0.47	0.68	0.70	1.01	0.06	0.08	0.34
AD-53815	AD-56622.1	0.47	0.66	0.88	0.95	0.06	0.10	0.10
AD-53815	AD-56628.1	1.02	1.15	1.04	0.99	0.00	0.12	0.02
AD-53815	AD-56634.1	0.75	0.90	0.97	1.03	0.11	0.04	0.07
AD-53815	AD-56640.1	0.58	0.76	0.81	1.01	0.10	0.05	0.12
AD-53815	AD-56646.1	0.77	0.94	0.82	0.99	0.09	0.12	0.14
AD-53815	AD-56652.1	0.61	0.74	0.78	0.89	0.00	0.00	0.03
AD-53815	AD-56611.1	0.93	1.02	1.16	0.89	0.05	0.15	0.05
AD-53815	AD-56647.1	0.38	0.58	0.79	0.94	0.05	0.08	0.00
AD-53815	AD-56653.1	0.47	0.46	0.63	0.84	0.12	0.04	0.04

(continued)

Parent duplex	Duplex ID	200nM Avg	20nM Avg	2nM Avg	0.2nM-384	200nM SD	20nM SD	2nM SD
AD-53815	AD-56612.1	0.41	0.61	0.88	0.85	0.03	0.09	0.09
AD-53815	AD-56618.1	0.64	0.60	1.03	1.08	0.21	0.09	0.01
AD-53815	AD-56624.1	0.46	0.61	0.85	1.05	0.04	0.17	0.15
AD-53815	AD-56630.1	0.49	0.69	0.87	1.01	0.01	0.00	0.15
AD-53815	AD-56636.1	0.49	0.57	0.82	1.13	0.01	0.05	0.03
AD-53815	AD-56642.1	0.43	0.55	0.82	1.09	0.00	0.08	0.03
AD-53815	AD-56648.1	0.48	0.66	0.80	0.96	0.00	0.04	0.08
AD-53815	AD-56654.1	0.43	0.53	0.72	0.84	0.01	0.00	0.07
AD-53815	AD-56613.1	0.54	0.61	0.81	0.91	0.16	0.08	0.19
AD-53815	AD-56619.1	0.55	0.67	1.02	1.06	0.04	0.07	0.07
AD-53815	AD-56614.1	0.42	0.56	0.86	0.90	0.05	0.04	0.10
AD-53815	AD-56620.1	0.41	0.52	0.85	0.84	0.01	0.12	0.08
AD-53815	AD-56626.1	0.59	0.68	0.90	1.12	0.01	0.03	0.10
AD-53815	AD-56632.1	0.60	0.73	0.91	1.05	0.04	0.09	0.10
AD-53815	AD-56638.1	0.68	0.89	0.94	1.19	0.03	0.03	0.18
AD-53815	AD-56644.1	0.84	0.89	1.09	1.09	0.08	0.08	0.06
AD-53815	AD-56650.1	0.86	0.95	1.05	1.05	0.10	0.01	0.10
AD-53815	AD-56656.1	0.53	0.64	0.92	0.88	0.09	0.04	0.14
AD-53815	AD-56662.1	0.55	0.61	0.96	1.03	0.02	0.09	0.01
AD-53815	AD-56668.1	0.76	0.79	0.99	1.10	0.07	0.11	0.06
AD-53815	AD-56673.1	0.81	0.87	1.12	1.09	0.01	0.15	0.13
AD-53815	AD-56678.1	0.84	0.76	1.12	1.05	0.04	0.24	0.05
AD-53815	AD-56683.1	0.88	0.93	1.08	1.06	0.05	0.10	0.06
AD-53815	AD-56688.1	0.80	0.86	0.93	0.99	0.10	0.11	0.19
AD-53815	AD-56657.1	0.45	0.63	0.84	0.88	0.20	0.04	0.09
AD-53815	AD-56663.1	0.35	0.49	0.77	1.03	0.00	0.07	0.04
AD-53815	AD-56669.1	0.53	0.68	0.99	1.11	0.00	0.18	0.03
AD-53815	AD-56674.1	0.44	0.64	0.84	1.03	0.06	0.01	0.17
AD-53815	AD-56679.1	0.52	0.67	0.77	1.01	0.01	0.06	0.14
AD-53815	AD-56684.1	0.43	0.59	0.84	1.08	0.01	0.03	0.04
AD-53815	AD-56689.1	0.55	0.57	0.73	0.95	0.09	0.01	0.11
AD-53815	AD-56693.1	0.45	0.48	0.65	0.84	0.04	0.02	0.11
AD-53815	AD-56658.1	0.46	0.55	0.85	0.84	0.21	0.09	0.07
AD-53815	AD-56664.1	0.35	0.60	0.80	0.91	0.13	0.03	0.14
AD-53815	AD-56670.1	0.62	0.61	0.90	1.11	0.17	0.06	0.00
AD-53815	AD-56680.1	0.74	0.90	1.00	0.91	0.05	0.01	0.05
AD-53815	AD-56685.1	0.64	0.64	0.77	1.07	0.15	0.01	0.15

(continued)

Parent duplex	Duplex ID	200nM Avg	20nM Avg	2nM Avg	0.2nM-384	200nM SD	20nM SD	2nM SD
AD-53815	AD-56690.1	0.39	0.61	0.75	0.97	0.13	0.03	0.08
AD-53815	AD-56694.1	0.41	0.53	0.67	0.94	0.01	0.00	0.04
AD-53815	AD-56659.1	0.57	0.58	0.84	0.95	0.25	0.09	0.05
AD-53815	AD-56665.1	0.38	0.51	0.78	1.01	0.05	0.07	0.17
AD-53815	AD-56671.1	0.32	0.45	0.78	0.94	0.03	0.05	0.01
AD-53815	AD-56676.1	0.31	0.55	0.81	1.02	0.03	0.13	0.02
AD-53815	AD-56681.1	0.54	0.75	0.88	1.02	0.02	0.07	0.11
AD-53815	AD-56686.1	0.50	0.74	0.86	1.03	0.01	0.10	0.10
AD-53815	AD-56691.1	0.44	0.56	0.79	1.03	0.01	0.00	0.05
AD-53815	AD-56695.1	0.37	0.70	0.67	0.89	0.01	0.29	0.11
AD-53815	AD-56660.1	0.36	0.73	0.83	0.93	0.02	0.22	0.10
AD-53815	AD-56666.1	0.39	0.47	0.74	0.94	0.02	0.05	0.13
AD-53815	AD-56672.1	0.63	0.55	0.87	1.03	0.25	0.10	0.04
AD-53815	AD-56677.1	0.54	0.70	0.85	0.99	0.24	0.11	0.00
AD-53815	AD-56682.1	0.48	0.57	0.90	0.96	0.11	0.09	0.05
AD-53815	AD-56687.1	0.81	0.94	1.06	1.08	0.07	0.02	0.05
AD-53815	AD-56692.1	0.45	0.64	0.73	0.95	0.03	0.13	0.05
AD-53815	AD-56696.1	0.40	0.48	0.66	0.95	0.01	0.04	0.06
AD-53815	AD-56661.1	0.52	0.54	0.75	0.98	0.22	0.06	0.04
AD-53815	AD-56667.1	0.40	0.68	0.87	1.03	0.03	0.03	0.11
AD-53806	AD-53806.11	0.28	0.44	0.74	0.98	0.05	0.01	0.13
AD-53806	AD-53806.13	0.31	0.36	0.65	0.92	0.01	0.08	0.06
AD-53806	AD-53806.12	0.53	0.56	0.70	1.04	0.00	0.01	0.15
AD-53806	AD-53806.5	0.34	0.54	0.85	0.87	0.01	0.00	0.10
AD-53806	AD-53806.6	0.41	0.51	0.77	0.91	0.05	0.04	0.08
AD-53806	AD-53806.7	0.39	0.58	0.75	0.97	0.02	0.16	0.14
AD-53806	AD-53806.8	0.35	0.49	0.69	0.91	0.06	0.03	0.09
AD-53806	AD-53806.9	0.36	0.55	0.77	1.01	0.04	0.07	0.13
AD-53806	AD-53806.10	0.29	0.44	0.73	0.93	0.04	0.10	0.14
AD-53806	AD-56979.1	0.43	0.50	0.78	0.96	0.01	0.03	0.11
AD-53806	AD-56979.2	0.32	0.47	0.65	1.02	0.02	0.11	0.05
AD-53806	AD-56975.3	0.27	0.57	0.72	0.83	0.01	0.16	0.08
AD-53806	AD-56975.4	0.55	0.67	0.81	0.92	0.11	0.10	0.04
AD-53806	AD-56975.5	0.34	0.54	0.71	0.94	0.04	0.22	0.10
AD-53806	AD-56975.1	0.38	0.53	0.74	0.93	0.13	0.14	0.02
AD-53806	AD-56975.2	0.50	0.62	0.82	0.98	0.09	0.16	0.11
AD-53806	AD-56983.1	0.49	0.72	0.89	1.11	0.10	0.09	0.21

(continued)

Parent duplex	Duplex ID	200nM Avg	20nM Avg	2nM Avg	0.2nM-384	200nM SD	20nM SD	2nM SD
AD-53806	AD-56983.2	0.74	0.89	1.14	1.16	0.10	0.06	0.02
AD-53806	AD-56983.3	0.91	1.05	1.02	1.04	0.09	0.10	0.08
AD-53806	AD-56983.4	0.40	0.57	0.83	1.05	0.03	0.02	0.08
AD-53806	AD-56983.5	0.33	0.51	0.83	0.90	0.03	0.04	0.03
AD-53806	AD-56977.3	0.44	0.49	0.62	0.95	0.17	0.16	0.06
AD-53806	AD-56977.1	0.27	0.58	0.81	0.88	0.06	0.07	0.08
AD-53806	AD-56977.2	0.41	0.60	0.81	0.90	0.01	0.07	0.12
AD-53806	AD-56976.1	0.40	0.64	0.85	0.90	0.14	0.21	0.01
AD-53806	AD-56976.2	0.37	0.47	0.70	1.01	0.09	0.10	0.13
AD-53806	AD-56980.1	0.47	0.54	0.83	0.97	0.12	0.02	0.14
AD-53806	AD-56980.2	0.44	0.55	0.81	1.08	0.15	0.11	0.08
AD-53806	AD-56984.1	0.41	0.63	0.81	1.08	0.04	0.07	0.14
AD-53806	AD-56984.2	0.32	0.58	0.86	1.04	0.02	0.17	0.07
AD-53806	AD-56987.1	0.37	0.63	0.82	1.11	0.08	0.08	0.05
AD-53806	AD-56987.2	0.33	0.59	0.79	1.02	0.05	0.05	0.13
AD-53806	AD-56991.1	0.36	0.57	0.73	1.08	0.01	0.07	0.18
AD-53806	AD-56993.1	0.41	0.54	0.75	0.99	0.12	0.09	0.06
AD-53806	AD-56995.1	0.35	0.45	0.67	1.00	0.07	0.02	0.12
AD-53806	AD-56978.1	0.35	0.67	0.88	0.91	0.04	0.22	0.05
AD-53806	AD-56978.2	0.47	0.55	0.78	1.12	0.03	0.01	0.07
AD-53806	AD-56981.1	0.45	0.65	0.86	1.08	0.01	0.16	0.15
AD-53806	AD-56985.1	0.53	0.61	1.08	1.14	0.02	0.09	0.07
AD-53806	AD-56988.1	0.62	0.81	0.91	1.13	0.01	0.05	0.20
AD-53806	AD-56988.2	0.76	0.94	0.85	1.14	0.17	0.10	0.11
AD-53806	AD-56988.3	0.55	0.79	0.86	1.19	0.04	0.05	0.16
AD-53806	AD-56982.1	0.40	0.65	0.84	1.07	0.04	0.10	0.09
AD-53806	AD-56982.2	0.38	0.50	0.70	1.01	0.03	0.03	0.08
AD-53806	AD-56986.1	0.45	0.57	0.80	1.12	0.02	0.11	0.15
AD-53806	AD-56986.2	0.49	0.59	0.79	1.04	0.01	0.05	0.17
AD-53806	AD-56989.1	0.69	0.84	0.95	1.12	0.08	0.06	0.12
AD-53806	AD-56990.1	0.49	0.56	0.79	1.08	0.03	0.02	0.13
AD-53806	AD-56992.1	0.61	0.70	0.90	1.14	0.01	0.04	0.14
AD-53806	AD-56992.2	0.48	0.63	0.87	0.99	0.05	0.10	0.07
AD-53806	AD-56994.1	0.88	0.89	0.97	1.11	0.02	0.06	0.13
AD-53806	AD-56994.2	0.34	0.42	0.73	0.98	0.01	0.05	0.05
AD-53806	AD-56996.1	0.50	0.59	0.77	0.95	0.07	0.12	0.10
AD-53806	AD-57001.1	0.44	0.54	0.77	1.08	0.01	0.05	0.12

(continued)

Parent duplex	Duplex ID	200nM Avg	20nM Avg	2nM Avg	0.2nM-384	200nM SD	20nM SD	2nM SD
AD-53806	AD-57007.1	0.62	0.68	0.91	1.11	0.04	0.02	0.19
AD-53806	AD-57013.1	0.65	0.78	0.94	1.17	0.05	0.04	0.22
AD-53806	AD-57019.1	0.57	0.74	0.87	1.14	0.01	0.09	0.13
AD-53806	AD-57022.1	0.46	0.48	0.72	0.98	0.14	0.01	0.17
AD-53806	AD-57025.1	0.37	0.47	0.68	0.92	0.04	0.11	0.06
AD-53806	AD-56997.1	0.41	0.56	0.77	0.88	0.00	0.10	0.09
AD-53806	AD-57002.1	0.46	0.58	0.81	1.04	0.03	0.03	0.08
AD-53806	AD-57008.1	0.68	0.75	0.91	1.13	0.02	0.03	0.15
AD-53806	AD-57014.1	0.80	0.82	0.99	1.17	0.02	0.01	0.12
AD-53806	AD-57020.1	0.51	0.53	0.81	1.07	0.17	0.03	0.07
AD-53806	AD-57020.2	0.37	0.46	0.68	1.02	0.04	0.07	0.13
AD-53806	AD-57026.1	0.34	0.51	0.68	0.97	0.01	0.08	0.06
AD-53806	AD-57003.1	0.76	0.90	0.94	1.11	0.02	0.16	0.11
AD-53806	AD-57009.1	0.81	0.88	0.93	0.98	0.01	0.03	0.10
AD-53806	AD-57015.1	0.72	0.92	0.90	1.04	0.01	0.05	0.15
AD-53806	AD-57023.1	0.41	0.50	0.75	1.00	0.08	0.07	0.06
AD-53806	AD-57027.1	0.38	0.46	0.68	0.93	0.11	0.00	0.07
AD-53806	AD-56998.1	0.45	0.57	0.94	0.98	0.01	0.06	0.11
AD-53806	AD-57004.1	0.39	0.61	0.80	1.13	0.03	0.04	0.13
AD-53806	AD-57010.1	0.43	0.64	0.81	1.00	0.01	0.07	0.15
AD-53806	AD-57016.1	0.44	0.71	0.80	0.97	0.01	0.25	0.05
AD-53806	AD-56999.2	0.49	0.60	0.69	1.04	0.04	0.02	0.16
AD-53806	AD-56999.1	0.39	0.55	0.68	0.96	0.01	0.09	0.10
AD-53806	AD-57021.1	0.40	0.58	0.71	1.02	0.03	0.03	0.11
AD-53806	AD-57024.1	0.41	0.49	0.68	1.02	0.14	0.00	0.10
AD-53806	AD-57005.1	0.45	0.56	0.87	1.06	0.03	0.03	0.20
AD-53806	AD-57011.1	0.53	0.63	0.92	1.02	0.02	0.07	0.10
AD-53806	AD-57017.1	0.48	0.60	0.81	1.07	0.00	0.01	0.12
AD-53806	AD-57000.2	0.50	0.60	0.74	0.93	0.04	0.01	0.02
AD-53806	AD-57000.3	0.54	0.49	0.72	0.97	0.22	0.08	0.00
AD-53806	AD-57000.1	0.70	0.76	0.80	0.95	0.02	0.05	0.04
AD-53806	AD-57006.2	0.48	0.75	0.76	0.94	0.00	0.31	0.12
AD-53806	AD-57006.3	0.45	0.57	0.71	0.98	0.08	0.09	0.12
AD-53806	AD-57006.1	0.64	0.76	0.84	0.97	0.00	0.11	0.10
AD-53806	AD-57012.1	0.53	0.83	0.79	0.93	0.04	0.42	0.02
AD-53806	AD-57018.1	0.67	0.73	0.72	0.93	0.07	0.04	0.03

[0439] siRNAs with a variety of chemical modifications based on the parent sequences of AD-53815 and AD-53806 were also screened for *in vitro* efficacy by transfection in Hep3B cells at 10nM and 0.1nM. The results of this structure-activity relationship screen are shown in Table 7, and are expressed as the average fraction message remaining relative to control +/- SD.

Table 7. Efficacy screens for lead optimization of AD-53815 and AD-53806 by transfection in a human cells.

Parent duplex	Duplex ID	Trans 10nM Avg	Trans 10nM SD	Trans 0.1nM Avg	Trans 0.1nM SD
AD-53815	AD-53815.5	0.14	0.05	0.24	ND
AD-53815	AD-53815.4	0.18	0.07	0.38	ND
AD-53815	AD-56633.1	0.18	0.10	0.24	ND
AD-53815	AD-56617.1	0.13	0.06	0.25	ND
AD-53815	AD-56623.1	0.14	0.05	0.24	ND
AD-53815	AD-56629.1	0.14	0.02	0.17	ND
AD-53815	AD-56635.1	0.12	0.02	0.22	ND
AD-53815	AD-56641.1	0.15	0.01	0.16	ND
AD-53815	AD-56625.1	0.12	0.03	0.29	ND
AD-53815	AD-56631.1	0.13	0.01	0.20	ND
AD-53815	AD-56637.1	0.22	0.14	0.16	ND
AD-53815	AD-56643.1	0.18	0.08	0.16	ND
AD-53815	AD-56649.1	0.16	0.00	0.19	ND
AD-53815	AD-56655.1	0.24	0.11	0.24	ND
AD-53815	AD-56615.1	0.15	0.00	0.32	ND
AD-53815	AD-56621.1	0.20	0.07	0.41	ND
AD-53815	AD-56627.1	0.17	0.04	0.31	ND
AD-53815	AD-56639.1	0.19	0.08	0.24	ND
AD-53815	AD-56645.1	0.19	0.09	0.27	ND
AD-53815	AD-56651.1	0.29	0.09	0.68	ND
AD-53815	AD-56610.1	0.21	0.11	0.23	ND
AD-53815	AD-56616.1	0.16	0.04	0.29	ND
AD-53815	AD-56622.1	0.18	0.07	0.36	ND
AD-53815	AD-56628.1	0.28	0.07	0.60	ND
AD-53815	AD-56634.1	0.16	0.04	0.29	ND
AD-53815	AD-56640.1	0.21	0.09	0.26	ND
AD-53815	AD-56646.1	0.27	0.21	0.37	ND
AD-53815	AD-56652.1	0.26	0.08	0.29	ND
AD-53815	AD-56611.1	0.35	0.11	0.96	ND
AD-53815	AD-56647.1	0.17	0.09	0.13	ND
AD-53815	AD-56653.1	0.17	0.09	0.28	ND
AD-53815	AD-56612.1	0.17	0.07	0.24	ND
AD-53815	AD-56618.1	0.14	0.00	0.26	ND
AD-53815	AD-56624.1	0.15	0.02	0.27	ND
AD-53815	AD-56630.1	0.13	0.01	0.24	ND

(continued)

Parent duplex	Duplex ID	Trans 10nM Avg	Trans 10nM SD	Trans 0.1nM Avg	Trans 0.1nM SD
AD-53815	AD-56636.1	0.17	0.08	0.22	ND
AD-53815	AD-56642.1	0.12	0.03	0.13	ND
AD-53815	AD-56648.1	0.15	0.05	0.21	ND
AD-53815	AD-56654.1	0.22	0.10	0.24	ND
AD-53815	AD-56613.1	0.17	0.07	0.40	ND
AD-53815	AD-56619.1	0.21	0.12	0.30	ND
AD-53815	AD-56614.1	0.12	0.01	0.23	ND
AD-53815	AD-56620.1	0.12	0.02	0.15	ND
AD-53815	AD-56626.1	0.14	0.03	0.20	ND
AD-53815	AD-56632.1	0.12	0.02	0.21	ND
AD-53815	AD-56638.1	0.15	0.10	0.23	ND
AD-53815	AD-56644.1	0.23	0.11	0.17	ND
AD-53815	AD-56650.1	0.13	0.03	0.20	ND
AD-53815	AD-56656.1	0.26	0.03	0.27	ND
AD-53815	AD-56662.1	0.13	0.06	0.18	ND
AD-53815	AD-56668.1	0.19	0.05	0.20	ND
AD-53815	AD-56673.1	0.18	0.05	0.21	ND
AD-53815	AD-56678.1	0.17	0.00	0.20	ND
AD-53815	AD-56683.1	0.29	0.22	0.27	ND
AD-53815	AD-56688.1	0.19	0.02	0.18	ND
AD-53815	AD-56657.1	0.18	0.14	0.34	ND
AD-53815	AD-56663.1	0.11	0.04	0.18	ND
AD-53815	AD-56669.1	0.11	0.02	0.31	ND
AD-53815	AD-56674.1	0.14	0.00	0.21	ND
AD-53815	AD-56679.1	0.14	0.05	0.19	ND
AD-53815	AD-56684.1	0.14	0.03	0.19	ND
AD-53815	AD-56689.1	0.18	0.09	0.18	ND
AD-53815	AD-56693.1	0.19	0.11	0.21	ND
AD-53815	AD-56658.1	0.19	0.13	0.30	ND
AD-53815	AD-56664.1	0.15	0.07	0.20	ND
AD-53815	AD-56670.1	0.18	0.10	0.26	ND
AD-53815	AD-56680.1	0.27	0.05	0.31	ND
AD-53815	AD-56685.1	0.14	0.02	0.28	ND
AD-53815	AD-56690.1	0.10	0.03	0.18	ND
AD-53815	AD-56694.1	0.15	0.06	0.17	ND
AD-53815	AD-56659.1	0.16	0.04	0.27	ND
AD-53815	AD-56665.1	0.14	0.06	0.26	ND
AD-53815	AD-56671.1	0.11	0.01	0.29	ND

