Compositions and Methods for Inhibiting Gene Expression of LPA

BACKGROUND

Lipoprotein(a) [Lp(a)] is a heterogeneous low density lipoprotein (LDL)-like particle containing a lipid core and apolipoprotein B (apoB-100) with a unique constituent, apolipoprotein (a) (apo(a)), that is attached to apoB-100 through a disulfide bond.

The apo(a) gene (*LPA*) is expressed predominantly in the liver and expression is restricted to human and non-human primates. Lp(a) levels in humans are genetically defined and do not change significantly with diet, exercise, or other lifestyle changes. *LPA* varies in length depending upon the number of Kringle KIV2 domains present and its expression is inversely correlated with the number of domains present. Normal Lp(a) levels range from 0.1-25 mg/dl, with about 25% of the population in the United States of America having Lp(a) levels of 30 mg/dl or higher.

Analysis of Lp(a) levels in multiple studies have implicated high Lp(a) levels as an independent risk factor for cardiovascular disease, stroke, and other related disorders including atherosclerotic stenosis. In addition, genome-wide association analyses have also implicated LPA as a genetic risk factor for diseases such as atherosclerotic stenosis.

When therapeutic lipoprotein apheresis is used to lower both Lp(a) and LDL levels in hyperlipidemic patients, significant reductions of cardiovascular events have been observed. Therefore there exists a need for therapeutics and treatments related to these and other LPA-related diseases.

SUMMARY

In one aspect, the present disclosure refers to an apo(a) gene (LPA) RNA interference (RNAi) agent comprising a sense strand and an antisense strand, wherein the antisense strand comprises the sequence of any one of SEQ ID NO:1280, SEQ ID NO:1281, SEQ ID NO:1282, SEQ ID NO:1283, SEQ ID NO:1246, SEQ ID NO:1242, SEQ ID NO:1244, SEQ ID NO:1248, SEQ ID NO:1250, SEQ ID NO:1252, or SEQ ID NO:1254, and wherein the sense strand comprises a sequence that is complementary to the sequence of the antisense strand.

In another aspect, the present disclosure refers to a pharmaceutical composition comprising the LPA RNAi agent of the present disclosure and a pharmaceutically acceptable excipient.

In yet another aspect, the present disclosure refers to the use of the LPA RNAi agent of any one of the present disclosure in the preparation of a medicament for treating cardiovascular disease or aortic valve stenosis in a subject in need thereof.

In yet another aspect, the present disclosure refers to the use of the LPA RNAi agent of any one of the present disclosure in the preparation of a medicament for treating peripheral artery disease or coronary artery disease in a subject in need thereof

Described herein are LPA (also termed apo(a)) RNA interference (RNAi) agents (also termed RNAi trigger, or trigger) and compositions containing LPA RNAi agents for selectively and efficiently inhibiting expression of the *LPA* gene. *LPA* is the name of the gene which encodes apolipoprotein (a) (apo(a)), a key component of the lipoprotein (a) particle (Lp(a)). The LPA RNAi agents described herein can be used in the prevention or treatment or the preparation of a medicament for the prevention or treatment of diseases including, but not limited to: Berger's disease, peripheral artery disease, coronary artery disease, metabolic syndrome, acute coronary syndrome, aortic valve stenosis, aortic valve regurgitation, aortic dissection, retinal artery occlusion, cerebrovascular disease, mesenteric ischemia, superior mesenteric artery occlusion, renal artery stenosis, stable/unstable angina, acute coronary syndrome, heterozygous or homozygous familial hypercholesterolemia, hyperapobetalipoproteinemia, cerebrovascular atherosclerosis, cerebrovascular disease, and venous thrombosis.

Each LPA RNAi agent includes at least a sense strand and an antisense strand. The sense strand and the antisense strand can be partially, substantially, or fully complementary to each other. The length of the RNAi agent sense and antisense strands described herein each can be 17 to 30 nucleotides in length. In some examples, the sense and antisense strands are independently 17 to 26 nucleotides in length. The sense and antisense strands can be either the same length or different lengths. The RNAi agents described herein, upon delivery to a cell expressing the LPA gene, inhibit the expression of the LPA gene *in vitro* or *in vivo*.

A sense strand of an LPA RNAi agent comprises a nucleotide sequence having at least 90% identity over a core stretch of at least 17 consecutive nucleotides to a sequence in an *LPA* mRNA. In some examples, the sense strand nucleotide sequence having at least 90% identity to a sequence in the *LPA* mRNA is 17, 18, 19, 20, 21, 22, or 23 nucleotides in length. An antisense strand of an LPA RNAi agent comprises a nucleotide sequence having at least 90% complementary over a core stretch of at least 16 consecutive nucleotides to a sequence in the *LPA* mRNA and the corresponding sense strand. In some examples, the antisense strand

nucleotide sequence having at least 90% complementarity to a sequence in the *LPA* mRNA or the corresponding sense strand is 17, 18, 19, 20, 21, 22, or 23 nucleotides in length.

In some examples, one or more LPA RNAi agents are delivered to target cells or tissues using any oligonucleotide delivery technology known in the art. Nucleic acid delivery methods include, but are not limited to, by encapsulation in liposomes, by iontophoresis, or by incorporation into other vehicles, such as hydrogels, cyclodextrins, biodegradable nanocapsules, and bioadhesive microspheres, proteinaceous vectors or Dynamic Polyconjugates™ (DPCs (see, for example WO 2000/053722, WO 2008/0022309, WO 2011/104169, and WO 2012/083185, each of which is incorporated herein by reference). In some examples, an LPA RNAi agent is conjugated to a targeting group. In some examples, the targeting group can include a cell receptor ligand, such as a galactose cluster, including a galactose cluster comprising an N-acetyl-galactosamine trimer.

In some examples are described pharmaceutical compositions comprising one or more LPA RNAi agents. In some examples, an LPA RNAi agent is optionally combined with one or more additional (i.e., second, third, etc.) therapeutics. An additional therapeutic can be another LPA RNAi agent (e.g., an LPA RNAi agent which targets a different sequence within the LPA target). An additional therapeutic can also be a small molecule drug, antibody, antibody fragment, and/or vaccine. The LPA RNAi agents, with or without the one or more additional therapeutics, can be combined with one or more excipients to form pharmaceutical compositions.

In some examples, compositions for delivering an LPA RNAi agent to a liver cell, particularly hepatocytes, *in vivo* are described, comprising: an LPA RNAi agent conjugated to a targeting group. In some examples, the targeting group is a asialoglycoprotein ligand.

Also described are methods of treating a human subject having a pathological state or at risk of developing a pathological state mediated at least in part by LPA expression, the methods comprising the step(s) of administering to the subject a therapeutically effective amount of an LPA RNAi agent or LPA RNAi agent-containing composition. The method of treating a subject with an LPA RNAi agent or LPA RNAi agent-containing composition can optionally be combined with one or more steps of administering one or more additional (i.e., second) therapeutics or treatments. The LPA RNAi agent and additional therapeutics can be administered in a single composition or they may be administered separately. Examples of additional therapeutics include, but are not limited to, HMg Co-A reductase inhibitors (statins), ezetimibe, PCSK-9 inhibitors, CTEP inhibitors, therapies targeting ANGPTL3, therapies targeting APOC3, and niacin.

Use of the described LPA RNAi agents can be used in methods for therapeutic prevention or treatment of diseases including, but not limited to: Berger's disease, peripheral artery disease, coronary artery disease, metabolic syndrome, acute coronary syndrome, aortic valve stenosis, aortic valve regurgitation, aortic dissection, retinal artery occlusion, cerebrovascular disease, mesenteric ischemia, superior mesenteric artery occlusion, renal artery stenosis, stable/unstable angina, acute coronary syndrome, heterozygous or homozygous familial hypercholesterolemia, hyperapobetalipoproteinemia, cerebrovascular atherosclerosis, cerebrovascular disease, and venous thrombosis. Such methods comprise administration of an LPA RNAi agent as described herein to a subject, e.g., a human or animal subject.

The pharmaceutical compositions 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 made by any way commonly known in the art, such as, but not limited to, topical (e.g., by a transdermal patch), pulmonary (e.g., by inhalation or insufflation of powders or aerosols, including by nebulizer, intratracheal, intranasal), epidermal, transdermal, oral or parenteral. Parenteral administration includes, but is not limited to, intravenous, intraarterial, subcutaneous, intraperitoneal or intramuscular injection or infusion; subdermal (e.g., via an implanted device), intracranial, intraparenchymal, intrathecal, and intraventricular, administration. In some examples, the pharmaceutical compositions described herein are administered by subcutaneous injection.