(continued)

Parent duplex	Duplex ID	Trans 10nM Avg	Trans 10nM SD	Trans 0.1nM Avg	Trans 0.1nM SD
AD-53815	AD-56676.1	0.14	0.06	0.20	ND
AD-53815	AD-56681.1	0.15	0.03	0.30	ND
AD-53815	AD-56686.1	0.15	0.03	0.26	ND
AD-53815	AD-56691.1	0.11	0.02	0.16	ND
AD-53815	AD-56695.1	0.14	0.06	0.24	ND
AD-53815	AD-56660.1	0.10	0.03	0.37	ND
AD-53815	AD-56666.1	0.18	0.13	0.22	ND
AD-53815	AD-56672.1	0.14	0.02	0.35	ND
AD-53815	AD-56677.1	0.15	0.04	0.23	ND
AD-53815	AD-56682.1	0.14	0.06	0.28	ND
AD-53815	AD-56687.1	0.24	0.01	0.53	ND
AD-53815	AD-56692.1	0.09	0.01	0.36	ND
AD-53815	AD-56696.1	0.16	0.09	0.26	ND
AD-53815	AD-56661.1	0.21	0.15	0.48	ND
AD-53815	AD-56667.1	0.22	0.16	0.26	ND
AD-53806	AD-53806.11	0.19	0.05	0.25	0.06
AD-53806	AD-53806.13	0.21	0.07	0.21	0.16
AD-53806	AD-53806.12	0.21	0.08	0.21	0.02
AD-53806	AD-53806.5	0.22	0.01	0.29	0.06
AD-53806	AD-53806.6	0.24	0.07	0.33	0.12
AD-53806	AD-53806.7	0.19	0.02	0.24	0.11
AD-53806	AD-53806.8	0.20	0.01	0.23	0.05
AD-53806	AD-53806.9	0.22	0.01	0.19	0.06
AD-53806	AD-53806.10	0.17	0.01	0.21	0.07
AD-53806	AD-56979.1	0.18	0.00	0.29	0.14
AD-53806	AD-56979.2	0.24	0.11	0.24	0.12
AD-53806	AD-56975.3	0.26	0.09	0.28	0.18
AD-53806	AD-56975.4	0.35	0.02	0.50	0.23
AD-53806	AD-56975.5	0.17	0.01	0.21	0.18
AD-53806	AD-56975.1	0.24	0.09	0.32	0.12
AD-53806	AD-56975.2	0.19	0.04	0.16	0.02
AD-53806	AD-56983.1	0.17	0.01	0.32	0.18
AD-53806	AD-56983.2	0.28	0.07	0.63	0.15
AD-53806	AD-56983.3	1.22	0.61	0.83	0.02
AD-53806	AD-56983.4	0.25	0.10	0.24	0.10
AD-53806	AD-56983.5	0.17	0.01	0.26	0.15
AD-53806	AD-56977.3	0.31	0.11	0.28	0.23
AD-53806	AD-56977.1	0.22	0.04	0.34	0.12

(continued)

Parent duplex	Duplex ID	Trans 10nM Avg	Trans 10nM SD	Trans 0.1nM Avg	Trans 0.1nM SD
AD-53806	AD-56977.2	0.22	0.05	0.29	0.16
AD-53806	AD-56976.1	0.21	0.09	0.34	0.20
AD-53806	AD-56976.2	0.17	0.03	0.25	0.04
AD-53806	AD-56980.1	0.22	0.04	0.20	0.02
AD-53806	AD-56980.2	0.19	0.01	0.20	0.06
AD-53806	AD-56984.1	0.24	0.11	0.22	0.10
AD-53806	AD-56984.2	0.19	0.01	0.21	0.10
AD-53806	AD-56987.1	0.19	0.05	0.29	0.19
AD-53806	AD-56987.2	0.24	0.03	0.24	0.09
AD-53806	AD-56991.1	0.17	0.01	0.17	0.08
AD-53806	AD-56993.1	0.14	0.09	0.22	0.06
AD-53806	AD-56995.1	0.19	0.07	0.27	0.13
AD-53806	AD-56978.1	0.27	0.12	0.36	0.12
AD-53806	AD-56978.2	0.24	0.03	0.20	0.01
AD-53806	AD-56981.1	0.22	0.03	0.28	0.17
AD-53806	AD-56985.1	0.21	0.00	0.28	0.04
AD-53806	AD-56988.1	0.20	0.02	0.24	0.02
AD-53806	AD-56988.2	0.20	0.03	0.27	0.13
AD-53806	AD-56988.3	0.23	0.03	0.27	0.01
AD-53806	AD-56982.1	0.23	0.06	0.24	0.00
AD-53806	AD-56982.2	0.21	0.06	0.18	0.07
AD-53806	AD-56986.1	0.23	0.05	0.20	0.06
AD-53806	AD-56986.2	0.24	0.04	0.25	0.13
AD-53806	AD-56989.1	0.31	0.02	0.43	0.00
AD-53806	AD-56990.1	0.27	0.00	0.28	0.10
AD-53806	AD-56992.1	0.27	0.06	0.31	0.01
AD-53806	AD-56992.2	0.22	0.10	0.30	0.14
AD-53806	AD-56994.1	0.97	0.05	0.85	0.09
AD-53806	AD-56994.2	0.22	0.09	0.26	0.01
AD-53806	AD-56996.1	0.18	0.04	0.31	0.08
AD-53806	AD-57001.1	0.24	0.09	0.23	0.08
AD-53806	AD-57007.1	0.25	0.01	0.27	0.03
AD-53806	AD-57013.1	0.30	0.08	0.33	0.02
AD-53806	AD-57019.1	0.29	0.03	0.28	0.02
AD-53806	AD-57022.1	0.20	0.06	0.21	0.05
AD-53806	AD-57025.1	0.23	0.12	0.25	0.15
AD-53806	AD-56997.1	0.20	0.05	0.25	0.11
AD-53806	AD-57002.1	0.21	0.07	0.28	0.01

(continued)

Parent duplex	Duplex ID	Trans 10nM Avg	Trans 10nM SD	Trans 0.1nM Avg	Trans 0.1nM SD
AD-53806	AD-57008.1	0.26	0.01	0.31	0.01
AD-53806	AD-57014.1	0.32	0.03	0.43	0.05
AD-53806	AD-57020.1	0.19	0.00	0.23	0.01
AD-53806	AD-57020.2	0.20	0.08	0.28	0.22
AD-53806	AD-57026.1	0.34	0.24	0.37	0.24
AD-53806	AD-57003.1	0.34	0.04	0.45	0.15
AD-53806	AD-57009.1	0.30	0.07	0.40	0.02
AD-53806	AD-57015.1	0.32	0.01	0.47	0.04
AD-53806	AD-57023.1	0.17	0.06	0.27	0.13
AD-53806	AD-57027.1	0.20	0.03	0.19	0.11
AD-53806	AD-56998.1	0.23	0.09	0.29	0.24
AD-53806	AD-57004.1	0.24	0.13	0.30	0.12
AD-53806	AD-57010.1	0.23	0.09	0.23	0.11
AD-53806	AD-57016.1	0.21	0.03	0.23	0.06
AD-53806	AD-56999.2	0.25	0.10	0.35	0.05
AD-53806	AD-56999.1	0.24	0.08	0.28	0.21
AD-53806	AD-57021.1	0.18	0.04	0.29	0.17
AD-53806	AD-57024.1	0.20	0.09	0.28	0.11
AD-53806	AD-57005.1	0.18	0.10	0.29	0.17
AD-53806	AD-57011.1	0.21	0.07	0.26	0.12
AD-53806	AD-57017.1	0.20	0.07	0.29	0.21
AD-53806	AD-57000.2	0.20	0.04	0.29	0.21
AD-53806	AD-57000.3	0.22	0.11	0.30	0.16
AD-53806	AD-57000.1	0.25	0.14	0.38	0.33
AD-53806	AD-57006.2	0.22	0.14	0.31	0.18
AD-53806	AD-57006.3	0.19	0.09	0.31	0.25
AD-53806	AD-57006.1	0.20	0.12	0.41	0.29
AD-53806	AD-57012.1	0.16	0.05	0.36	0.17
AD-53806	AD-57018.1	0.20	0.37	0.10	0.14

[0440] To determine whether any of the siRNAs from the *in vitro* SAR screen are more effective at silencing PCSK9 than the parent siRNA (AD-53815) PCSK9 transgenic mice were administered a single 3 mg/kg dose of the siRNAs shown in Figure 4, and 72 hours post-dosing, PCSK9 protein levels were determined by ELISA assay. The results, shown in Figure 5, demonstrate that AD-57928 is surpringly effective at silencing PCSK9. Figure 6 shows that, not only does a single dose of AD-57928 effectively knock-down PCSK9 protein, but there is also a dose response using AD-57928.

Example 4. Split Dosing Study Using AD-57928

[0441] The ability of AD-57928 to suppress expression of PCSK9 protein was assessed by measuring levels of human PCSK9 (hPCSK9) protein in serum of hPCSK9 transgenic mice following administration of AD-57928. AD-57928 was administered subcutaneously using six different dosing schedules that included a "loading phase" during the first week (one dose of 0.5 mg/kg, 1 mg/kg or 2 mg/kg daily for 5 subsequent days), followed by a "maintenance phase" (once or

twice weekly dosing of either 0.5 mg/kg, 1 mg/kg or 2 mg/kg for 5 weeks), as is described in Table 8 below. The last dose was administered at day 38. Each dosing schedule was tested using a group of 3 mice that included two males and one female. A control group received injections with PBS.

Table 8. Dosing Schedules for administration of AD-57928

Test Article	**Week 1**		**Weeks 2-6**	
	Loading Dose (mg/kg)	Total Dose (mg/kg)	Maintenance dose (mg/kg)	Total Weekly Dose (mg/kg)
PBS	5x	0	2x	0
AD-57928	5x2	10	2x2	4
AD-57928	5x2	10	1x2	2
AD-57928	5x1	5	2x1	2
AD-57928	5x1	5	1x1	1
AD-57928	5x0.5	2.5	2x0.5	1
AD-57928	5x0.5	2.5	1x0.5	0.5

[0442] Serum was collected 3 days prior to administration of the first dose and on days 1, 4, 7, 10, 14, 17, 21, 24, 28, 31, 35, 38, 42, 45, 52, 59 and 65 after the first dose. PCSK9 protein levels in serum were assessed by ELISA assay. The results are shown in Figures 6, 7 and 8.

[0443] Reduced of hPCSK9 serum protein levels were observed 72 hours following the first dose, and were sustained through day 38. Administration of AD-57928 at the loading doses of 5x2 mg/kg, 5x1 mg/kg and 5x0.5 mg/kg resulted in ~90%, ~70% and ~60% reduction of hPCSK9 serum protein levels, respectively (see Figures 6-8). In the group dosed using the 2x maintenance dosing schedule, the reduced levels of hPCSK9 were sustained for 1 week longer than in the group dosed using the 1x maintenance dosing schedule, and returned to baseline 4 weeks after the last dose (see Figures 6-8).

Example 5. Phosphorothioate Titration

[0444] In order to determine the effect of the number and position of phosphorothioate modifications on the ability of dsRNA to inhibit the expression of PCSK9, a number of siRNAs based on the parent sequences of AD-57928, AD-53806 and AD-53830 as shown in Table 9 were prepared and tested. To determine whether any of the siRNAs are more effective at silencing PCSK9 than AD-57928, PCSK9 transgenic mice were administered a single 0.3 mg/kg dose of the siRNA in Table 9, and 72 hours post-dosing, PCSK9 protein levels were determined by ELISA assay. The results, shown in Figure 9, demonstrate that AD-57928 is surpringly effective at silencing PCSK9. AD-58893, AD-58894, AD-58896, AD-58897, AD-58898 and AD-58899 were also able to silence PCSK9 as compared to the control.

Table 9. siRNAs used in phosphorothiate titration experiment

Duplex ID	Sense Sequence	SEQ ID NO:	Antisense Sequence	SEQ ID NO:	Chemistry
AD-57928	CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	1557	asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1567	TOFFEE with 6 PS, and 3OMe on 3'end of AS
AD-58893	CfsuAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	1558	asCfaAfaAfgCfaAfaacAfgGfuCfuAfgasa	1568	TOFFEE with 3 outer PS
AD-58894	CfusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	1559	aCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsaa	1569	TOFFEE with 3 inner PS
AD-58895	CfuAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	1560	asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1570	TOFFEE with just 4 antisense PS
AD-58896	CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	1561	aCfaAfaAfgCfaAfaacAfgGfuCfuAfgaa	1571	TOFFEE with just 2 sense PS
AD-58897	CfsusAfsgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	1562	asCfsasAfaAfgCfaAfaacAfgGfuCfuAfsgsasa	1572	TOFFEE with 9 PS
AD-58898	CfsusAfsgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	1563	asCfsaAfaAfgCfsaAfaacAfsgGfuCfuAfsgsasa	1573	TOFFEE with 10PS
AD-58899	CfsusAfsgAfcCfuGfUfUfuUfgCfuUfuUfsgUfL96	1564	asCfsaAfaAfgCfsaAfaacAfsgGfuCfuAfsgsasa	1574	TOFFEE with 11PS
AD-58900	CfsasAfgCfaGfaCfAfUfuUfaUfcUfuUfuUfL96	1565	asAfsaAfaGfaUfaAfaugUfcUfgCfuUfgscsu	1575	6PS version of AD-53806
AD-58902	UfsusUfuCfuAfgAfCfCfuGfuUfuUfgCfuUfL96	1566	asAfsgCfaAfaAfcAfgguCfuAfgAfaAfasgsu	1576	6PS version of AD-53830

Example 6. Liver Drug Levels of AD-57928 and **AD-58895**

[0445] The goal of this study was to quantify siRNA levels in the liver of wild-type mice in order to define appropriate conditions for drug level screening. The siRNAs used in the experiment were AD-57928 and AD-58895 (that produced no decrease in PCSK9 protein level in Example 5). AD-58895 was used as a comparator to define timepoints at which a difference in drug level reflective of efficacy is observable.

[0446] A total of 33 C57B6 female mice were used in the experiment (3 mice per group). These mice were administered a single subcutaneous dose of either AD-57928, AD-58895 or PBS as a control. Livers were collected at 4, 24, 48, 72, 96 and 168 hours post-dose. Duplicate tissue aliquots per sample were collected, and the concentration of siRNA in the liver was measured using a newly designed antisense sequence specific qRT-PCR assay. The measured amount of AD-57928 and AD-58895 per gram of liver over time is shown in Figure 10, and the amount of AD-57928 and AD-58895 expressed as a percentage of total theretical dose is shown in Figure 11. The limit of detection (LOD) of the qRT-PCR assay was ~1 ng/ g of liver, and the assay showed good performance and accurate duplicates reproducibility. The results indicate that AD-57928 is more stable in the liver and AD-58895 is less stable, and both can be detected across all timepoints. At 7 days post dose, the level of AD-57928 is >100 fold above the LOD of the qRT-PCR assay, and the level of AD-58895 is >10 fold above LOD. The concentrations of AD-57928 and AD-58895 differ on average >10 fold according to their predicted stability and the observed efficacy. The timepoint between 72 and 120 hours post dose may be appropriate for siRNA concentration based screens.

Example 7. Optimization of AD-57928

[0447] In order to enhance the *in vivo* activity and stability of AD-57928, additional iRNA agents based on the parent sequences of AD-57928 were prepared and tested (Table 10; the "Sense" sequences in Table 10 are disclosed as SEQ ID NOS: 1653-1658, respectively, in order of appearance, and the "Antisense" sequences are disclosed as SEQ ID NOS: 1659-1664, respectively, in order of appearance; the same sense and antisense sequences disclosed in Table 10 are also disclosed in Figure 12A).

[0448] The unmodified sense and antisense sequences for AD-60212 are:

Sense - 5'- CUAGACCUGUTUUGCUUUUGU - 3' (A-122088.3; SEQ ID NO:1665); and
Antisense - 5'- ACAAAAGCAAAACAGGUCUAGAA - 3'(A-120190.19; SEQ ID NO:1666).

[0449] In general, these compounds contained fewer 2'-fluro modifications and fluoro-modified uridines were removed. The *in vitro* potency of these duplexes was tested by transfection of HeLa and Hep3b cells. As shown in Figure 12B, AD-59849, AD-59228, and AD-60212 have IC_{50} values comparable to the parent (AD-57928).

[0450] The ability of these duplexes to persist *in vivo* in the liver was also determined by administering 1 mg/kg of each duplex to wild-type mice and determining the siRNA level by quantitative PCR. As depicted in Figure 13, all of the duplexes show greater persistence in the liver than the parent duplex starting at the post-120 hours administration timepoint.

[0451] The ability of these duplexes to suppress expression of PCSK9 protein was also assessed *in vivo* by measuring levels of PCSK9 protein, LDL, HDL, total cholesterol (Tc), triglycerides (Tgs), alanine transaminase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) in the serum of non-human primates (NHP). The presence of injection site reation was also monitored. The duplexes were administered using a dosing schedule that included a "loading phase" during the first week (one dose of 2 mg/kg daily for 5 subsequent days, qdx5), followed by a "maintenance phase" (three weekly doses of 2 mg/kg for 3 weeks, qwx3), as is described in Table 11 below.

Table 10. Additional iRNA Agents.

Duplex	Sense ID	Sense	AntiSense ID	Antisense
AD-57928 (parent)	A-117428	CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	A-117429	asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa
AD-59849	A-121244	CfsusAfgAfcCfuGfUfUfuUfgcuuuuguL96	A-121239	asCfsaAfaagCfaAfaacAfgGfucuAfgsasa
AD-60688	A-120188	csusagacCfuGfuuuugcuuuuguL96	A-121239	asCfsaAfaagCfaAfaacAfgGfucuAfgsasa
AD-59223	A-120188	csusagacCfuGfuuuugcuuuuguL96	A-120190	asCfsaAfAfAfgCfaAfaAfcAfgGfuCfuagsasa
AD-60212	A-122088	csusagacCfuGfudTuugcuuuuguL96	A-120190	asCfsaAfAfAfgCfaAfaAfcAfgGfuCfuagsasa
AD-59228	A-120197	CfsusAfgAfcCfuGfUfUfuUfgCfsuUfsuUfsgsUfsL96	A-120202	asCfsaAfaAfsgCfaAfaacAfgGfuCfsuAfgsasa

Table 11. Dosing Schedules

Test Article	Group Number	N	Dose Level (mg/kg)	Dose Frequency	Cumulative dose (mg/kg)
AD-57928	1	3 females	2	qdx5+qwx3, 8 doses	16
AD-59849	2		2	qdx5+qwx3, 8 doses	16
AD-60688	3		2	qdx5+qwx3, 8 doses	16
AD-59223	4		2	qdx5+qwx3, 8 doses	16
AD-60212	5		2	qdx5+qwx3, 8 doses	16
AD-59228	6		2	qdx5+qwx3, 8 doses	16
Blood : Days -9, -6, -3, 4, 7, 10, 14, 17, 21, 24, 28, 31, 35, 42, 49, 56, 63 (first dose, Day 1) Injection site observation: Yes Readouts: PCSK9 protein, LDL, HDL, Tc, Trigs, ALT, AST, ALP					

[0452] As shown in Figures 14A and 14B, all compounds except for AD-60688 achieve greater than 80% PCSK9 silencing and individual animals in the AD-60212 group achieve greater than 90% PCSK9 silencing. Figure 15 demonstrates that, in the absence of statins, all compounds except for AD-60688 achieve 60% LDL cholesterol lowering and individual animals in the AD-59223 group achieve up to 77% LDL cholesterol lowering. Surprisingly, and as depicted in Figure 18, the indicated agents maintained cholesterol lowering 46 days following the last dose of the indicated agents. Even more surprisingly, and as depicted in Figure 19, AD-60212 and AD-59849 maintain up to 60% LDL cholesterol lowering to at least day 120 (93 days after the final dose), longer than any effect observed for an RNAi agent *in vivo,* indicating that, following a loading phase, these compounds may be administered at a frequency of once a month, once every two months, once every three months, once every four months, once every five months, or once every six months during the maintenance phase.

Example 8. Preparation of Additional AD-57928-Based PCSK9 Sequences

[0453] Additional iRNA agents based on the parent sequences of AD-57928 were prepared (see Table 12, below) and tested *in vitro* for potency by transfecting HeLa and Hep3B cells with these agents. The IC_{50} values for these agents are shown in Table 13.

Table 12. PCSK9 sequences

Duplex ID	Sense strand	Sense (5' to 3')	SEQ ID NO:	Antisense	Antisense (5' to 3')	SEQ ID NO:
AD-57928.45	A-117428.1	CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	1577	A-117429.1	asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1605
AD-60928.1	A-122701.2	CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgAfL96	1578	A-122702.2	usCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1606
AD-60929.1	A-122703.2	GfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	1579	A-122704.2	asCfsaAfaAfgCfaAfaacAfgGfuCfuAfcsusu	1607
AD-60930.1	A-122705.2	GfsasAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	1580	A-122706.2	asCfsaAfaAfgCfaAfaacAfgGfuCfuUfcsusu	1608
AD-60931.1	A-122707.3	GfsasUfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	1581	A-122708.2	asCfsaAfaAfgCfaAfaacAfgGfuCfaUfcsusu	1609
AD-60932.1	A-122707.4	GfsasUfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	1582	A-122709.2	asCfsaAfaAfgCfaAfaacAfgGfuCfaUfcsasa	1610
AD-60933.1	A-122710.2	CfsasUfcAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	1583	A-122711.2	asCfsaAfaAfgCfaAfaacAfgGfuGfaUfgsasa	1611
AD-60934.1	A-122712.2	CfsusUfcUfcCfuGfUfUfuUfgCfuUfuUfgUfL96	1584	A-122713.2	asCfsaAfaAfgCfaAfaacAfgGfaGfaAfgsasa	1612
AD-60927.1	A-122714.2	CfsusAfcUfgCfuGfUfUfuUfgCfuUfuUfgUfL96	1585	A-122715.2	asCfsaAfaAfgCfaAfaacAfgCfaGfuAfgsasa	1613
AD-57928.45	A-117428.1	CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	1586	A-117429.1	asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1614
AD-60906.1	A-117428.1	CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	1587	A-122309.1	asCfsaAfaAfgCf(Ayh)AfaacAfgGfuCfuAfgsasa	1615
AD-60907.1	A-117428.1	CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	1588	A-122310.1	asCfsaAfaAfgCfa(Ayh)aacAfgGfuCfuAfgsasa	1616
AD-60908.1	A-117428.1	CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	1589	A-122311.1	asCfsaAfaAfgCfaAf(Ayh)acAfgGfuCfuAfgsasa	1617
AD-60909.1	A-117428.1	CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	1590	A-122312.1	asCfsaAfaAfgCfaAfa(Ayh)cAfgGfuCfuAfgsasa	1618
AD-60910.1	A-117428.1	CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96 Cfsus(Ayh)(Gyh)(Ayh)(Cyh)CfuGfUfUfuUf(Gyh)Cf(Uyh) Uf(Uyh)Uf(Gyh)UfL96	1591	A-122313.1	asCfsaAfaAfgCf(Ayh)AfaacAf(Gyh)GfuCf(Uyh)Afg sasa	1619
AD-60911.1	A-122307.1	Uf(Uyh)Uf(Gyh)UfL96 (Cyh)u(Ayh)(Gyh)(Ayh)(Cyh)CfuGfUfUfuUf(Gyh)Cf(Uyh)	1592	A-117429.1	asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1620
AD-60912.1	A-122308.1	Uf(Uyh)Uf(Gyh)UfL96	1593	A-117429.1	asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1621
AD-60913.1	A-122307.1	Cfsus(Ayh)(Gyh)(Ayh)(Cyh)CfuGfUfUfuUf(Gyh)Cf(Uyh) Uf(Uyh)Uf(Gyh)UfL96	1594	A-122309.1	asCfsaAfaAfgCf(Ayh)AfaacAfgGfuCfuAfgsasa	1622
AD-60914.1	A-122307.1	Cfsus(Ayh)(Gyh)(Ayh)(Cyh)CfuGfUfUfuUf(Gyh)Cf(Uyh) Uf(Uyh)Uf(Gyh)UfL96	1595	A-122310.1	asCfsaAfaAfgCfa(Ayh)aacAfgGfuCfuAfgsasa	1623
AD-60915.1	A-122307.1	Cfsus(Ayh)(Gyh)(Ayh)(Cyh)CfuGfUfUfuUf(Gyh)Cf(Uyh) Uf(Uyh)Uf(Gyh)UfL96	1596	A-122311.1	asCfsaAfaAfgCfaAf(Ayh)acAfgGfuCfuAfgsasa	1624
AD-57928.45	A-117428.1	CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	1597	A-117429.1	asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1625

(continued)

Duplex ID	Sense strand	Sense (5' to 3')	SEQ ID NO:	Antisense	Antisense (5' to 3')	SEQ ID NO:
		Cfsus(Ayh)(Gyh)(Ayh)(Cyh)CfuGfUfUfuUf(Gyh)Cf(Uyh)				
AD-60916.1	A-122307.1	Uf(Uyh)Uf(Gyh)UfL96	1598	A-122312.1	asCfsaAfaAfgCfaAfa(Ayh)cAfgGfuCfuAfgsasa	1626
		Cfsus(Ayh)(Gyh)(Ayh)(Cyh)CfuGfUfUfuUf(Gyh)Cf(Uyh)			asCfsaAfaAfgCf(Ayh)AfaacAf(Gyh)GfuCf(Uyh)Afg	
AD-60917.1	A-122307.1	Uf(Uyh)Uf(Gyh)UfL96	1599	A-122313.1	sasa	1627
		(Cyh)u(Ayh)(Gyh)(Ayh)(Cyh)CfuGfUfUfuUf(Gyh)Cf(Uyh)				
AD-60918.1	A-122308.1	Uf(Uyh)Uf(Gyh)UfL96	1600	A-122309.1	asCfsaAfaAfgCf(Ayh)AfaacAfgGfuCfuAfgsasa	1628
		(Cyh)u(Ayh)(Gyh)(Ayh)(Cyh)CfuGfUfUfuUf(Gyh)Cf(Uyh)				
AD-60919.1	A-122308.1	Uf(Uyh)Uf(Gyh)UfL96	1601	A-122310.1	asCfsaAfaAfgCfa(Ayh)aacAfgGfuCfuAfgsasa	1629
		(Cyh)u(Ayh)(Gyh)(Ayh)(Cyh)CfuGfUfUfuUf(Gyh)Cf(Uyh)				
AD-60920.1	A-122308.1	Uf(Uyh)Uf(Gyh)UfL96	1602	A-122311.1	asCfsaAfaAfgCfaAf(Ayh)acAfgGfuCfuAfgsasa	1630
		(Cyh)u(Ayh)(Gyh)(Ayh)(Cyh)CfuGfUfUfuUf(Gyh)Cf(Uyh)				
AD-60921.1	A-122308.1	Uf(Uyh)Uf(Gyh)UfL96	1603	A-122312.1	asCfsaAfaAfgCfaAfa(Ayh)cAfgGfuCfuAfgsasa	1631
		(Cyh)u(Ayh)(Gyh)(Ayh)(Cyh)CfuGfUfUfuUf(Gyh)Cf(Uyh)			asCfsaAfaAfgCf(Ayh)AfaacAf(Gyh)GfuCf(Uyh)Afg	
AD-60922.1	A-122308.1	Uf(Uyh)Uf(Gyh)UfL96	1604	A-122313.1	sasa	1632

Table 13. IC_{50} values for the iRNA agents identified in Table 12.

Duplex ID	Hela IC_{50}(nM)	Hep3b IC_{50}(nM)
AD-57928.47	0.0026	0.0005
AD-60928.1	0.0000	0.0009
AD-60929.1	0.0010	0.0027
AD-60930.1	0.0055	0.0019
AD-60931.1	0.0028	0.0019
AD-60932.1	0.0039	0.0036
AD-60933.1	0.0349	0.1518
AD-60934.1	0.2115	0.5420
AD-60927.1	>10	-
AD-57928.45	<3.57225e-005	0.0007
AD-60906.1	0.0048	0.0007
AD-60907.1	0.0001	<3.57225e-005
AD-60908.1	0.0003	0.0072
AD-60909.1	-	0.0142
AD-60910.1	0.0001	0.0030
AD-60911.1	0.0955	0.1935
AD-60912.1	0.1834	0.4106
AD-60913.1	0.2693	0.5715
AD-60914.1	0.2292	0.4319
AD-60915.1	0.2069	0.3185
AD-57928.45	0.0057	0.0027
AD-60916.1	0.0802	0.2040
AD-60917.1	0.1420	0.0976
AD-60918.1	0.4101	0.3268
AD-60919.1	0.3202	0.5143
AD-60920.1	0.5199	0.5978
AD-60921.1	0.7969	2.0875
AD-60922.1	1.1078	1.0307

Example 9. Repeat-Dose Efficacy of AD-57928

[0454] The repeat-dose efficacy of AD-57928 in suppressing expression of PCSK9 protein was assessed *in vivo* by measuring the levels of PCSK9 protein, LDL, HDL, total cholesterol (Tc), triglycerides (Tgs), alanine transaminase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) in the serum of non-human primates (NHP). The presence of injection site reation was also monitored. AD-57928 duplexes were subcutaneously administered using the dosing schedules described in Table 14 below. Group 5 animals were re-dosed with a single 25 mg/kg dose on day 92. One additional group of animals was administered a single dose of 25 mg/kg. "2xw" is two times per week; "q2w" is once every two weeks; and "q1w" is once per week.

Table 14. Dosing Schedules

Test Article	Group Number	N	Dose Level (mg/kg)	Dose Frequency	Cumulative dose (mg)
AD-57928	1	3 females	1	2xw,12 doses	12
	2		2	2xw, 12 doses	24
	3		1	q2w, 6 doses	6
	4		2	q2w, 6 doses	12
	5		0.5	q1w, 6 doses	3
	6		1	q1w, 10 doses	10
	7		2	q1w, 10 doses	20
Blood : Days -9, -6, -3, 1 (pre-bleeds) 3-129 (efficacy bleeds) Injection site observation: Yes Readouts: PCSK9 protein, LDL, HDL, Tc, Trigs, ALT, AST, ALP					

[0455] As depicted in Figure 16A, the most effective regimen for lowering LDL was a twice weekly regimen (2xw) which achieved about a 60% reduction in LDL levels. The same cumulative dose administered less frequently was less efficacious than the twice a week regimen. Figure 16B demonstrates that the 2xw regimen achieved greater than 80% PCSK9 silencing.

[0456] Figures 17A and 17B demonstrate that a single 25 mg/kg dose of AD-57928 has the same onset of LDL and PCSK9 lowering, the same nadir of PCSK9 and LDL lowering, and equivalent rate of LDL lowering as a lower multiple-dose of 2 mg/kg AD-57928 administered two times per week (2xw). These graphs also demonstrate that there is a trend towards faster PCSK9 lowering with the single 25 mg/kg dose and that recovery of both PCSK9 levels and LDL levels starts about 20 days after nadir is reached (day 7) for the 25 mg/kg single dose. The nadir for the 25 mg/kg single dose is at Day 7.

Example 10. Tolerability of Optimized AD-57928 iRNA Agents

[0457] The additional iRNA agents prepared based on the parent sequences of AD-57928 described in Figure 12A (and Table 10) were assessed for tolerability in rats. Male rats were subcutaneously administered 225 mg/kg of the indicated iRNA agents on days 1, 8, and 15, and sacrificed and necropsied on day 16 (see Table 15). The animals were observed for any clinical symptoms on a daily basis and the body weights of the anmals were determined pre-study and weekly during the study. On day 16, blood from the animals was assessed hematologically, for coagulation and for serum chemistry; the drug metabolism and pharmacokinetics of the agents were determined using liver samples from the animals; and the heart, lungs (insufflated), kidneys, liver, spleen, testes, and first and last injection sites were analyzed for any changes. There were no changes in clinical signs, visual injection site observations, serum chemistry, coagulation or microscopic pathology of the liver, spleen lung, heart, or testes. Table 16 provides a summary of the liver weights, the final body weights, the results of the hematological analyses and the pathology severity scores for the final injection sites and kidneys for each agent tested.

Table 15. Dosing Schedules

Dose Group	TA	Dose (mg/kg)	Dose Vol. (mL/ kg)	No. Males	Dosing Schedule	Nx Day
1	PBS	0	5	3	SC on Days 1, 8, and 15	Day 16
2	AD-57928 (parent)	225		3		
3	AD-59849	225		3		
4	AD-59223	225		3		

(continued)

Dose Group	TA	Dose (mg/kg)	Dose Vol. (mL/ kg)	No. Males	Dosing Schedule	Nx Day
5	AD-59228	225		3		
6	AD-60688	225		3		
7	AD-60212	225		3		

Table 16. Tolerability Summary

	AD-57928 (parent)	AD-59849	AD-59223	AD-59228	AD-60688	AD-60212
No. PS	6	6	6	13	6	6
No. 2'F	21	15	12	21	9	12
No. dT	0	0	0	0	0	1
[Liver] (μg/g)	907±62	1139±160	1277±231	1999±424	1624±147	1258±286
Final BW (% from control)	-2.1%	-4.6%	-2.1%	-6.8%	-0.5%	-2.9%
Day 16 Hematology	No Change	No Change	↑WBC, ↑LYM, hemolysis	No Change	No Change	No Change
Day 16 Final Inj. Site Inflammation	3/3 (1.7)	3/3 (1.3)	2/3 (1.5)	3/3 (2.3)	2/3 (1.0)	3/3 (1.3)
Day 16 Basophilic Granules, Kidney	3/3 (2.0)	3/3 (2.3)	3/3 (1.0)	3/3 (2.0)	3/3 (1.3)	3/3 (1.3)
Pathology Severity Scores: 1 = minimal; 2 = slight; 3 = moderate BW = Body Weight WBC = White Blood Cell LYM = Lymphocytes						

SEQUENCE LISTING

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Claims

1. A double stranded RNAi agent capable of inhibiting the expression of Proprotein convertase subtilisin kexin 9 (PCSK9) in a cell, wherein said double stranded RNAi agent comprises:

   (a) a sense strand complementary to an antisense strand, wherein said antisense strand comprises a region complementary to part of an mRNA encoding PCSK9, wherein each strand is about 17 to about 30 nucleotides

in length, wherein said antisense strand comprises at least 17 nucleotides from the nucleobase sequence ACAAAAGCAAAACAGGUCUAG (SEQ ID NO: 412) and the double stranded RNAi agent is represented by formula (III):

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

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

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';
wherein the modifications on the nucleotides are 2'-O-methyl or 2'-fluoro modifications; and
wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker; or

(b) an antisense strand consisting of the nucleotide sequence asCfsaAfAfAfgCfaAfaAfcAfgGfuCfuagsasa and a sense strand consisting of the nucleotide sequence csusagacCfuGfudTuugcuuuugu,
wherein a, g, c, and u are 2'-O-methyl (2'-OMe) modified A, G, C, and U nucleotides, respectively; Af, Gf, Cf and Uf are 2'-fluoro A, G, C and U modified nucleotides, respectively; dT is a deoxy-thymine nucleotide and s is a phosphorothioate linkage;
and wherein the sense strand is conjugated to at least one ligand.

2. The double stranded RNAi agent of claim 1, wherein

(a) the antisense strand comprises the nucleobase sequence ACAAAAGCAAAACAGGUCUAGAA (SEQ ID NO: 418);
(b) the sense strand comprises the nucleobase sequence of AGACCUGUUUUGCUUUUGU (SEQ ID NO: 191);
(c) the sense strand comprises the nucleobase sequence of CUAGACCUGUUUUGCUUUUGU (SEQ ID NO: 197);
(d) the antisense strand comprises the nucleobase sequence ACAAAAGCAAAACAGGUCUAGAA (SEQ ID NO: 418) and the sense strand comprises the nucleobase sequence CUAGACCUGUUUUGCUUUUGU (SEQ ID NO: 197);
(e) the antisense strand comprises the nucleobase sequence ACAAAAGCAAAACAGGUCUAG (SEQ ID NO: 412) and the sense strand comprises the nucleobase sequence AGACCUGUUUUGCUUUUGU (SEQ ID NO: 191); or
(f) the antisense strand comprises the nucleobase sequence ACAAAAGCAAAACAGGUCUAGAA (SEQ ID NO: 418) and the sense strand comprises the nucleobase sequence CUAGACCUGUTUUGCUUUUGU (SEQ ID NO: 1665).

3. The double stranded RNAi agent of claim 1, wherein the double stranded region is 17-23 nucleotide pairs in length, 17-25 nucleotide pairs in length, 23-27 nucleotide pairs in length, 19-21 nucleotide pairs in length, or 21-23 nucleotide pairs in length.

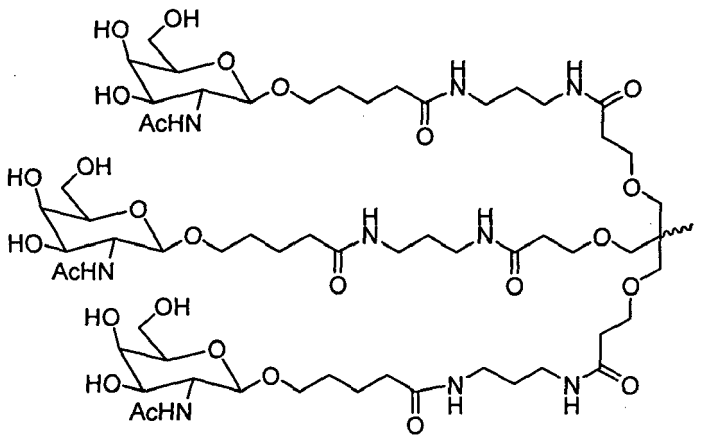
4. The double stranded RNAi agent of claim 1, wherein the dsRNA comprises:

(a) an antisense strand consisting of the nucleotide sequence aCfaAfaAfgCfaAfaacAfgGfuCfuAfgsAfsa (SEQ

ID NO: 1151) and a sense strand consisting of the nucleotide sequence CfuAfgAfcCfuGfUfUfuUfgCfuUfuUfgUf (SEQ ID NO: 600);
(b) an antisense strand consisting of the nucleotide sequence aCfaAfAfAfgCfaAfaacAfgGfuCfuAfgsAfsa (SEQ ID NO: 1246) and a sense strand consisting of the nucleotide sequence CfuAfgAfcCfuGfUfUfuUfgCfuuuUfgUf (SEQ ID NO: 695);
(c) an antisense strand consisting of the nucleotide sequence aCfaaaAfgCfaAfaacAfgGfuCfuAfgsAfsa (SEQ ID NO: 1253) and a sense strand consisting of the nucleotide sequence CfuAfgAfcCfuGfUfUfuUfgCfuUfUfUfgUf (SEQ ID NO: 702);
(d) an antisense strand consisting of the nucleotide sequence aCfaAfAfAfgCfaAfaacAfgGfuCfusAfsg (SEQ ID NO: 1263) and a sense strand consisting of the nucleotide sequence AfgAfcCfuGfUfUfuUfgCfuuuUfgUf (SEQ ID NO: 712);
(e) an antisense strand consisting of the nucleotide sequence aCfaaaAfgCfaAfaacAfgGfuCfusAfsg (SEQ ID NO: 1269) and a sense strand consisting of the nucleotide sequence AfgAfcCfuGfUfUfuUfgCfuUfUfUfgUf (SEQ ID NO: 718);
(f) an antisense strand consisting of the nucleotide sequence asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa (SEQ ID NO: 1369) and a sense strand consisting of the nucleotide sequence CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUf (SEQ ID NO: 818);
(g) an antisense strand consisting of the nucleotide sequence asCfsaAfaagCfaAfaacAfgGfucuAfgsasa, and a sense strand consisting of the nucleotide sequence CfsusAfgAfcCfuGfUfUfuUfgcuuuugu; or
(h) an antisense strand consisting of the nucleotide sequence asCfsaAfaAfsgCfaAfaacAfgGfuCfsuAfgsasa (SEQ ID NO: 1400) and a sense strand consisting of the nucleotide sequence CfsusAfgAfcCfuGfUfUfuUfgCfsuUfsuUfsgsUfs (SEQ ID NO: 849);

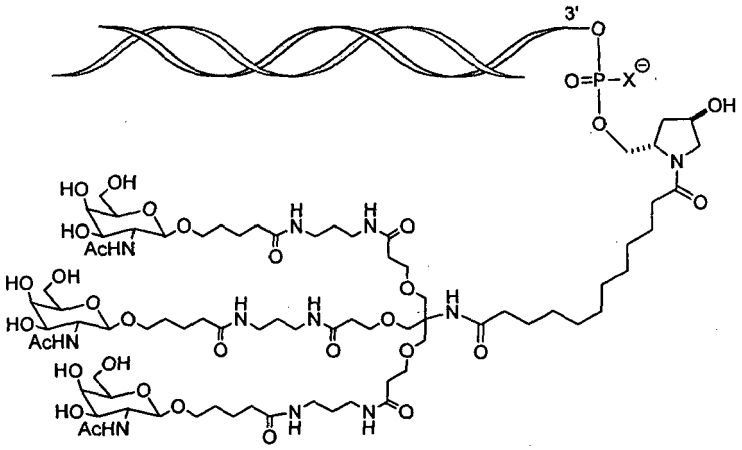
wherein a, g, c, and u are 2'-O-methyl (2'-OMe) modified A, G, C, and U nucleotides, respectively; Af, Gf, Cf and Uf are 2'-fluoro A, G, C and U modified nucleotides, respectively; dT is a deoxy-thymine nucleotide and s is a phosphorothioate linkage.

5. The double stranded RNAi agent of any one of claims 1 to 4, wherein the ligand is



6. The double stranded RNAi agent of any one of claims 1 to 5, wherein the ligand is attached to the 3' end of the sense strand.

7. The double stranded RNAi agent of claim 6, wherein the RNAi agent is conjugated to the ligand as shown in the following schematic



wherein X is O or S.