The described LPA RNAi agents and/or compositions can be used in methods for therapeutic treatment of diseases, including but not limited to: Berger's disease, peripheral artery disease, coronary artery disease, metabolic syndrome, acute coronary syndrome, aortic valve stenosis, aortic valve regurgitation, aortic dissection, retinal artery occlusion, cerebrovascular disease, mesenteric ischemia, superior mesenteric artery occlusion, renal artery stenosis, stable/unstable angina, acute coronary syndrome, heterozygous or homozygous familial hypercholesterolemia, hyperapobetalipoproteinemia, cerebrovascular atherosclerosis, cerebrovascular disease, and venous thrombosis. Such methods comprise administration of an LPA RNAi agent as described herein to a subject, e.g., a human or animal subject.

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

Other features and advantages of the invention will be apparent from the following detailed description, and from the claims.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1. Graph illustrating serum Lp(a) protein levels in Lp(a) transgenic (Tg) mice following a single subcutaneous administration of 0.5 mg/kg (dashed line) or 2 mg/kg (solid line) of indicated LPA RNAi agent. Lp(a) levels were normalized to day 1 and saline control.

FIG. 2. Graph illustrating serum Lp(a) protein levels in Lp(a) Tg mice following administration of three subcutaneous doses of 1 mg/kg (dashed line) or 3 mg/kg (solid line) of indicated LPA RNAi agent, administered once a week for three weeks (dose on days 1, 8, and 15). Lp(a) levels were normalized to day 1 and saline control.

FIG. 3. Graph illustrating Lp(a) particle levels in Cynomolgus monkey serum following administration of a single 2 mg/kg AD01196 LPA RNAi agent dosed 1:1 (wt/wt) with delivery polymer on day 1. Lp(a) levels were normalized to two pre-dose values (shown as day 0).

FIG. 4. Graph illustrating Lp(a) particle levels in Cynomolgus monkey serum following administration of 4 mg/kg or 6 mg/kg LPA RNAi agent dosed 1:1 (wt/wt) with delivery polymer on day 1 and day 71. Lp(a) levels were normalized to two pre-dose values (shown as day 0). 4 mg/kg dose = black circles; 6 mg/kg dose = gray squares.

FIG. 5. Graph illustrating Lp(a) particle levels in Cynomolgus monkey serum following three weekly subcutaneous doses of 3 mg/kg of AD02819 LPA RNAi agent on days 1, 8, and 15. Lp(a) levels were normalized to three pre-dose values (shown as day 0).

FIG. 6. Graph illustrating Lp(a) particle levels in Cynomolgus monkey serum following a single subcutaneous administration of 3 mg/kg of LPA RNAi agent on day 1. AD03460 and AD03536 groups received an additional 1 mg/kg dose of LPA RNAi agent on day 48. Lp(a) levels were normalized to three pre-dose values (shown as day 0).

DETAILED DESCRIPTION

Described herein are RNAi agents for inhibiting expression of the LPA gene (referred to herein as LPA RNAi agents). The RNAi agents described herein, upon delivery to a cell expressing the *LPA* gene, inhibit or knockdown expression of LPA *in vitro* and/or *in vivo* through the biological process of RNA interference (RNAi). As used herein, unless specifically noted otherwise, LPA may refer to an *LPA* gene, an *LPA* mRNA, or an LP(a) protein, as appropriate.

An LPA RNAi agent comprises a sense strand and an antisense strand. The sense strand and

antisense strand each contain a core sequence 17-23 nucleobases in length. An antisense strand core sequence is 100% (perfectly) complementary or at least 90% (substantially) complementary to a nucleotide sequence (sometimes referred to, e.g., as a target sequence) present in an *LPA* mRNA. A sense strand core sequence is 100% (perfectly) complementary or at least 90% (substantially) complementary to a sequence in the antisense strand and thus the sense strand core sequence is perfectly identical or at least 90% identical to a nucleotide sequence (target sequence) present in the LPA mRNA. A sense strand core sequence can be the same length as a corresponding antisense core sequence or it can be a different length. In some embodiments, the antisense strand core sequence is 17, 18, 19, 20, 21, 22, or 23 nucleotides in length. In some embodiments, the sense strand core sequence is 17, 18, 19, 20, 21, 22, or 23 nucleotides in length.

LPA RNAi agent sense and antisense strands anneal to form a duplex. A sense strand and an antisense strand of an LPA RNAi agent are partially, substantially, or fully complementary to each other. Within the complementary duplex region, the sense strand core sequence is at least 90% complementary or 100% complementary to the antisense core sequence. In some embodiments, the sense strand core sequence contains a sequence of at least 17, at least 18, at least 19, at least 20, or at least 21 nucleotides that is at least 90% or 100% complementary to a corresponding 17, 18, 19, 20, or 21 nucleotide sequence of the antisense strand core sequence (i.e., the sense strand and antisense core sequences of an LPA RNAi agent have a region of at least 17, at least 18, at least 19, at least 20, or at least 21 nucleotides that is at least 90% base paired or 100% base paired.)