8. The double stranded RNAi agent of any one of claims 1 to 7, wherein the sense strand has a total of 21 nucleotides and the antisense strand has a total of 23 nucleotides.

9. An in vitro cell containing the double stranded RNAi agent of any one of claims 1 to 8.

10. A pharmaceutical composition comprising the double stranded RNAi agent of any one of claims 1 to 8.

11. The pharmaceutical composition of claim 10, wherein

(a) said RNAi agent is to be administered in an unbuffered solution, wherein preferably said unbuffered solution is saline or water; or
(b) said RNAi agent is to be administered with a buffer solution, wherein preferably said buffer solution comprises acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof, and wherein most preferably said buffer solution is phosphate buffered saline (PBS).

12. A method of inhibiting PCSK9 expression in a cell, the method comprising:

(a) contacting the cell with the double stranded RNAi agent of any one of claims 1 to 8 or a pharmaceutical composition of claim 10 or 11; and
(b) maintaining the cell produced in step (a) for a time sufficient to obtain degradation of the mRNA transcript of a PCSK9 gene, thereby inhibiting expression of the PCSK9 gene in the cell,

wherein methods for treatment of the human or animal body by therapy are excluded.

13. A dsRNA of any one of claims 1 to 8 or the pharmaceutical composition of claim 10 or 11 for use in a method of treating a subject having a disorder mediated by PCSK9 expression.

14. The dsRNA or pharmaceutical composition for use of claim 13, wherein

(a) the subject is a human;
(b) the disorder is hypercholesterolemia;
(c) the double stranded RNAi agent is to be administered at a dose of about 0.01 mg/kg to about 10 mg/kg, about 0.5 mg/kg to about 50 mg/kg, or about 10 mg/kg to about 30 mg/kg; and/or
(d) the double stranded RNAi agent is to be administered subcutaneously or intravenously.

15. The dsRNA or pharmaceutical composition for use of claim 13 or 14,
wherein said RNAi agent is to be administered in a dosing regimen that includes a loading phase followed by a maintenance phase,
wherein the loading phase comprises administering a dose of 2 mg/kg, 1 mg/kg or 0.5 mg/kg five times a week, and wherein the maintenance phase comprises administering a dose of 2 mg/kg, 1 mg/kg or 0.5 mg/kg once a week,

twice a week, three times a week, once every two weeks, once every three weeks, once a month, once every two months, once every three months, once every four months, once every five months, or once every six months.

Patentansprüche

1. Doppelsträngiges RNAi Agens, das die Expression von Proprotein Konvertase Subtilisin Kexin 9 (PCSK9) in einer Zelle inhibieren kann, wobei das doppelsträngige RNAi Agens umfasst:

(a) einen Sinnstrang der komplementär zu einem Antisinnstrang ist, wobei der Antisinnstrang einen Bereich umfasst, der zu einem Teil einer PCSK9-kodierenden mRNA komplementär ist, wobei jeder Strang etwa 17 bis etwa 30 Nukleotide lang ist, wobei der Antisinnstrang mindestens 17 Nukleotide der Nukleobasensequenz ACAAAAGCAAAACAGGUCUAG (SEQ ID Nr: 412) umfasst und das doppelsträngige RNAi Agens durch die Formel (III) dargestellt ist

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

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

wobei:

i, j, k und l unabhängig voneinander 0 oder 1 sind;
p, p', q und q' unabhängig voneinander 0-6 sind;
N_a und N_a' unabhängig voneinander eine Oligonukleotidsequenz darstellen, die 0-25 Nukleotide umfasst, die entweder modifiziert oder unmodifiziert oder Kombinationen davon sind, wobei jede Sequenz mindestens zwei unterschiedlich modifizierte Nukleotide umfasst;
N_b und N_b' unabhängig voneinander eine Oligonukleotidsequenz darstellen, die 0-10 Nukleotide umfasst, die entweder modifiziert oder unmodifiziert oder Kombinationen davon sind;
n_p, n_p', n_q und n_q', von denen jedes anwesend sein kann oder nicht, jeweils unabhängig voneinander ein Überhangnukleotid darstellen;
XXX, YYY, ZZZ, X'X'X', Y'Y'Y' und Z'Z'Z' jeweils unabhängig voneinander ein Motiv von drei identischen Modifikationen auf drei aufeinanderfolgenden Nukleotiden darstellen;
Modifikationen von N_b sich von der Modifikation von Y, und Modifkationen von N_b' sich von der Modifikation von Y' unterscheiden;
wobei die Modifkationen der Nukleotide 2'-O-Methyl oder 2'-Fluor Modifikationen sind; und
wobei der Ligand eines oder mehrere GalNAc Derivate ist/sind, die über einen bivalenten oder trivalenten verzweigten Linker verbunden sind; oder

(b) einen Antisinnstrang, der aus der Nukleotidsequenz asCfsaAfAfAfgCfaAfaAfcAfgGfuCfuagsasa besteht und einen Sinnstrang,
der aus der Nukleotidsequenz csusagacCfuGfudTuugcuuuugu besteht,
wobei a, g, c und u 2'-O-Methyl (2'-OMe) modifizierte A, G, C bzw. U Nukleotide sind; Af, Gf, Cf und Uf Nukleotide 2'-Fluor-modifizierte A, G, C bzw. U Nukleotide sind; dT ein Desoxy-Thymin Nukleotid ist und s eine Phosphorothioatverknüpfung ist;
und wobei der Sinnstrang an mindestens einen Liganden konjugiert ist.

2. Doppelsträngiges RNAi Agens nach Anspruch 1, wobei

(a) der Antisinnstrang die Nukleobasensequenz ACAAAAGCAAAACAGGUCUAGAA (SEQ ID Nr: 418) umfasst;
(b) der Sinnstrang die Nukleobasensequenz AGACCUGUUUUGCUUUUGU (SEQ ID Nr: 191) umfasst;
(c) der Sinnstrang die Nukleobasensequenz CUAGACCUGUUUUGCUUUUGU (SEQ ID Nr: 197) umfasst;
(d) der Antisinnstrang die Nukleobasensequenz ACAAAAGCAAAACAGGUCUAGAA (SEQ ID Nr: 418) umfasst und der Sinnstrang die Nukleobasensequenz CUAGACCUGUUUUGCUUUUGU (SEQ ID Nr: 197) umfasst;
(e) der Antisinnstrang die Nukleobasensequenz ACAAAAGCAAAACAGGUCUAG (SEQ ID Nr: 412) umfasst und der Sinnstrang die Nukleobasensequenz AGACCUGUUUUGCUUUUGU (SEQ ID Nr: 191) umfasst; oder
(f) der Antisinnstrang die Nukleobasensequenz ACAAAAGCAAAACAGGUCUAGAA (SEQ ID Nr: 418) umfasst und der Sinnstrang die Nukleobasensequenz CUAGACCUGUTUUGCUUUUGU (SEQ ID NO: 1665) umfasst.

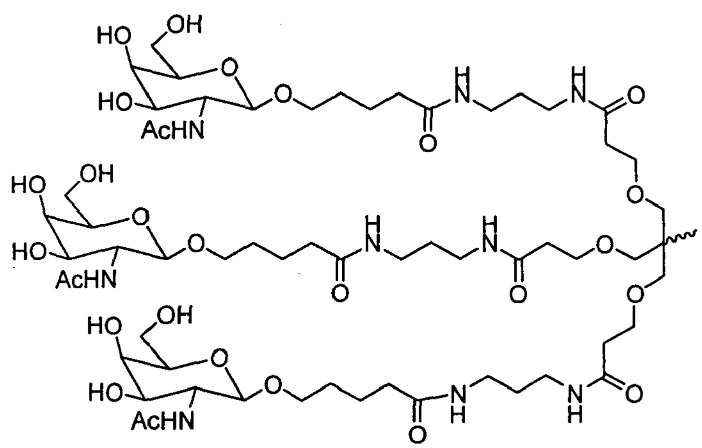
3. Doppelsträngiges RNAi Agens nach Anspruch 1, wobei die doppelsträngige Region 17-23 Nukleotidpaare lang, 17-25 Nukleotidpaare lang, 23-27 Nukleotidpaare lang, 19-21 Nukleotidpaare lang oder 21-23 Nukleotidpaare lang ist.

4. Doppelsträngiges RNAi Agens nach Anspruch 1, wobei die dsRNA umfasst:

(a) einen Antisinnstrang, der aus der Nukleotidsequenz aCfaAfaAfgCfaAfaacAfgGfuCfuAfgsAfsa (SEQ ID Nr: 1151) besteht und einen Sinnstrang, der aus der Nukleotidsequenz CfuAfgAfcCfuGfUfUfuUfgCfuUfuUfgUf (SEQ ID Nr: 600) besteht;
(b) einen Antisinnstrang, der aus der Nukleotidsequenz aCfaAfAfAfgCfaAfaacAfgGfuCfuAfgsAfsa (SEQ ID Nr: 1246) besteht und einen Sinnstrang, der aus der Nukleotidsequenz CfuAfgAfcCfuGfUfUfuUfgCfuuuUfgUf (SEQ ID Nr: 695) besteht;
(c) einen Antisinnstrang, der aus der Nukleotidsequenz aCfaaaAfgCfaAfaacAfgGfuCfuAfgsAfsa (SEQ ID Nr: 1253) besteht und einen Sinnstrang, der aus der Nukleotidsequenz CfuAfgAfcCfuGfUfUfuUfgCfuUfUfUfgUf (SEQ ID Nr: 702) besteht;
(d) einen Antisinnstrang, der aus der Nukleotidsequenz aCfaAfAfAfgCfaAfaacAfgGfuCfusAfsg (SEQ ID Nr: 1263) besteht und einen Sinnstrang, der aus der Nukleotidsequenz AfgAfcCfuGfUfUfuUfgCfuuuUfgUf (SEQ ID Nr: 712) besteht;
(e) einen Antisinnstrang, der aus der Nukleotidsequenz aCfaaaAfgCfaAfaacAfgGfuCfusAfsg (SEQ ID Nr: 1269) besteht und einen Sinnstrang, der aus der Nukleotidsequenz AfgAfcCfuGfUfUfuUfgCfuUfUfUfgUf (SEQ ID Nr: 718) besteht;
(f) einen Antisinnstrang, der aus der Nukleotidsequenz asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa (SEQ ID Nr: 1369) besteht und einen Sinnstrang, der aus der Nukleotidsequenz CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUf (SEQ ID Nr: 818) besteht;
(g) einen Antisinnstrang, der aus der Nukleotidsequenz asCfsaAfaagCfaAfaacAfgGfucuAfgsasa besteht und einen Sinnstrang, der aus der Nukleotidsequenz CfsusAfgAfcCfuGfUfUfuUfgcuuuugu besteht; oder
(h) einen Antisinnstrang, der aus der Nukleotidsequenz asCfsaAfaAfsgCfaAfaacAfgGfuCfsuAfgsasa (SEQ ID Nr: 1400) besteht und einen Sinnstrang, der aus der Nukleotidsequenz CfsusAfgAfcCfuGfUfUfuUfgCfsuUfsu-UfsgsUfs (SEQ ID Nr: 849) besteht;

wobei a, g, c und u 2'-O-Methyl (2'-OMe) modifizierte A, G, C bzw. U Nukleotide sind; Af, Gf, Cf und Uf Nukleotide 2'-Fluor-modifizierte A, G, C bzw. U Nukleotide sind; dT ein Desoxy-Thymin Nukleotid ist und s eine Phosphorothioatverknüpfung ist.

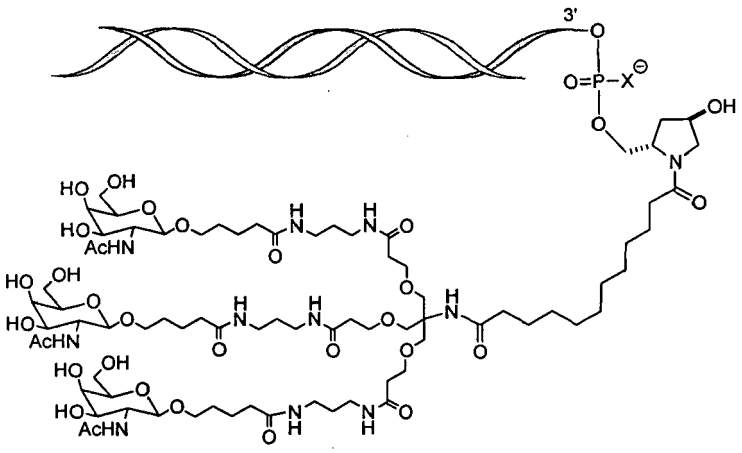
5. Doppelsträngiges RNAi Agens nach einem der Ansprüche 1 bis 4, wobei der Ligand



ist.

6. Doppelsträngiges RNAi Agens nach einem der Ansprüche 1 bis 5, wobei der Ligand an das 3'-Ende des Sinnstrangs gebunden ist.

7. Doppelsträngiges RNAi Agens nach Anspruch 6, wobei das RNAi Agens mit dem Liganden wie im folgenden Schema gezeigt konjugiert ist



wobei X O oder S ist.

8. Doppelsträngiges RNAi Agens nach einem der Ansprüche 1 bis 7, wobei der Sinnstrang insgesamt 21 Nukleotide und der Antisinnstrang insgesamt 23 Nukleotide hat.

9. In vitro Zelle, enthaltend das doppelsträngige RNAi Agens nach einem der Ansprüche 1 bis 8.

10. Pharmazeutische Zusammensetzung, umfassend das doppelsträngige RNAi Agens nach einem der Ansprüche 1 bis 8.

11. Pharmazeutische Zusammensetzung nach Anspruch 10, wobei

(a) das RNAi Agens in einer ungepufferten Lösung zu verabreichen ist, wobei vorzugsweise die ungepufferte Lösung eine Salzlösung oder Wasser ist; oder
(b) das RNAi Agens mit einer gepufferten Lösung zu verabreichen ist; wobei vorzugsweise die Pufferlösung Azetat, Zitrat, Prolamin, Karbonat oder Phosphat oder eine Kombination davon umfasst, und wobei am stärksten bevorzugt die Pufferlösung Phosphat-gepufferte Salzlösung (PBS) ist.

12. Verfahren zum Inhibieren der PCSK9 Expression in einer Zelle, wobei das Verfahren umfasst:

(a) in Kontakt bringen der Zelle mit dem doppelsträngigen RNAi Agens nach einem der Ansprüche 1 bis 8 oder einer pharmazeutischen Zusammensetzung nach Anspruch 10 oder 11; und
(b) Aufrechterhalten der in Schritt (a) hergestellten Zelle für eine Zeit, die ausreicht, Abbau des mRNA Transkripts eines PCSK9 Gens zu erhalten, wodurch die Expression des PCSK9 Gens in der Zelle inhibiert wird,

wobei Verfahren zur Behandlung des menschlichen oder tierischen Körpers mittels Therapie ausgeschlossen sind.

13. dsRNA nach einem der Ansprüche 1 bis 8 oder pharmazeutische Zusammensetzung nach Anspruch 10 oder 11 für die Verwendung in einem Verfahren zum Behandeln eines Individuums das eine Störung hat, die durch PCSK9 Expression vermittelt wird.

14. dsRNA oder pharmazeutische Zusammensetzung für die Verwendung nach Anspruch 13, wobei

(a) das Individuum ein Mensch ist;
(b) die Störung Hypercholesterinämie ist;
(c) das doppelsträngige RNAi Agens in einer Dosis von etwa 0,01 mg/kg bis etwa 10 mg/kg, etwa 0,5 mg/kg bis etwa 50 mg/kg oder etwa 10 mg/kg bis etwa 30 mg/kg zu verabreichen ist; und/oder
(d) das doppelsträngige RNAi Agens subkutan oder intravenös zu verabreichen ist.

15. dsRNA oder pharmazeutische Zusammensetzung für die Verwendung nach Anspruch 13 oder 14, wobei das RNAi Agens gemäß eines Dosierungsschemas zu verabreichen ist, das eine Anfangsphase, gefolgt von einer Aufrechterhaltungsphase umfasst,
wobei die Anfangsphase das Verabreichen einer Dosis von 2 mg/kg, 1 mg/kg oder 0,5 mg/kg fünfmal pro Woche umfasst, und
wobei die Aufrechterhaltungsphase das Verabreichen einer Dosis von 2 mg/kg, 1 mg/kg oder 0,5 mg/kg einmal pro Woche, zweimal pro Woche, dreimal pro Woche, einmal alle zwei Wochen, einmal alle drei Wochen, einmal im Monat, einmal alle zwei Monate, einmal alle drei Monate, einmal alle vier Monate, einmal alle fünf Monate oder einmal alle sechs Monate umfasst.

Revendications

1. Agent ARNi double brin capable d'inhiber l'expression de la proprotéine convertase subtilisine kexine 9 (PCSK9) dans une cellule, dans lequel ledit agent ARNi double brin comprend :

(a) un brin sens complémentaire d'un brin antisens, dans lequel ledit brin antisens comprend une région complémentaire d'une partie d'un ARNm codant PCSK9, dans lequel chaque brin a une longueur d'environ 17 à environ 30 nucléotides, dans lequel ledit brin antisens comprend au moins 17 nucléotides provenant de la séquence de bases nucléiques ACAAAAGCAAAACAGGUCUAG (SEQ ID No: 412) et l'agent ARNi double brin est représenté par la formule (III) :

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

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

dans laquelle :

i, j, k, et 1 sont chacun indépendamment 0 ou 1 ; p, p', q, et q' sont chacun indépendamment 0-6 ;
chaque N_a et N_a' représente indépendamment une séquence d'oligonucléotides comprenant de 0 à 25 nucléotides qui sont soit modifiés, soit non modifiés ou des combinaisons de ceux-ci, chaque séquence comprenant au moins deux nucléotides modifiés différemment ;
chaque N_b et $N_{b'}$ représente indépendamment une séquence d'oligonucléotides comprenant de 0 à 10 nucléotides qui sont soit modifiés, soit non modifiés ou des combinaisons de ceux-ci ;
chaque n_p, n_p', n_q, et n_q', chacun d'eux pouvant être présent ou non, représente indépendamment un nucléotide d'extrémité sortante ;
XXX, YYY, ZZZ, X'X'X', Y'Y'Y', et Z'Z'Z' chacun représente indépendamment un motif de trois modifications identiques sur trois nucléotides consécutifs ;
les modifications sur N_b diffèrent de la modification sur Y et les modifications sur N_b' diffèrent de la modification sur Y' ;
dans lequel les modifications sur les nucléotides sont des modifications 2'-O-méthyle ou 2'-fluoro ; et
dans lequel le ligand est un ou plusieurs dérivés GalNAc attachés par un lieur ramifié bivalent ou trivalent ; ou

(b) un brin antisens consistant en la séquence de nucléotides asCfsaAfAfAfgCfaAfaAfcAfgGfuCfuagsasa et un brin sens consistant en la séquence de nucléotides csusagacCfuGfudTuugcuuuugu,

dans lequel a, g, c, et u sont respectivement des nucléotides A, G, C, et U modifiés par un 2'-O-méthyle (2'-OMe); Af, Gf, Cf et Uf sont respectivement des nucléotides A, G, C, et U modifiés par un 2'-fluoro; dT est un nucléotide désoxy-thymine et s une liaison phosphorothioate ; et dans lequel le brin sens est conjugué à au moins un ligand.

2. Agent ARNi double brin selon la revendication 1, dans lequel

(a) le brin antisens comprend la séquence de bases nucléiques ACAAAAGCAAAACAGGUCUAGAA (SEQ ID No: 418) ;
(b) le brin sens comprend la séquence de bases nucléiques AGACCUGUUUUGCUUUUGU (SEQ ID No: 191) ;
(c) le brin sens comprend la séquence de bases nucléiques CUAGACCUGUUUUGCUUUUGU (SEQ ID No: 197) ;

(d) le brin antisens comprend la séquence de bases nucléiques ACAAAAGCAAAACAGGUCUAGAA (SEQ ID No: 418) et le brin sens comprend la séquence de bases nucléiques CUAGACCUGUUUUGCUUUUGU (SEQ ID No: 197) ;
(e) le brin antisens comprend la séquence de bases nucléiques ACAAAAGCAAAACAGGUCUAG (SEQ ID No: 412) et le brin sens comprend la séquence de bases nucléiques AGACCUGUUUUGCUUUUGU (SEQ ID No: 191) ; ou
(f) le brin antisens comprend la séquence de bases nucléiques ACAAAAGCAAAACAGGUCUAGAA (SEQ ID No: 418) et le brin sens comprend la séquence de bases nucléiques CUAGACCUGUTUUGCUUUUGU (SEQ ID No: 1665).

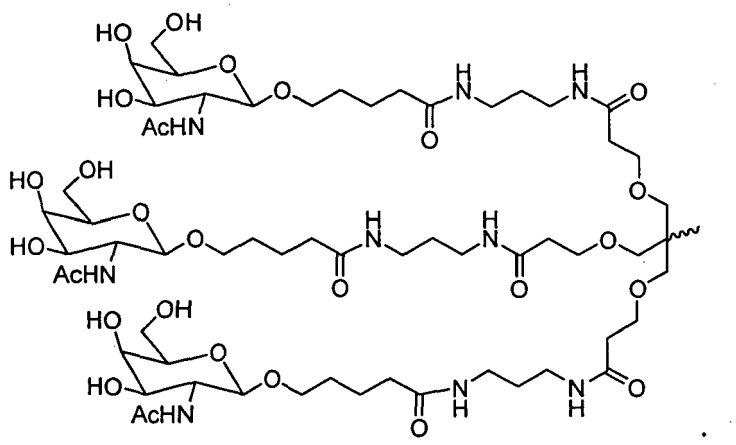
3. Agent ARNi double brin selon la revendication 1, dans lequel la région double brin a une longueur de 17 à 23 paires de nucléotides, une longueur de 17 à 25 paires de nucléotides, une longueur de 23 à 27 paires de nucléotides, une longueur de 19 à 21 paires de nucléotides, ou une longueur de 21 à 23 paires de nucléotides.

4. Agent ARNi double brin selon la revendication 1, dans lequel l'ARNdb comprend :

(a) un brin antisens consistant en la séquence de nucléotides aCfaAfaAfgCfaAfaacAfgGfuCfuAfgsAfsa (SEQ ID No: 1151) et un brin sens consistant en la séquence de nucléotides CfuAfgAfcCfuGfUfUfuUfgCfuUfuUfgUf (SEQ ID No: 600) ;
(b) un brin antisens consistant en la séquence de nucléotides aCfaAfAfAfgCfaAfaacAfgGfuCfuAfgsAfsa (SEQ ID No: 1246) et un brin sens consistant en la séquence de nucléotides CfuAfgAfcCfuGfUfUfuUfgCfuuuUfgUf (SEQ ID No: 695) ;
(c) un brin antisens consistant en la séquence de nucléotides aCfaaaAfgCfaAfaacAfgGfuCfuAfgsAfsa (SEQ ID No: 1253) et un brin sens consistant en la séquence de nucléotides CfuAfgAfcCfuGfUfUfuUfgCfuUfUfUfgUf (SEQ ID No: 702) ;
(d) un brin antisens consistant en la séquence de nucléotides aCfaAfAfAfgCfaAfaacAfgGfuCfusAfsg (SEQ ID No: 1263) et un brin sens consistant en la séquence de nucléotides AfgAfcCfuGfUfUfuUfgCfuuuUfgUf(SEQ ID No: 712) ;
(e) un brin antisens consistant en la séquence de nucléotides aCfaaaAfgCfaAfaacAfgGfuCfusAfsg (SEQ ID No: 1269) et un brin sens consistant en la séquence de nucléotides AfgAfcCfuGfUfUfuUfgCfuUfUfUfgUf(SEQ ID No: 718) ;
(f) un brin antisens consistant en la séquence de nucléotides asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa (SEQ ID No: 1369) et un brin sens consistant en la séquence de nucléotides CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUf (SEQ ID No: 818) ;
(g) un brin antisens consistant en la séquence de nucléotides asCfsaAfaagCfaAfaacAfgGfucuAfgsasa et un brin sens consistant en la séquence de nucléotides CfsusAfgAfcCfuGfUfUfuUfgcuuuugu ; ou
(h) un brin antisens consistant en la séquence de nucléotides asCfsaAfaAfsgCfaAfaacAfgGfuCfsuAfgsasa (SEQ ID No: 1400) et un brin sens consistant en la séquence de nucléotides CfsusAfgAfcCfuGfUfUfuUfgCf-suUfsuUfsgsUfs (SEQ ID No: 849) ;

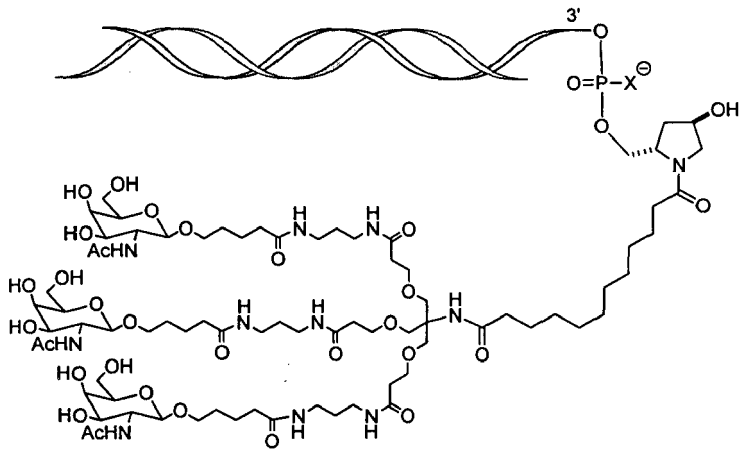
dans lequel a, g, c, et u sont respectivement des nucléotides A, G, C, et U modifiés par un 2'-O-méthyle (2'-OMe); Af, Gf, Cf et Uf sont respectivement des nucléotides A, G, C, et U modifiés par un 2'-fluoro; dT est un nucléotide désoxy-thymine et s est une liaison phosphorothioate.

5. Agent ARNi double brin selon l'une quelconque des revendications 1 à 4, dans lequel le ligand est



6. Agent ARNi double brin selon l'une quelconque des revendications 1 à 5, dans lequel le ligand est lié à l'extrémité 3' du brin sens.

7. Agent ARNi double brin selon la revendication 6, dans lequel l'agent ARNi est conjugué au ligand comme illustré sur le schéma suivant



où X est O ou S.

8. Agent ARNi double brin selon l'une quelconque des revendications 1 à 7, dans lequel le brin sens a un total de 21 nucléotides et le brin antisens a un total de 23 nucléotides.

9. Cellule *in vitro* contenant l'agent ARNi double brin selon l'une quelconque des revendications 1 à 8.

10. Composition pharmaceutique comprenant l'agent ARNi double brin selon l'une quelconque des revendications 1 à 8.

11. Composition pharmaceutique selon la revendication 10, dans laquelle

(a) l'agent ARNi doit être administré dans une solution non tamponnée, dans laquelle ladite solution non tamponnée est de préférence une solution salée ou de l'eau ; ou
(b) l'agent ARNi doit être administré avec une solution tampon, dans laquelle ladite solution tampon comprend de préférence un tampon acétate, citrate, prolamine, carbonate, ou phosphate ou une combinaison quelconque de ceux-ci, et dans laquelle de manière préférée entre toute ladite solution tampon est une solution salée à tampon phosphate (PBS).

12. Méthode d'inhibition de l'expression de PCSK9 dans une cellule, la méthode comprenant :

(a) la mise en contact de la cellule avec l'agent ARNi double brin selon l'une quelconque des revendications 1 à 8 ou une composition pharmaceutique selon la revendication 10 ou 11 ; et
(b) le maintien de la cellule obtenue à l'étape (a) pendant une durée suffisante pour obtenir la dégradation du transcrit d'ARNm d'un gène PCSK9, et inhiber ainsi l'expression du gène PCSK9 dans la cellule,

dans laquelle les méthodes de traitement visant le corps humain ou animal par thérapie sont exclues.

13. ARNdb selon l'une quelconque des revendications 1 à 8 ou composition pharmaceutique selon la revendication 10 ou 11 pour une utilisation pour traiter d'un sujet souffrant d'un désordre médié par l'expression de PCSK9.

14. ARNdb ou composition pharmaceutique pour une utilisation selon la revendication 13, dans lequel

(a) le sujet est un humain ;
(b) le désordre est l'hypercholestérolémie ;
(c) l'agent ARNi double brin doit être administré à une dose d'environ 0,01 mg/kg à environ 10 mg/kg, d'environ 0,5 mg/kg à environ 50 mg/kg, ou d'environ 10mg/kg à environ 30 mg/kg ; et/ou
(d) l'agent ARNi double brin doit être administré par voie sous-cutanée ou intraveineuse.

15. ARNdb ou composition pharmaceutique pour une utilisation selon la revendication 13 ou 14, dans lequel ledit agent ARNi doit être administré selon un schéma posologique qui comprend une phase d'attaque suivie d'une phase d'entretien,
dans lequel la phase d'attaque comprend l'administration d'une dose de 2 mg/kg, 1 mg/kg ou 0,5 mg/kg cinq fois par semaine, et
dans lequel la phase d'entretien comprend l'administration d'une dose de 2 mg/kg, 1 mg/kg ou 0,5 mg/kg une fois par semaine, deux fois par semaine, trois fois par semaine, une fois toutes les deux semaines, une fois toutes les trois semaines, une fois par mois, une fois tous les deux mois, une fois tous les trois mois, une fois tous les quatre mois, une fois tous les cinq mois, ou une fois tous les six mois.

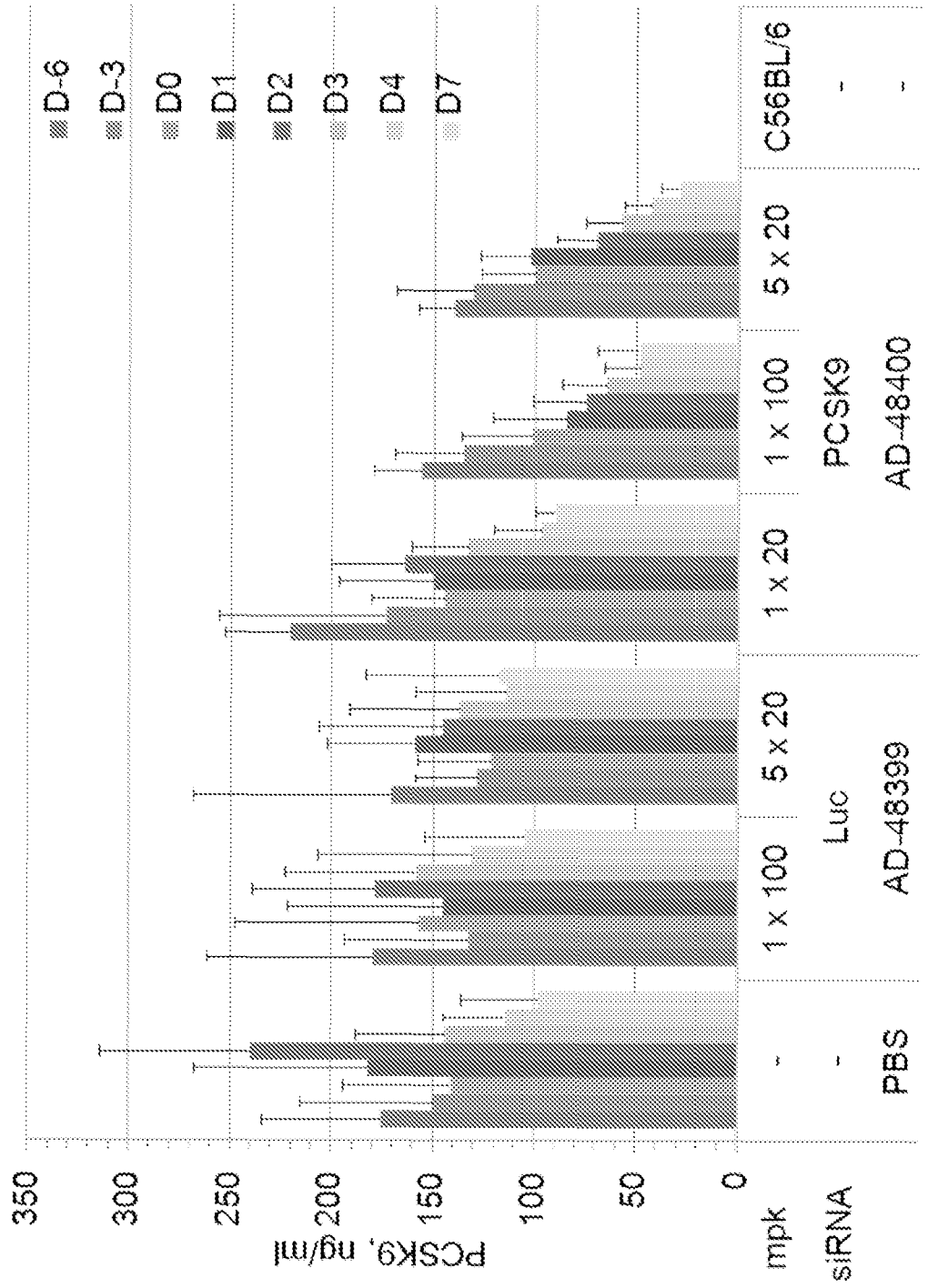

D-6
D-3
D0
D1
D2
D3
D4
D7
PCSK9, ng/ml
350
300
250
200
150
100
50
0
mpk
siRNA
-
PBS
1 x 100
AD-48399
5 x 20
1 x 20
Luc
1 x 100
AD-48400
5 x 20
PCSK9
C56BL/6
-
-

Figure 1

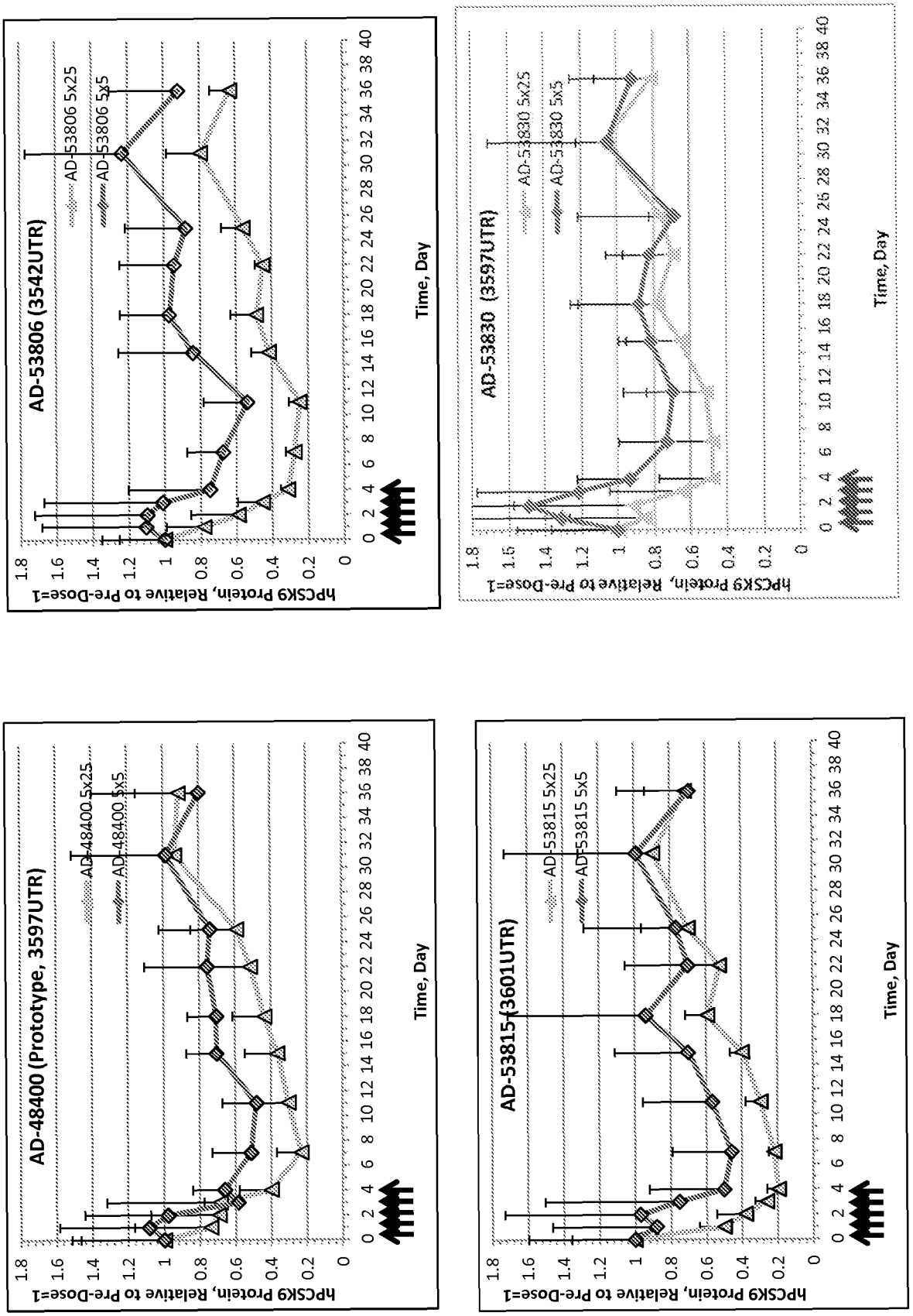

AD-53806 (3542UTR)
AD-53806 5x25
AD-53806 5x5
hPCSK9 Protein, Relative to Pre-Dose=1
Time, Day
AD-53830 (3597UTR)
AD-53830 5x25
AD-53830 5x5
hPCSK9 Protein, Relative to Pre-Dose=1
Time, Day
AD-48400 (Prototype, 3597UTR)
AD-48400 5x25
AD-48400 5x5
hPCSK9 Protein, Relative to Pre-Dose=1
Time, Day
AD-53815 (3601UTR)
AD-53815 5x25
AD-53815 5x5
hPCSK9 Protein, Relative to Pre-Dose=1
Time, Day

Figure 2A

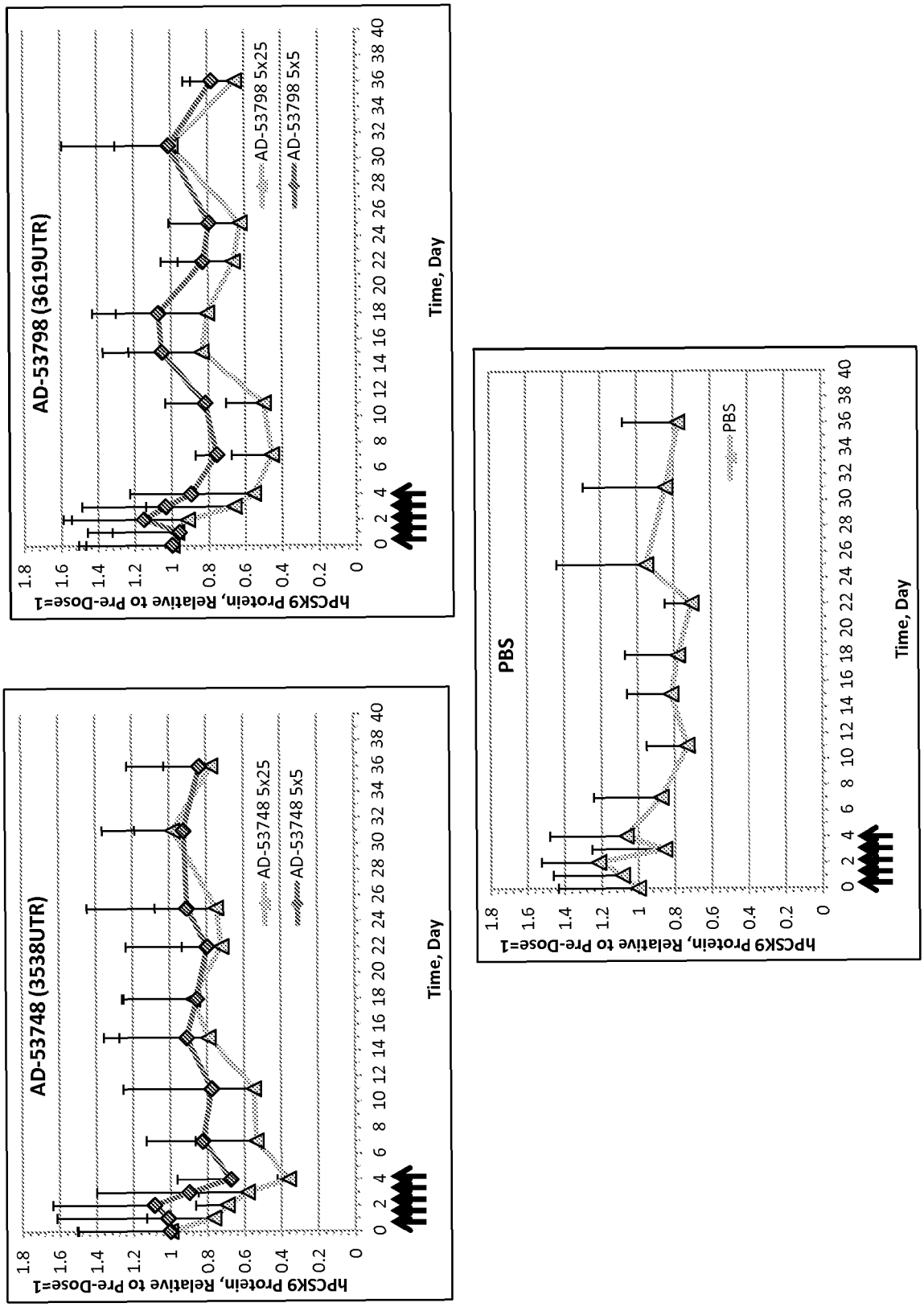

AD-53748 (3538UTR)
AD-53748 5x25
AD-53748 5x5
hPCSK9 Protein, Relative to Pre-Dose=1
Time, Day
AD-53798 (3619UTR)
AD-53798 5x25
AD-53798 5x5
PBS