As used herein, and unless otherwise indicated, the term "complementary," when used to describe a first nucleotide sequence (e.g., RNAi agent sense strand or LPA mRNA) in relation to a second nucleotide sequence (e.g., RNAi agent antisense strand), refers to the ability of an oligonucleotide or polynucleotide comprising the first nucleotide sequence to hybridize (form base pair hydrogen bonds) and form a duplex or double helical structure under certain conditions with an oligonucleotide or polynucleotide comprising the second nucleotide sequence. Complementary sequences include Watson-Crick base pairs or non-Watson-Crick base pairs and include natural or modified nucleotides or nucleotide mimics as long as the above requirements with respect to their ability to hybridize are fulfilled. "Perfectly complementary" or "fully complementary" means that all (100%) of the bases in a contiguous sequence of a first polynucleotide will hybridize with the same number of bases in a contiguous

sequence of a second polynucleotide. The contiguous sequence may comprise all or a part of a first or second nucleotide sequence. As used herein, "partial complementary" means that in a hybridized pair of nucleobase sequences, at least 70% of the bases in a contiguous sequence of a first polynucleotide will hybridize with the same number of bases in a contiguous sequence of a second polynucleotide. As used herein, "substantial complementary" means that in a hybridized pair of nucleobase sequences, at least 85% of the bases in a contiguous sequence of a first polynucleotide will hybridize with the same number of bases in a contiguous sequence of a second polynucleotide. The terms "complementary", "fully complementary" and "substantially complementary" as used herein may be used with respect to the base matching between the sense strand and the antisense strand of an RNAi agent, or between the antisense strand of an RNAi agent and a sequence of an LPA mRNA. Sequence identity or complementarity is independent of modification. For the purposes of determining identity or complementarity, for example, a and Af are complementary to U (or T) and identical to A.

The length of the LPA RNAi agent sense and antisense strands described herein are independently 17 to 30 nucleotides in length. In some embodiments, the sense and antisense strands are independently 17 to 26 nucleotides in length. In some embodiments, the sense and antisense strands are 19-26 nucleotides in length. In some embodiments, the described RNAi agent sense and antisense strands are independently 17, 18, 19, 20, 21, 22, 23, 24, 25, or 26 nucleotides in length. The sense and antisense strands can be either the same length or they can be different lengths. In some embodiments, a sense strand and an antisense strand are each 26 nucleotides in length. In some embodiments, a sense strand is 23 nucleotides in length and an antisense strand is 21 nucleotides in length. In some embodiments, a sense strand is 22 nucleotides in length and an antisense strand is 21 nucleotides in length. In some embodiments, a sense strand is 21 nucleotides in length and an antisense strand is 21 nucleotides in length. In some embodiments, a sense strand is 19 nucleotides in length and an antisense strand is 21 nucleotides in length.

The sense strand and/or the antisense strand may optionally and independently contain an additional 1, 2, 3, 4, 5, or 6 nucleotides (extension) at the 3′ end, the 5′ end, or both the 3′ and 5′ ends of the core sequences. The antisense strand additional nucleotides, if present, may or may not be complementary to the corresponding sequence in the LPA mRNA. The sense strand additional nucleotides, if present, may or may not be identical to the corresponding sequence in the LPA mRNA. The antisense strand additional nucleotides, if present, may or may not be

complementary to the corresponding sense strand's additional nucleotides, if present.

As used herein, an extension comprises 1, 2, 3, 4, 5, or 6 nucleotides at the 5' and/or 3' end of the sense strand core sequence and/or antisense strand core sequence. The extension nucleotides on a sense strand may or may not be complementary to nucleotides, either core sequence nucleotides or extension nucleotides, in the corresponding antisense strand. Conversely, the extension nucleotides on an antisense strand may or may not be complementary to nucleotides, either core sequence nucleotides or extension nucleotides, in the corresponding sense strand. In some embodiments, both the sense strand and the antisense strand of an RNAi agent contain 3′ and 5′ extensions. In some embodiments, one or more of the 3′ extension nucleotides of one strand base pairs with one or more 5′ extension nucleotides of the other strand. In other embodiments, one or more of 3′ extension nucleotides of one strand do not base pair with one or more 5′ extension nucleotides of the other strand. In some embodiments, an LPA RNAi agent has an antisense strand having a 3′ extension and a sense strand having a 5′ extension.