Figure 2B

Duplex	Sense		AS		Chemistry
AD-53815.5	A-110695.11	CfuAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	A-109545.18	aCfaAfaAfgCfaAfaacAfgGfuCfuAfgsAfsa	21/23 (Parent)
AD-56651.1	A-115523.1	(iC)uAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	A-115524.1	(iA)CfaAfaAfgCfaAfaacAfgGfuCfuAfgsAfs(iA)	21/23 + inverted base
AD-56610.1	A-115523.2	(iC)uAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	A-115525.1	aCfaAfaAfgCfaAfaacAfgGfuCfuAfgsAfs(iA)	21/23 + inverted base
AD-56634.1	A-115529.1	CbuAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	A-115530.1	AbCfaAfaAfgCfaAfaacAfgGfuCfuAfgsAfsAb	21/23 + L-Sugar
AD-56652.1	A-115533.1	CbuAfgAfcCfuGfUfUfuUfgCfuUfuugUfL96	A-115532.2	acaAfaAfgcaAfaacAfgGfuCfuAfgsAfsAb	21/23 + L-Sugar
AD-56663.1	A-115552.1	CfuAfgAfcCfuGfUfUfuUfgCfuuuUfgUfL96	A-115553.1	aCfaAfAfAfgCfaAfaacAfgGfuCfuAfgsAfsa	21/23
AD-56658.1	A-115564.1	CfuAfgAfcCfuGfUfUfuUfgCfuUfUfUfgUfL96	A-115565.1	aCfaaaAfgCfaAfaacAfgGfuCfuAfgsAfsa	21/23
AD-56676.1	A-115584.1	AfgAfcCfuGfUfUfuUfgCfuuuUfgUfL96	A-115585.1	aCfaAfAfAfgCfaAfaacAfgGfuCfusAfsg	19/21
AD-56666.1	A-115596.1	AfgAfcCfuGfUfUfuUfgCfuUfUfUfgUfL96	A-115597.1	aCfaaaAfgCfaAfaacAfgGfuCfusAfsg	19/21
AD-57928	A-117428	CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	A-117429	asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	6 PS version of parent

Figure 3

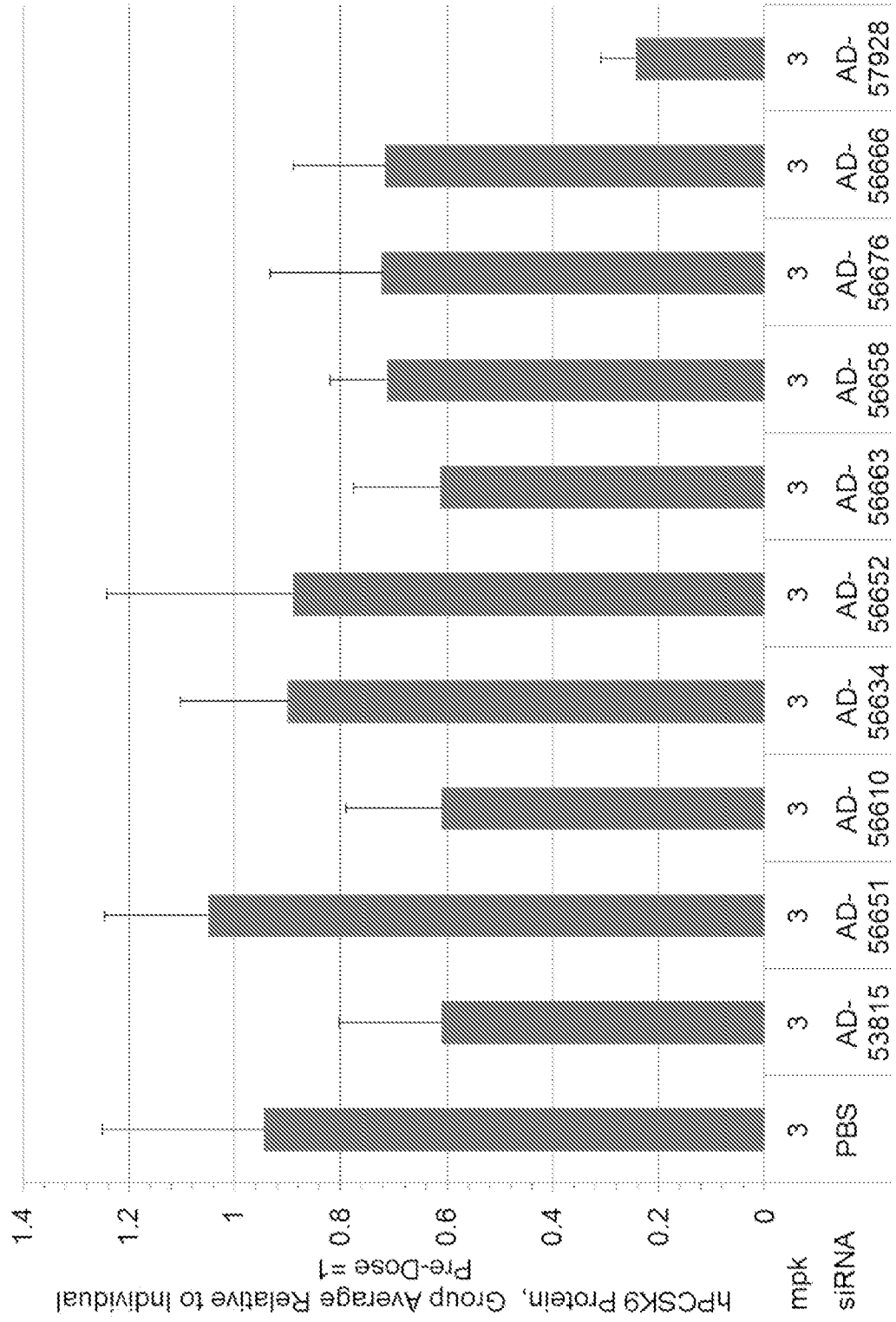

hPCSK9 Protein, Group Average Relative to Individual Pre-Dose =1
1.4
1.2
1
0.8
0.6
0.4
0.2
0
mpk
siRNA
3
PBS
3
AD-53815
3
AD-56651
3
AD-56610
3
AD-56634
3
AD-56652
3
AD-56663
3
AD-56658
3
AD-56676
3
AD-56666
3
AD-57928

Figure 4

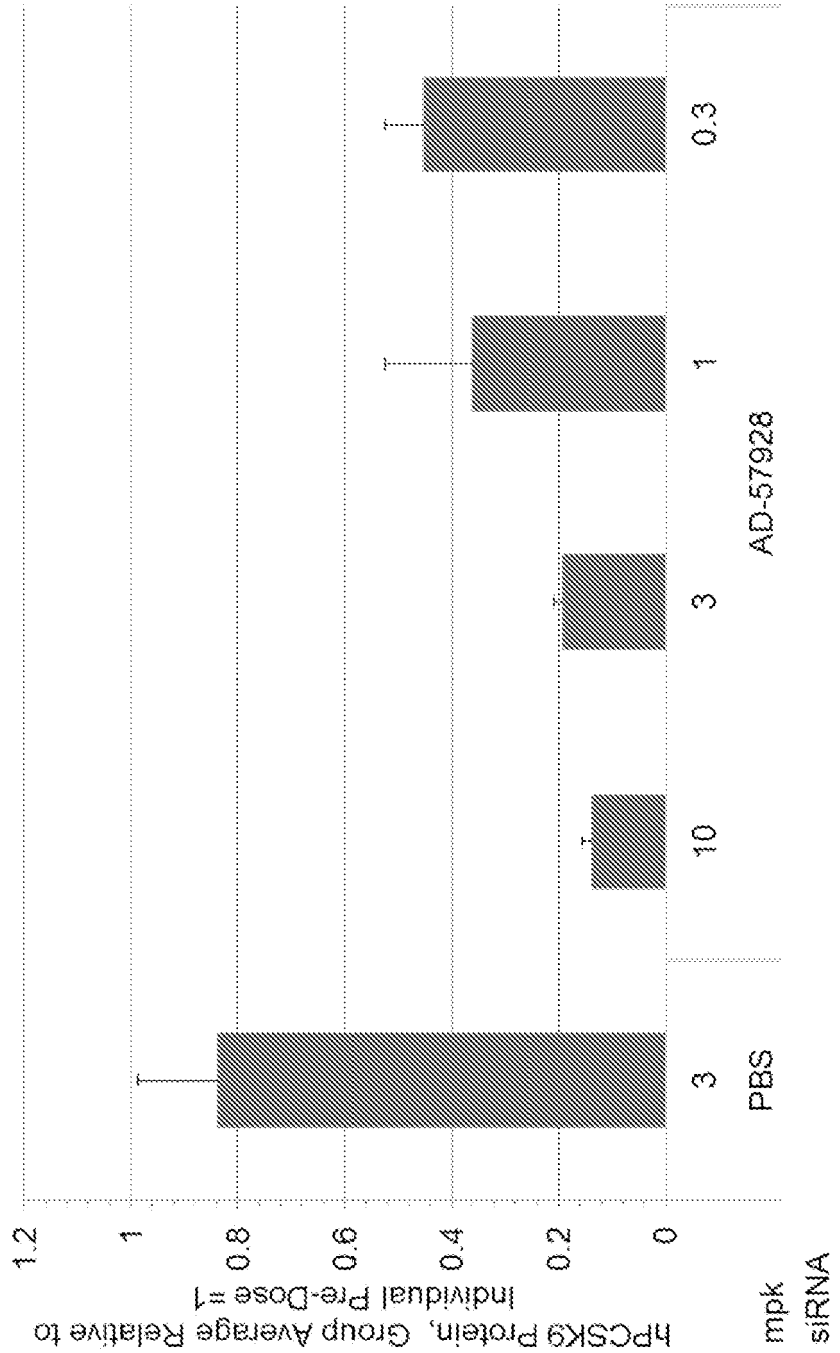

hPCSK9 Protein, Group Average Relative to Individual Pre-Dose =1
1.2
1
0.8
0.6
0.4
0.2
0
mpk
siRNA
3
PBS
10
3
1
0.3
AD-57928

Figure 5

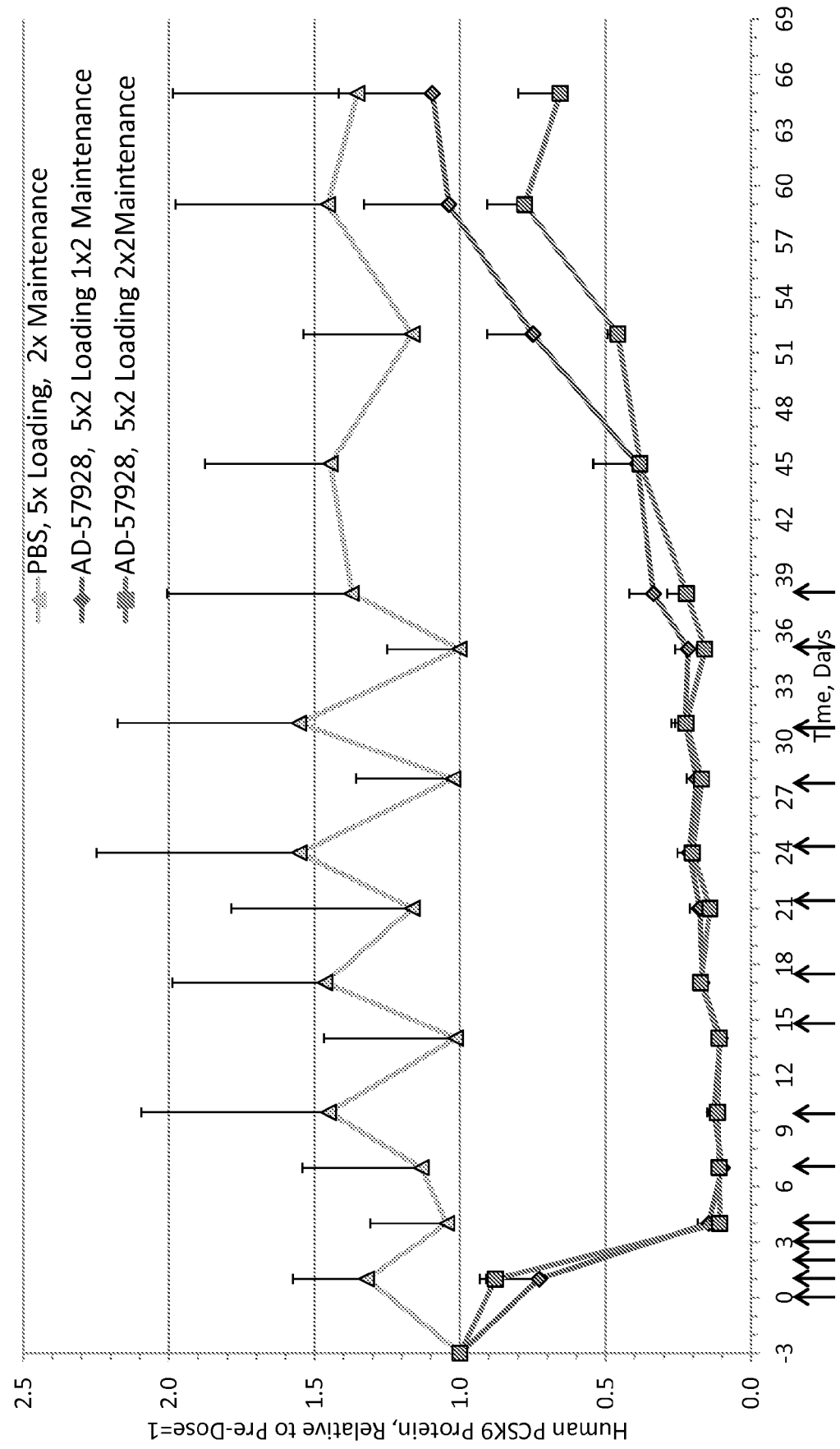

PBS, 5x Loading, 2x Maintenance
AD-57928, 5x2 Loading 1x2 Maintenance
AD-57928, 5x2 Loading 2x2Maintenance
Human PCSK9 Protein, Relative to Pre-Dose=1
2.5
2.0
1.5
1.0
0.5
0.0
-3
0
3
6
9
12
15
18
21
24
27
30
33
36
39
42
45
48
51
54
57
60
63
66
69
Time, Days

Figure 6

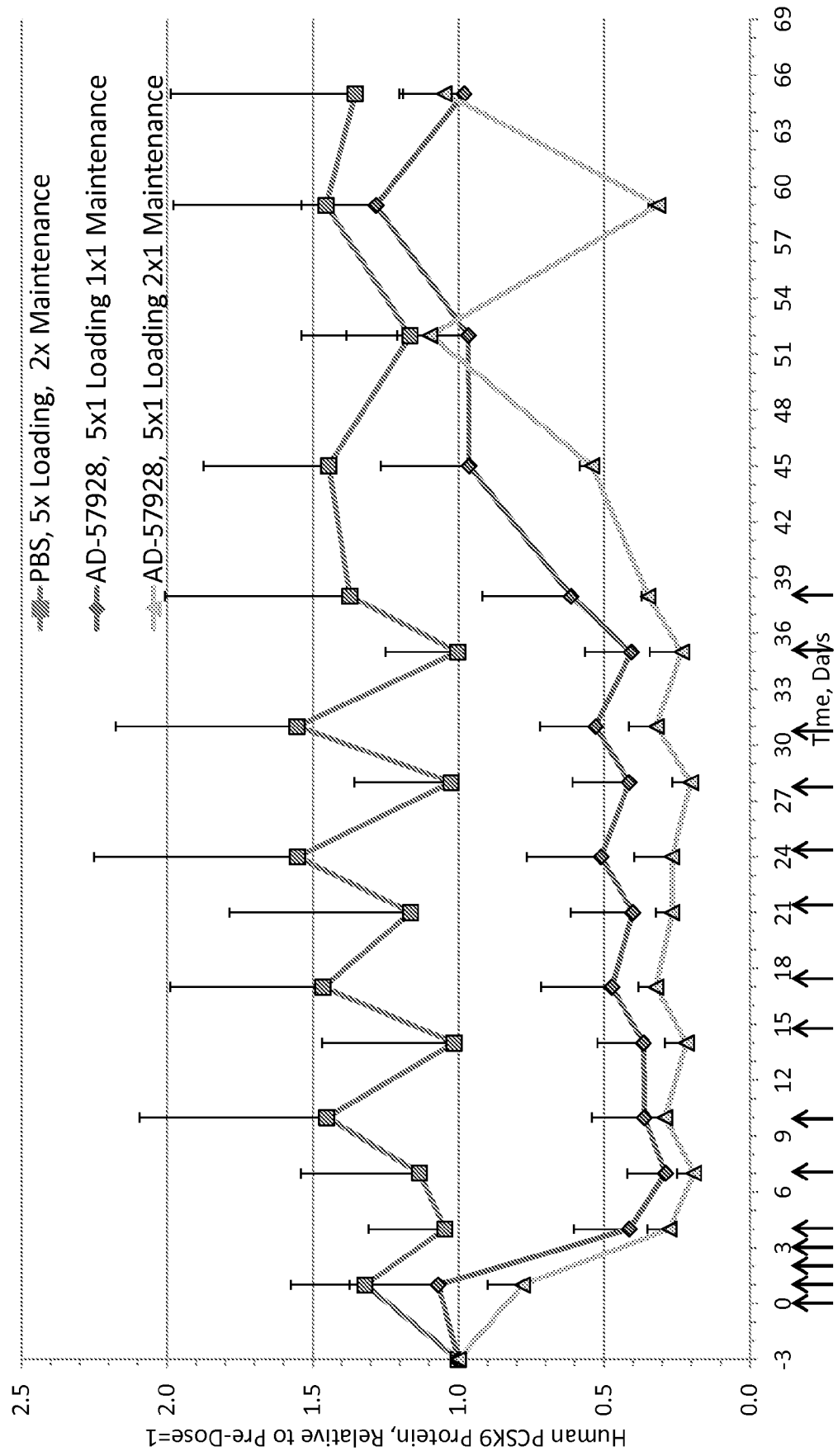

PBS, 5x Loading, 2x Maintenance
AD-57928, 5x1 Loading 1x1 Maintenance
AD-57928, 5x1 Loading 2x1 Maintenance
Human PCSK9 Protein, Relative to Pre-Dose=1
2.5
2.0
1.5
1.0
0.5
0.0
-3
0
3
6
9
12
15
18
21
24
27
30
33
36
39
42
45
48
51
54
57
60
63
66
69
Time, Days

Figure 7

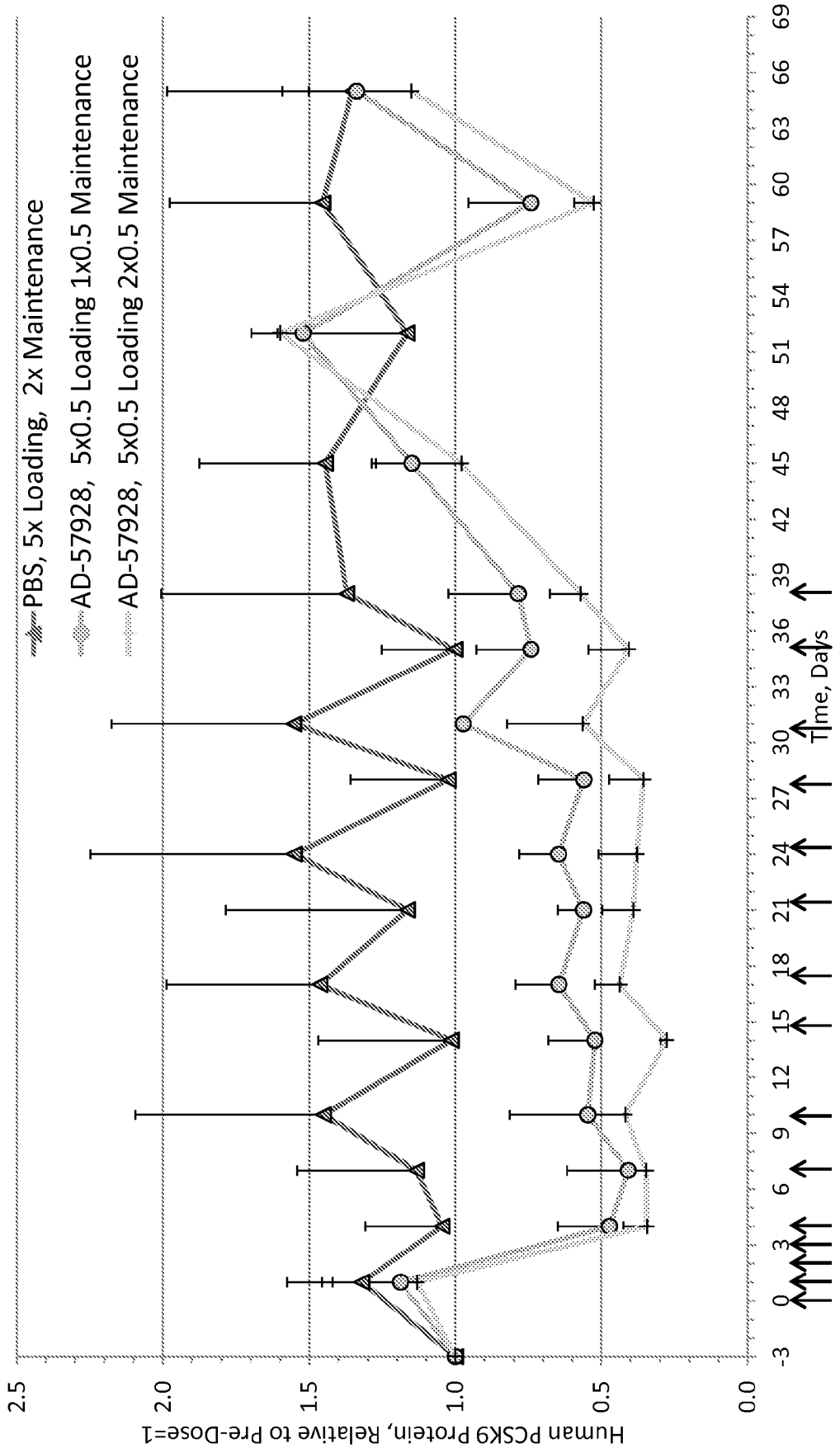

PBS, 5x Loading, 2x Maintenance
AD-57928, 5x0.5 Loading 1x0.5 Maintenance
AD-57928, 5x0.5 Loading 2x0.5 Maintenance
Human PCSK9 Protein, Relative to Pre-Dose=1
2.5
2.0
1.5
1.0
0.5
0.0
-3
0
3
6
9
12
15
18
21
24
27
30
33
36
39
42
45
48
51
54
57
60
63
66
69
Time, Days

Figure 8

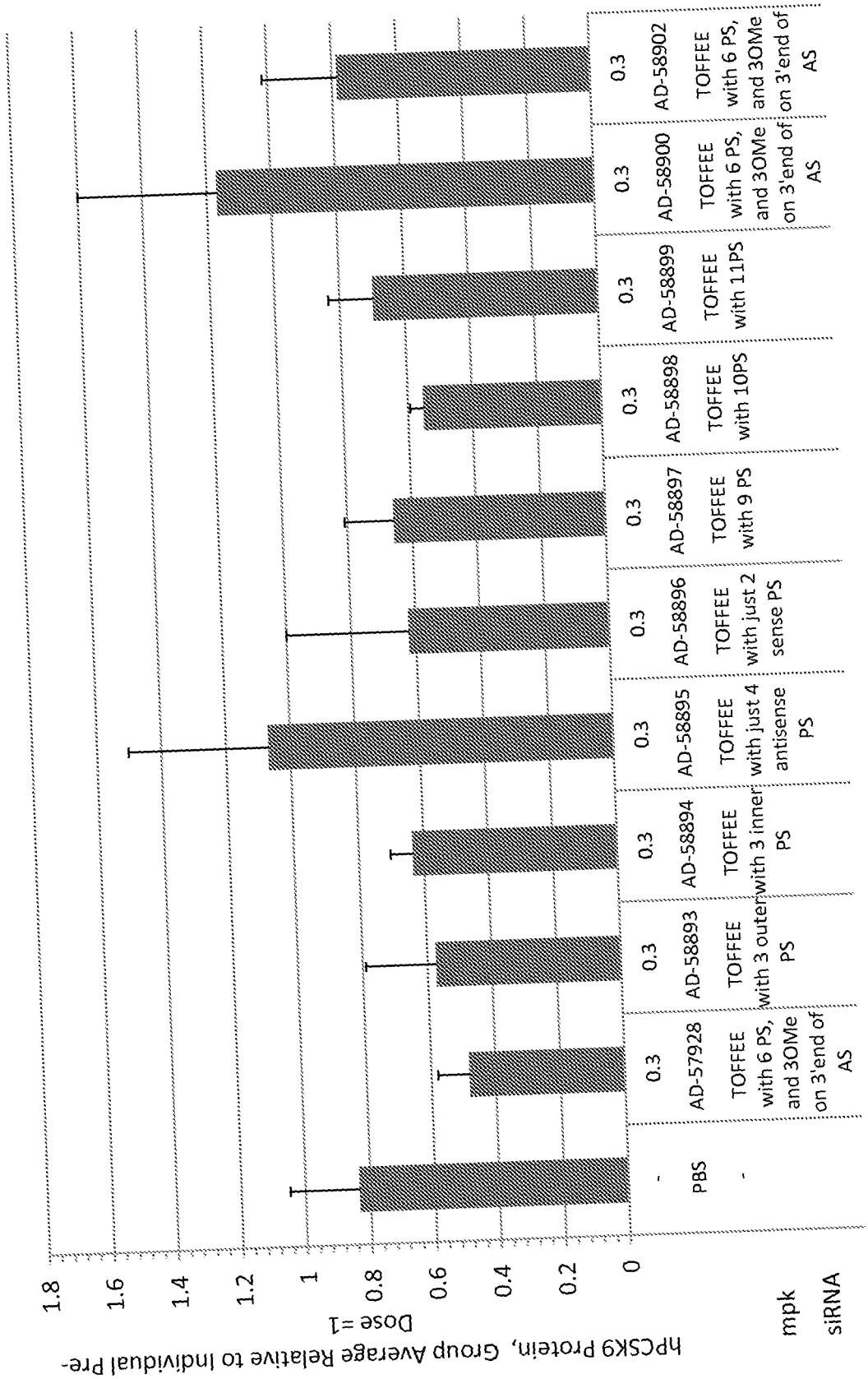

hPCSK9 Protein, Group Average Relative to Individual Pre-Dose =1
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
mpk
siRNA
-
PBS
-
0.3
AD-57928
TOFFEE with 6 PS, and 3OMe on 3'end of AS
0.3
AD-58893
TOFFEE with 3 outer PS
0.3
AD-58894
TOFFEE with 3 inner PS
0.3
AD-58895
TOFFEE with just 4 antisense PS
0.3
AD-58896
TOFFEE with just 2 sense PS
0.3
AD-58897
TOFFEE with 9 PS
0.3
AD-58898
TOFFEE with 10PS
0.3
AD-58899
TOFFEE with 11PS
0.3
AD-58900
TOFFEE with 6 PS, and 3OMe on 3'end of AS
0.3
AD-58902
TOFFEE with 6 PS, and 3OMe on 3'end of AS

Figure 9

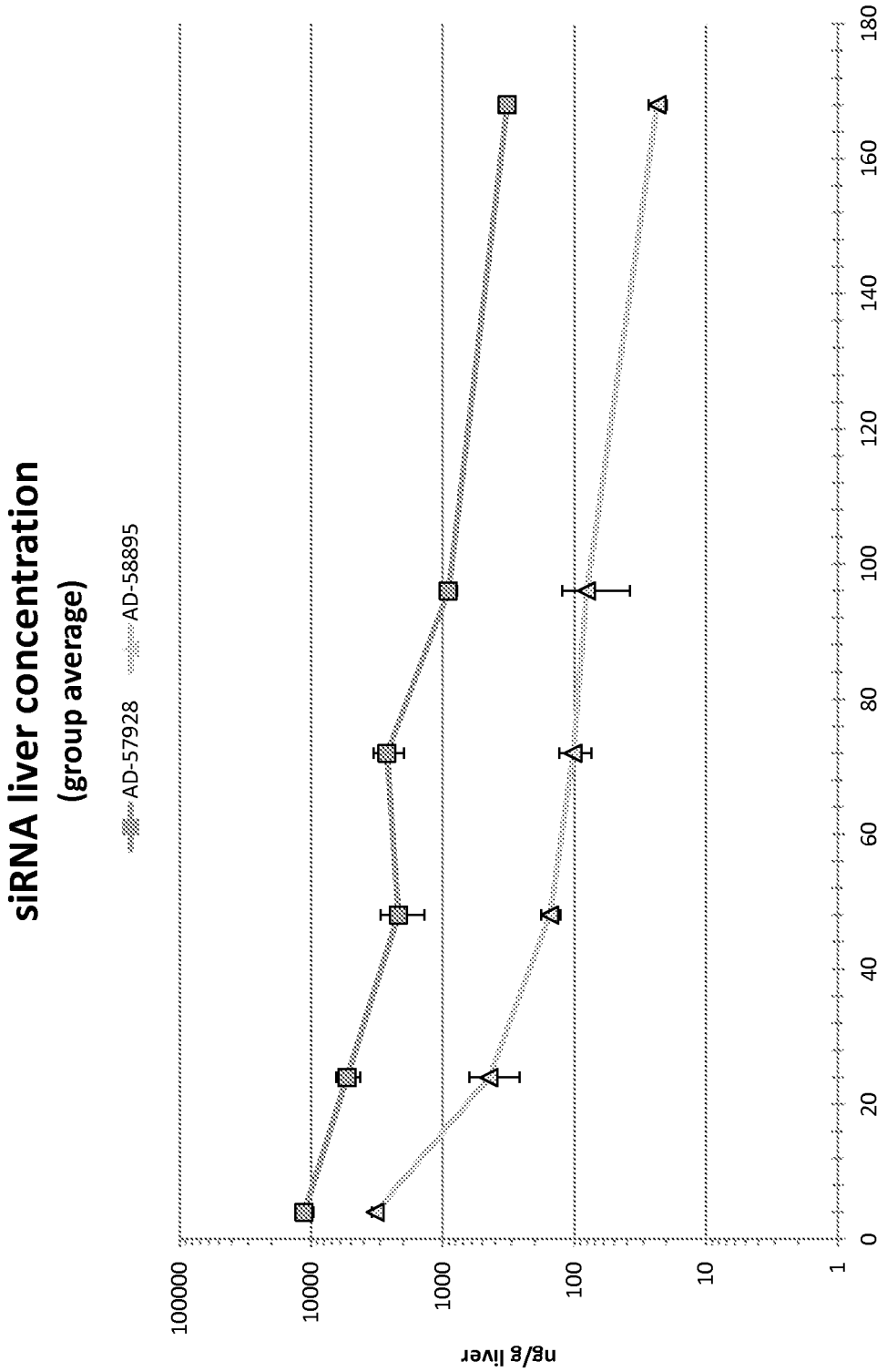

siRNA liver concentration
(group average)
AD-57928
AD-58895
ng/g liver
100000
10000
1000
100
10
1
0
20
40
60
80
100
120
140
160
180
Time, hrs post dose

Figure 10

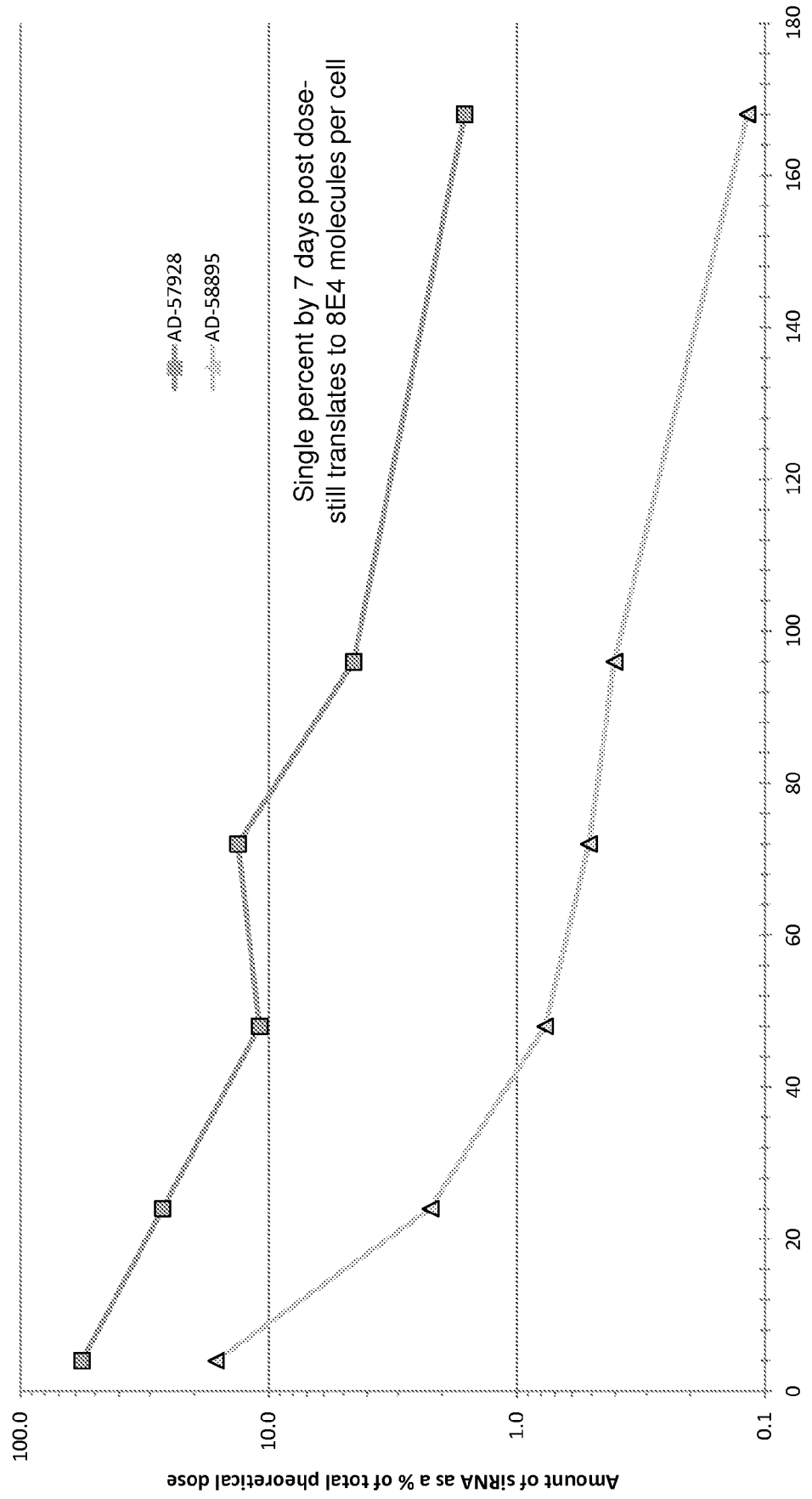

Amount of siRNA as a % of total pheoretical dose
100.0
10.0
1.0
0.1
0
20
40
60
80
100
120
140
160
180
Time, hrs post dose
AD-57928
AD-58895
Single percent by 7 days post dose-
still translates to 8E4 molecules per cell

Figure 11

A.

Duplex	Sense ID	Sense	AS ID	Antisense
AD-57928 (parent)	A-117428	CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	A-117429	asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa
AD-59849	A-121244	CfsusAfgAfcCfuGfUfUfuUfgcuuuuguL96	A-121239	asCfsaAfaagCfaAfaacAfgGfucuAfgsasa
AD-60688	A-120188	csusagacCfuGfuuuugcuuuuguL96	A-121239	asCfsaAfaagCfaAfaacAfgGfucuAfgsasa
AD-59223	A-120188	csusagacCfuGfuuuugcuuuuguL96	A-120190	asCfsaAfAfAfgCfaAfaAfcAfgGfuCfuagsasa
AD-60212	A-122088	csusagacCfuGfudTuugcuuuuguL96	A-120190	asCfsaAfAfAfgCfaAfaAfcAfgGfuCfuagsasa
AD-59228	A-120197	CfsusAfgAfcCfuGfUfUfuUfgCfsuUfsuUfsgsUfsL96	A-120202	asCfsaAfaAfsgCfaAfaacAfgGfuCfsuAfgsasa

B.

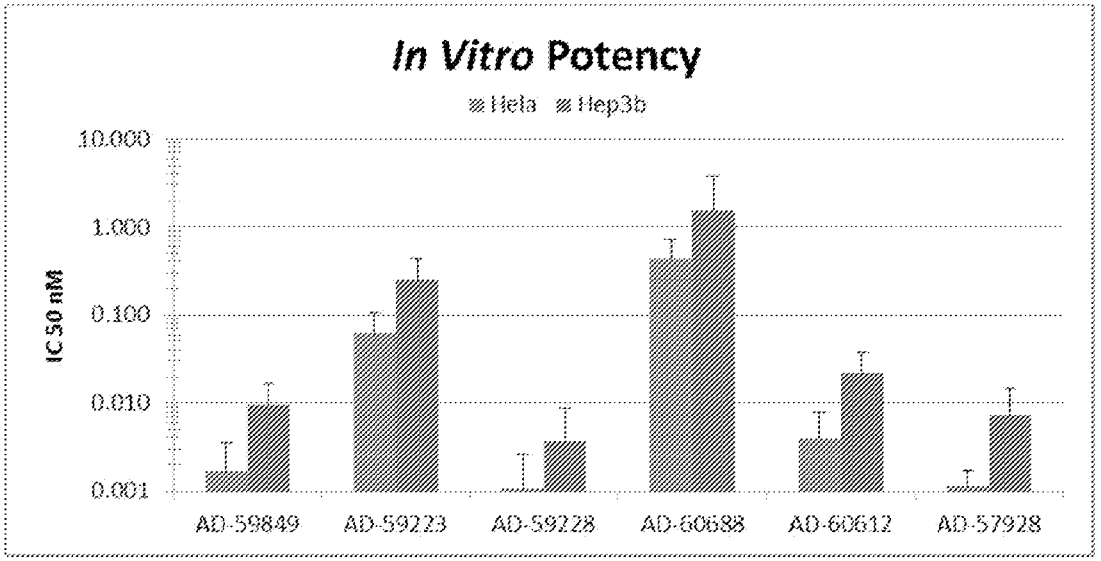


Figure 12

EP 2 929 031 B9

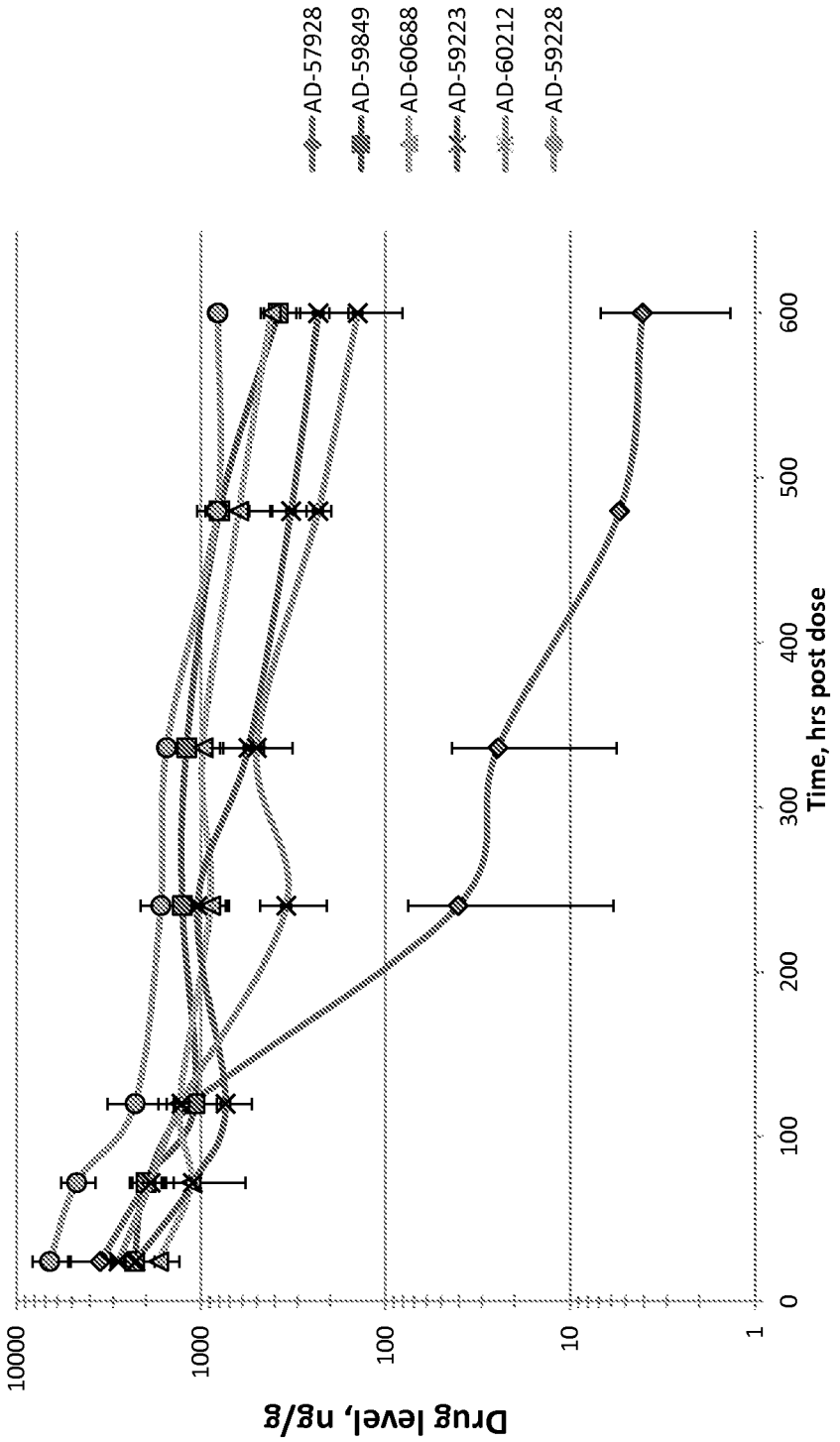

AD-57928
AD-59849
AD-60688
AD-59223
AD-60212
AD-59228
Drug level, ng/g
10000
1000
100
10
1
0
100
200
300
400
500
600
Time, hrs post dose