In some embodiments an LPA RNAi agent comprises an antisense strand having a 3′ extension of 1, 2, 3, 4, 5, or 6 nucleotides in length. In other embodiments, an LPA RNAi agent comprises an antisense strand having a 3′ extension of 1, 2, or 3 nucleotides in length. In some embodiments, one or more of the antisense strand extension nucleotides comprise uracil or thymidine nucleotides or nucleotides which are complementary to the corresponding LPA mRNA sequence. In some embodiments, a 3′ antisense strand extension includes or consists of, but is not limited to: Ab, AbAb, AUA, UGCUU, CUG, UG, UGCC, CUGCC, CGU, CUU, UGCCUA, CUGCCU, UGCCU, UGAUU, GCCUAU, T, TT (each listed 5′ to 3′).

In some embodiments, an LPA RNAi agent comprises an antisense strand having a 5′ extension of 1, 2, 3, 4, or 5 nucleotides in length. In other embodiments, an LPA RNAi agent comprises an antisense strand having a 5′ extension of 1 or 2 nucleotides in length. In some embodiments, one or more of the antisense strand extension nucleotides comprises uracil or thymidine nucleotides or nucleotides which are complementary to the corresponding LPA mRNA sequence. In some embodiments, the 5′ antisense strand extension includes or consists of, but is no limited to, UA, TU, U, T, CUC (each listed 5′ to 3′). An antisense strand may have any of the 3' extensions described above in combination with any of the 5′ antisense strand extensions described, if present.

In some embodiments, an LPA RNAi agent comprises a sense strand having a 3′ extension of 1, 2, 3, 4, or 5 nucleotides in length. In some embodiments, one or more of the sense strand extension nucleotides comprises adenosine, uracil, or thymidine nucleotides, AT dinucleotide, or nucleotides which correspond to nucleotides in the LPA mRNA sequence. In some embodiments, the 3′ sense strand extension includes or consists of, but is no limited to: T, UUAb, UAb, Ab, UT, TT, UUT, TTT, or TTTT (each listed 5′ to 3′).

In some embodiments, an LPA RNAi agent comprises a sense strand having a 5′ extension of 1, 2, 3, 4, 5, or 6 nucleotides in length. In some embodiments, one or more of the sense strand extension nucleotides comprise uracil or adenosine nucleotides or nucleotides which correspond to nucleotides in the LPA mRNA sequence. In some embodiments, the sense strand 5′ extension can be, but is not limited to: CA, AUAGGC, AUAGG, AUAG, AUA, A, AA, AC, GCA, GGCA, GGC, UAUCA, UAUC, Ab, UCA, UAU (each listed 5′ to 3′). A sense strand may have a 3′ extension and/or a 5' extension.

Examples of nucleotide sequences used in forming LPA RNAi agents are provided in Tables 1, 2A, 2B, 3A, and 3B. As used herein, the term "sequence" or "nucleotide sequence" refers to a succession or order of nucleobases, nucleotides, and/or nucleosides, whether modified or unmodified, described with a succession of letters using the standard nucleotide nomenclature and the key for modified nucleotides described herein.

RNAi agents include, but are not limited to: short interfering RNAs (siRNAs), double-strand RNAs (dsRNA), micro RNAs (miRNAs), short hairpin RNAs (shRNA), and dicer substrates (e.g., U.S. Patent Nos. 8084599, 8349809, and 8513207).

Unmodified LPA RNAi agent sense strand and antisense strand sequences are provided in Table 1. In forming LPA RNAi agents, each of the nucleotides in each of the sequences listed in Table 1 may be a modified nucleotide.

Table 1. Unmodified LPA RNAi agent antisense strand and sense strand sequences.

Antisense strand base sequence 5' → 3'	SEQ ID NO.	Sense strand base sequence 5' → 3'	SEQ ID NO.
TCGGCAGUCCCUUCUGCGUTT	1	ACGCAGAAGGGACUGCCGAT	190
TGUAGCACUCCUGCACCCCTT	2	GGGGUGCAGGAGUGCUACAT	191
TAAUAAGGGGCUGCCACAGTT	3	CUGUGGCAGCCCCUUAUUAT	192
TUAACAAUAAGGGGCUGCCTT	4	GGCAGCCCCUUAUUGUUAAT	193
TGUAUAACAAUAAGGGGCUTT	5	AGCCCCUUAUUGUUAUACAT	194
TCGUAUAACAAUAAGGGGCTT	6	GCCCCUUAUUGUUAUACGAT	195
TCGUCUGAGCAUUGUGUCATT	7	UGACACAAUGCUCAGACGAT	196
TGCGUCUGAGCAUUGUGUCTT	8	GACACAAUGCUCAGACGCAT	197
TUGCGUCUGAGCAUUGUGUTT	9	ACACAAUGCUCAGACGCAAT	198
TUCUGCGUCUGAGCAUUGUTT	10	ACAAUGCUCAGACGCAGAAT	199
TGGAUCUGGAUUUCGGCAGTT	11	CUGCCGAAAUCCAGAUCCAT	200
TCAGGAUCUGGAUUUCGGCTT	12	GCCGAAAUCCAGAUCCUGAT	201
TCAUCUGAGCAUCGUGUCATT	13	UGACACGAUGCUCAGAUGAT	202
TGCAUCUGAGCAUCGUGUCTT	14	GACACGAUGCUCAGAUGCAT	203
TUGCAUCUGAGCAUCGUGUTT	15	ACACGAUGCUCAGAUGCAAT	204
TUCUGCAUCUGAGCAUCGUTT	16	ACGAUGCUCAGAUGCAGAAT	205
TAAAGCCUCUAGGCUUGGATT	17	UCCAAGCCUAGAGGCUUUAT	206
TGUACCCCGGGGGUUUCCUTT	18	AGGAAACCCCCGGGGUACAT	207
TUGUACCCCGGGGGUUUCCTT	19	GGAAACCCCCGGGGUACAAT	208
TCUGUACCCCGGGGGUUUCTT	20	GAAACCCCCGGGGUACAGAT	209
TUCCAUAAUGGUAGUAGCATT	21	UGCUACUACCAUUAUGGAAT	210
TGUCCAUAAUGGUAGUAGCTT	22	GCUACUACCAUUAUGGACAT	211
TCUCUGUCCAUAAUGGUAGTT	23	CUACCAUUAUGGACAGAGAT	212
TCGACUAUGCUGGUGUGGUTT	24	ACCACACCAGCAUAGUCGAT	213
TCCGACUAUGCUGGUGUGGTT	25	CCACACCAGCAUAGUCGGAT	214
TUCCGACUAUGCUGGUGUGTT	26	CACACCAGCAUAGUCGGAAT	215
TGGUCCGACUAUGCUGGUGTT	27	CACCAGCAUAGUCGGACCAT	216
TUUUCUGGGGUCCGACUAUTT	28	AUAGUCGGACCCCAGAAAAT	217
TUUUUCUGGGGUCCGACUATT	29	UAGUCGGACCCCAGAAAAAT	218
TGCGAAUCUCAGCAUCUGGTT	30	CCAGAUGCUGAGAUUCGCAT	219
TCCAAGGGCGAAUCUCAGCTT	31	GCUGAGAUUCGCCCUUGGAT	220
TACCAAGGGCGAAUCUCAGTT	32	CUGAGAUUCGCCCUUGGUAT	221
TCACCAAGGGCGAAUCUCATT	33	UGAGAUUCGCCCUUGGUGAT	222
TACACCAAGGGCGAAUCUCTT	34	GAGAUUCGCCCUUGGUGUAT	223
TCCUGACACUGGGAUCCAUTT	35	AUGGAUCCCAGUGUCAGGAT	224
TUGCAAGGACACUUGAUUCTT	36	GAAUCAAGUGUCCUUGCAAT	225
TUUGCAAGGACACUUGAUUTT	37	AAUCAAGUGUCCUUGCAAAT	226
TUUGCUCCGUUGGUGCUUCTT	38	GAAGCACCAACGGAGCAAAT	227
TAAUGAGCCUCGAUAACUCTT	39	GAGUUAUCGAGGCUCAUUAT	228
TGAAUGAGCCUCGAUAACUTT	40	AGUUAUCGAGGCUCAUUCAT	229
TGGAUAAUAUUCUGUUGUCTT	41	GACAACAGAAUAUUAUCCAT	230
TCCAUGGUAUAACACCAAGTT	42	CUUGGUGUUAUACCAUGGAT	231