Figure 13

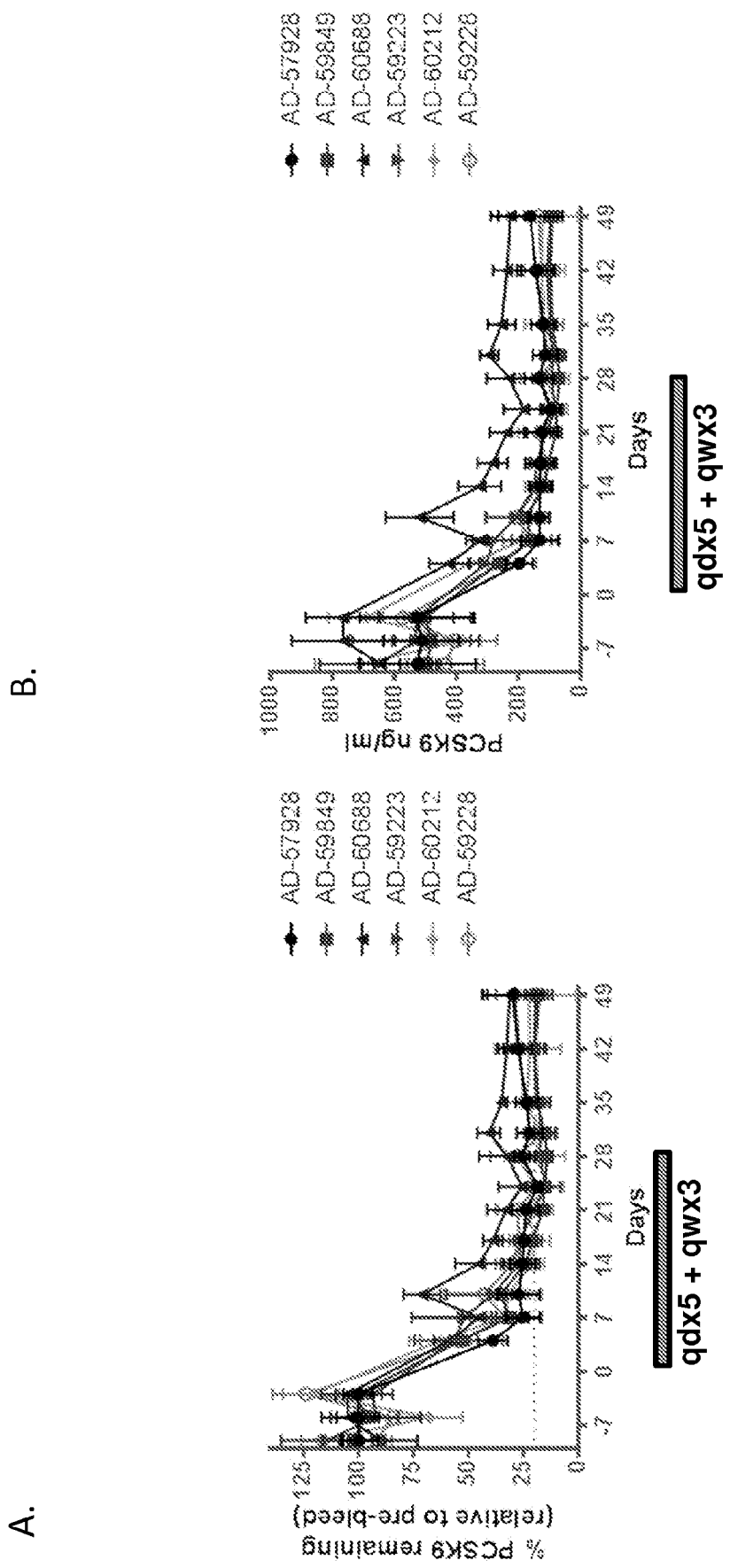

A.
% PCSK9 remaining
(relative to pre-bleed)
125
100
75
50
25
0
-7
0
7
14
21
28
35
42
49
Days
qdx5 + qwx3
AD-57928
AD-59849
AD-60688
AD-59223
AD-60212
AD-59228
B.
PCSK9 ng/ml
1000
800
600
400
200
0
-7
0
7
14
21
28
35
42
49
Days
qdx5 + qwx3
AD-57928
AD-59849
AD-60688
AD-59223
AD-60212
AD-59228

Figure 14

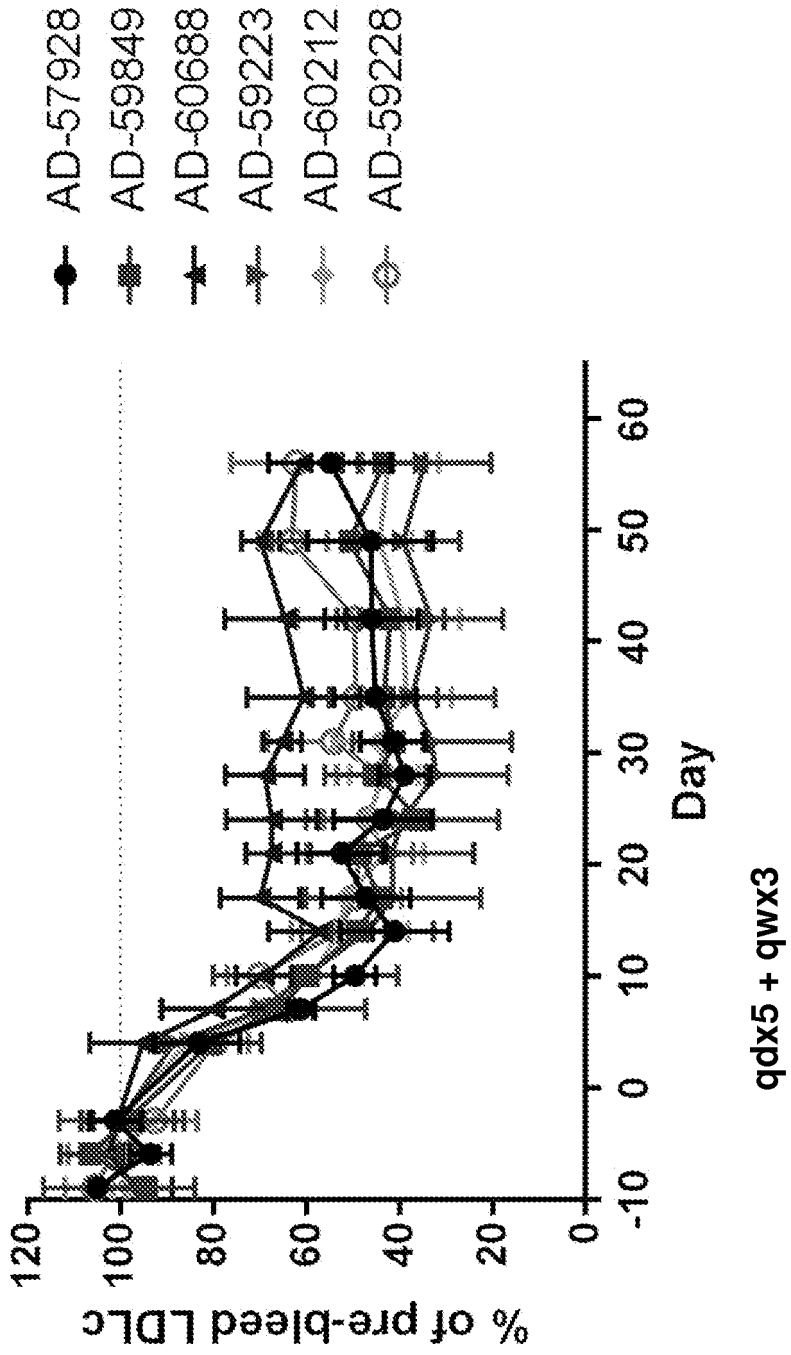

AD-57928
AD-59849
AD-60688
AD-59223
AD-60212
AD-59228
% of pre-bleed LDLc
120
100
80
60
40
20
0
-10
0
10
20
30
40
50
60
Day
qdx5 + qwx3

Figure 15

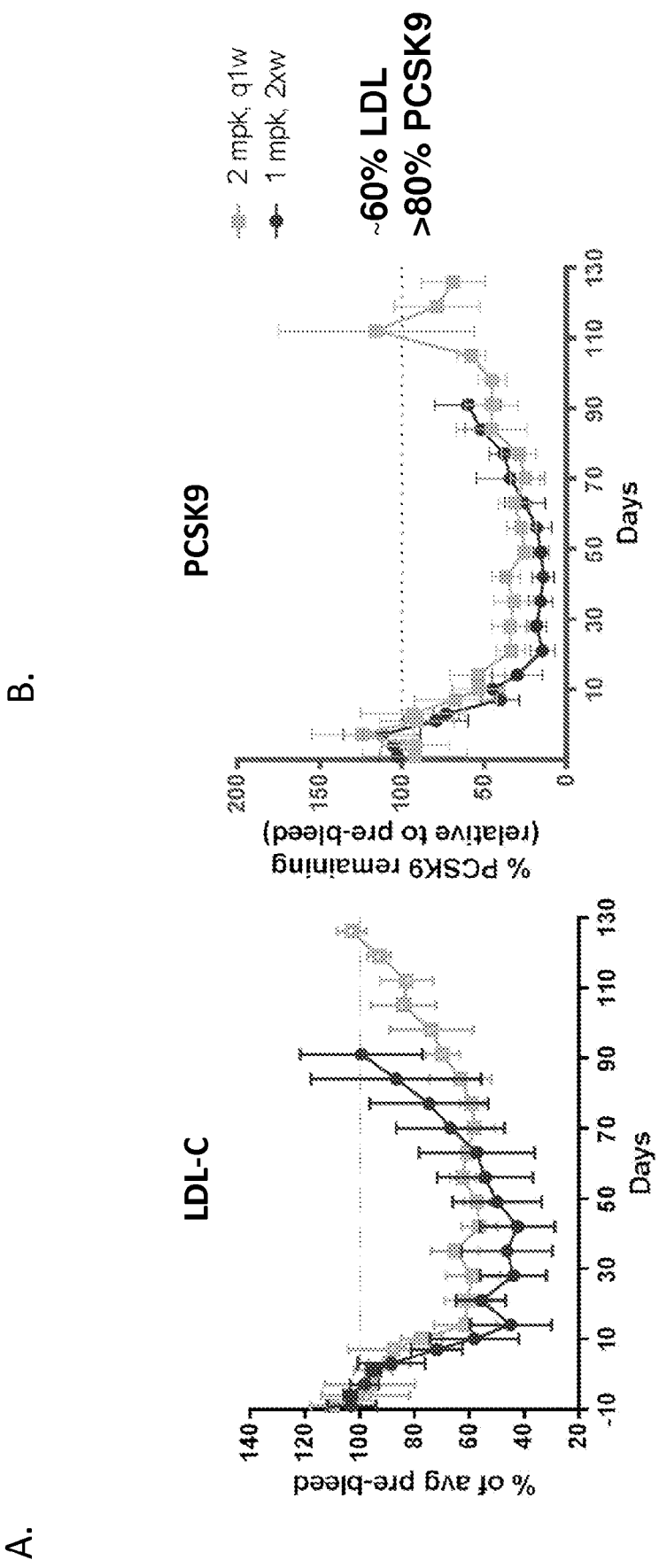

A.
LDL-C
% of avg pre-bleed
Days
B.
PCSK9
% PCSK9 remaining (relative to pre-bleed)
Days
2 mpk, q1w
1 mpk, 2xw
~60% LDL
>80% PCSK9

Figure 16

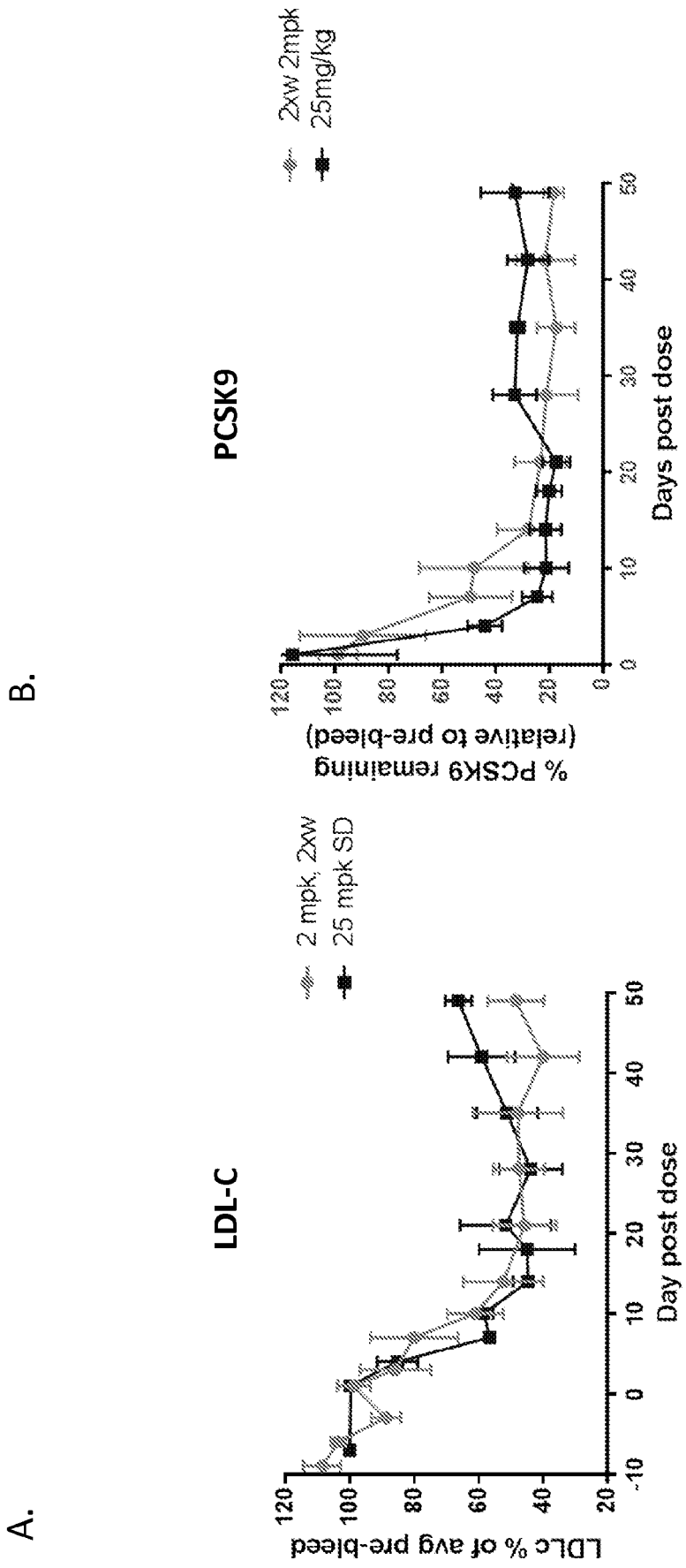

A.
LDL-C
2 mpk, 2xw
25 mpk SD
LDLc % of avg pre-bleed
120
100
80
60
40
20
-10
0
10
20
30
40
50
Day post dose
B.
PCSK9
2xw 2mpk
25mg/kg
% PCSK9 remaining
(relative to pre-bleed)
120
100
80
60
40
20
0
0
10
20
30
40
50
Days post dose

Figure 17

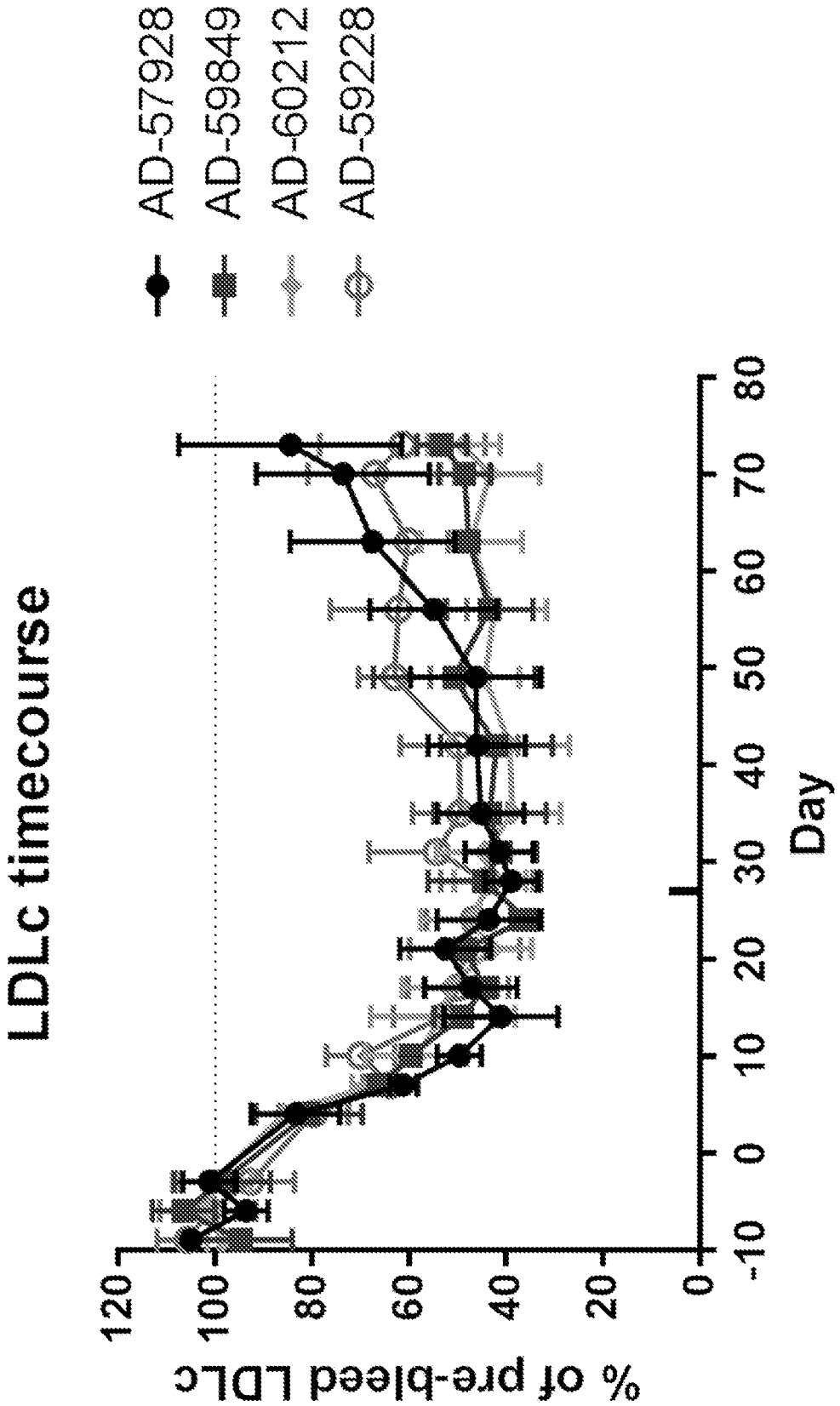

LDLc timecourse
AD-57928
AD-59849
AD-60212
AD-59228
% of pre-bleed LDLc
120
100
80
60
40
20
0
-10
0
10
20
30
40
50
60
70
80
Day

Figure 18

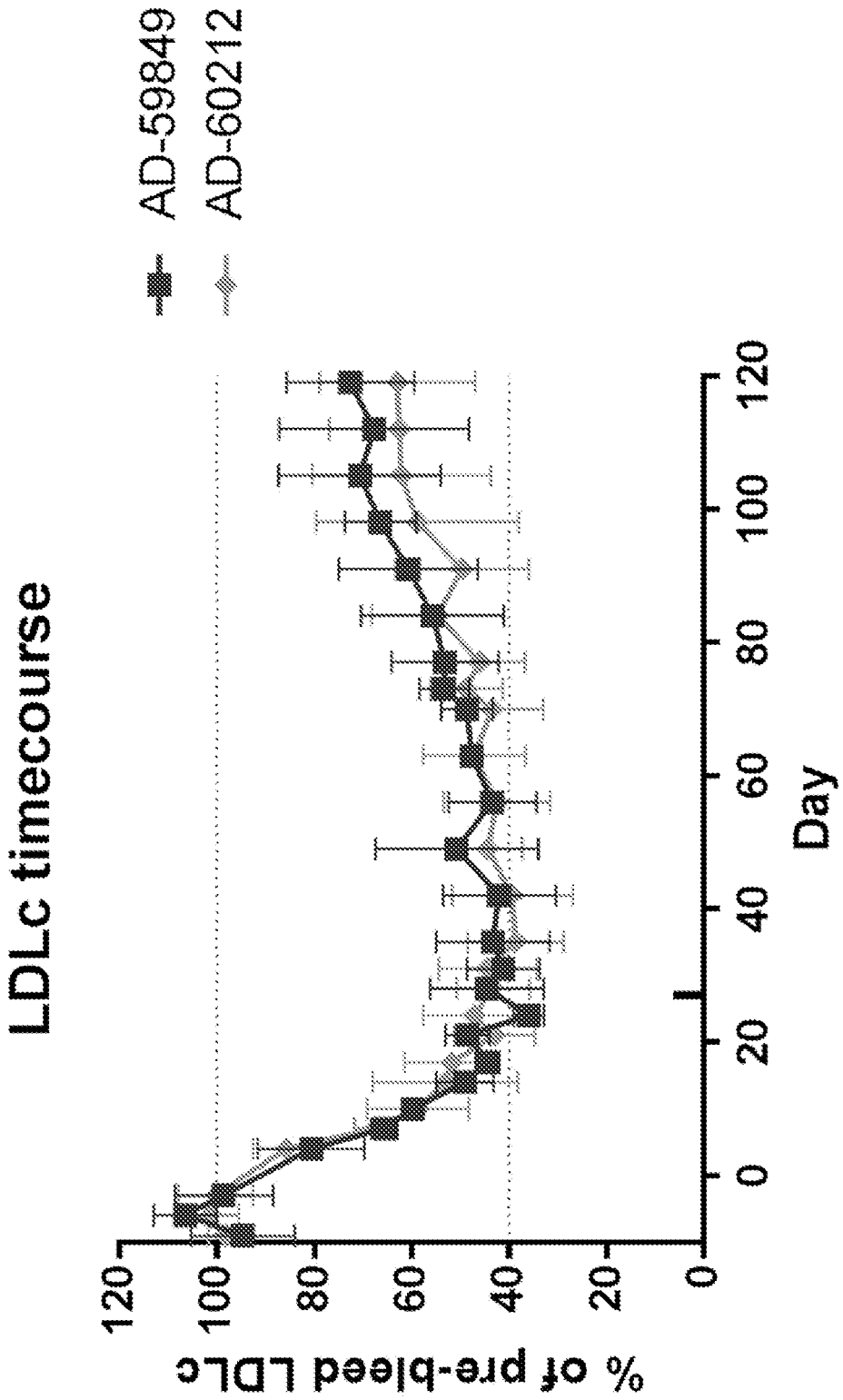

LDLc timecourse
AD-59849
AD-60212
% of pre-bleed LDLc
120
100
80
60
40
20
0
0
20
40
60
80
100
120
Day

Figure 19

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