TGAUCCAUGGUAUAACACCTT	43	GGUGUUAUACCAUGGAUCAT	232
TAUUGGGAUCCAUGGUAUATT	44	UAUACCAUGGAUCCCAAUAT	233
TCAUUGGGAUCCAUGGUAUTT	45	AUACCAUGGAUCCCAAUGAT	234
TACAUUGGGAUCCAUGGUATT	46	UACCAUGGAUCCCAAUGUAT	235
TGACAUUGGGAUCCAUGGUTT	47	ACCAUGGAUCCCAAUGUCAT	236
TGACAUUGUGUCAGGUUGCTT	48	GCAACCUGACACAAUGUCAT	237
TCACUGGACAUUGUGUCAGTT	49	CUGACACAAUGUCCAGUGAT	238
TACUUGAUUCUGUCACUGGTT	50	CCAGUGACAGAAUCAAGUAT	239
TGAGAAUGAGCCUCGAUAATT	51	UUAUCGAGGCUCAUUCUCAT	240
TCCAUUUGGGUAGUAUUCUTT	52	AGAAUACUACCCAAAUGGAT	241
TCACCAUUUGGGUAGUAUUTT	53	AAUACUACCCAAAUGGUGAT	242
TCCACCAUUUGGGUAGUAUTT	54	AUACUACCCAAAUGGUGGAT	243
TAUAACACCAAGGGCGAAUTT	55	AUUCGCCCUUGGUGUUAUAT	244
TACUGGGAUCCAUGGUAUATT	56	UAUACCAUGGAUCCCAGUAT	245
TCACUGGGAUCCAUGGUAUTT	57	AUACCAUGGAUCCCAGUGAT	246
TACCACCGUGGGAGUUGUGTT	58	CACAACUCCCACGGUGGUAT	247
TCAAGACUGACAUGUUCUUTT	59	AAGAACAUGUCAGUCUUGAT	248
TGGGAGUUGUGAGGACACUTT	60	AGUGUCCUCACAACUCCCAT	249
TUCUCAGGUGGUGCUUGUUTT	61	AACAAGCACCACCUGAGAAT	250
TCACAGGGCUUUUCUCAGGTT	62	CCUGAGAAAAGCCCUGUGAT	251
TGAUGCCAGUGUGGUAUCATT	63	UGAUACCACACUGGCAUCAT	252
TUGAUGCCAGUGUGGUAUCTT	64	GAUACCACACUGGCAUCAAT	253
TGACACCUGAUUCUGUUUCTT	65	GAAACAGAAUCAGGUGUCAT	254
TGGACACCUGAUUCUGUUUTT	66	AAACAGAAUCAGGUGUCCAT	255
TCUAGGACACCUGAUUCUGTT	67	CAGAAUCAGGUGUCCUAGAT	256
TAUAAGGGGCUGCCACAGGTT	68	CCUGUGGCAGCCCCUUAUAT	257
TAACAAUAAGGGGCUGCCATT	69	UGGCAGCCCCUUAUUGUUAT	258
TGUCCGACUAUGCUGGUGUTT	70	ACACCAGCAUAGUCGGACAT	259
TUCUCAGCAUCUGGAUUCCTT	71	GGAAUCCAGAUGCUGAGAAT	260
TCGAAUCUCAGCAUCUGGATT	72	UCCAGAUGCUGAGAUUCGAT	261
TAAGGGCGAAUCUCAGCAUTT	73	AUGCUGAGAUUCGCCCUUAT	262
TUGACACUGGGAUCCAUGGTT	74	CCAUGGAUCCCAGUGUCAAT	263
TCCGUUGGUGCUUCUUCAGTT	75	CUGAAGAAGCACCAACGGAT	264
TCUUGAUUCUGUCACUGGATT	76	UCCAGUGACAGAAUCAAGAT	265
TCACCGUGGGAGUUGUGAGTT	77	CUCACAACUCCCACGGUGAT	266
TUCUAGGACACCUGAUUCUTT	78	AGAAUCAGGUGUCCUAGAAT	267
TAGUCUCUAGGACACCUGATT	79	UCAGGUGUCCUAGAGACUAT	268
TCAAUAAGGGGCUGCCACATT	80	UAUAGCCCCUUAUUGUUAUACAT	269
TCUGCGUCUGAGCAUUGUGTT	81	UAUGCCCCUUAUUGUUAUACGAT	270
TACAGGAUCUGGAUUUCGGTT	82	UAUGACACAAUGCUCAGACGCAT	271
TCCGGGGGUUUCCUCAGUCTT	83	UAUACACAAUGCUCAGACGCAAT	272
TUGUCCAUAAUGGUAGUAGTT	84	UAUUUAUCGAGGCUCAUUCUCAT	273
TUCUGUCCAUAAUGGUAGUTT	85	UAUGAAACAGAAUCAGGUGUCAT	274
TACUCUGUCCAUAAUGGUATT	86	UAUACACCAGCAUAGUCGGACAT	275
TAACUCUGUCCAUAAUGGUTT	87	UAUUCCAGAUGCUGAGAUUCGAT	276
TGGGCGAAUCUCAGCAUCUTT	88	UAUAUGCUGAGAUUCGCCCUUAT	277

TAGGGCGAAUCUCAGCAUCTT	89	UAUCCAUGGAUCCCAGUGUCAAT	278
TAACACCAAGGGCGAAUCUTT	90	UGUGGCAGCCCCUUAUUGAT	279
TAGGACACUUGAUUCUGUCTT	91	CACAAUGCUCAGACGCAGAT	280
TGGACCAAGACUGACAUGUTT	92	CCGAAAUCCAGAUCCUGUAT	281
TGGUCAGGCCACCAUUUGGTT	93	GACUGAGGAAACCCCCGGAT	282
TAUCCAUGGUAUAACACCATT	94	CUACUACCAUUAUGGACAAT	283
TGGGAUCCAUGGUAUAACATT	95	ACUACCAUUAUGGACAGAAT	284
TUGGACAUUGUGUCAGGUUTT	96	UACCAUUAUGGACAGAGUAT	285
TAUUCUGUCACUGGACAUUTT	97	ACCAUUAUGGACAGAGUUAT	286
TGGUGCUUGUUCAGAAACATT	98	AGAUGCUGAGAUUCGCCCAT	287
TGGAGAAUGAGCCUCGAUATT	99	GAUGCUGAGAUUCGCCCUAT	288
TGUGGAGAAUGAGCCUCGATT	100	AGAUUCGCCCUUGGUGUUAT	289
TCCGUGGGAGUUGUGAGGATT	101	GACAGAAUCAAGUGUCCUAT	290
TGGACCACCGUGGGAGUUGTT	102	ACAUGUCAGUCUUGGUCCAT	291
TUGCUUGUUCAGAAGGAGCTT	103	CCAAAUGGUGGCCUGACCAT	292
TCUGAUGCCAGUGUGGUAUTT	104	UGGUGUUAUACCAUGGAUAT	293
TUAGGACACCUGAUUCUGUTT	105	UGUUAUACCAUGGAUCCCAT	294
TCUCUAGGACACCUGAUUCTT	106	AACCUGACACAAUGUCCAAT	295
TUCUCUAGGACACCUGAUUTT	107	AAUGUCCAGUGACAGAAUAT	296
TGUCUCUAGGACACCUGAUTT	108	UGUUUCUGAACAAGCACCAT	297
TGAGAAUGAGCCUCGAUAACUCUUAU	109	UAUCGAGGCUCAUUCUCCAT	298
TGACACCUGAUUCUGUUUCUGAGUAU	110	UCGAGGCUCAUUCUCCACAT	299
TCGUAUAACAAUAAGGGGCUGCCUAU	111	UCCUCACAACUCCCACGGAT	300
TGCGUCUGAGCAUUGUGUCAGGUUAU	112	CAACUCCCACGGUGGUCCAT	301
TUGCGUCUGAGCAUUGUGUCAGGUAU	113	GCUCCUUCUGAACAAGCAAT	302
TAAGGGCGAAUCUCAGCAUCUGGUAU	114	AUACCACACUGGCAUCAGAT	303
UUAACAAUAAGGGGCUGCAb	115	ACAGAAUCAGGUGUCCUAAT	304
UGUAUAACAAUAAGGGGCAb	116	GAAUCAGGUGUCCUAGAGAT	305
UCGUAUAACAAUAAGGGGAb	117	AAUCAGGUGUCCUAGAGAAT	306
UGCGUCUGAGCAUUGUGUAb	118	AUCAGGUGUCCUAGAGACAT	307
UUGCGUCUGAGCAUUGUGAb	119	UAUAUAGUUAUCGAGGCUCAUUCUCA	308
UCAGGAUCUGGAUUUCGGAb	120	UAUAUCAGAAACAGAAUCAGGUGUCA	309
UUGCAUCUGAGCAUCGUGAb	121	UAUAUCAGCCCCUUAUUGUUAUACGA	310
UCGACUAUGCUGGUGUGGAb	122	UAUAUCUGACACAAUGCUCAGACGCA	311
UUUUCUGGGGUCCGACUAAb	123	UAUAUUGACACAAUGCUCAGACGCAA	312
UGCGAAUCUCAGCAUCUGAb	124	UAUAUAGAUGCUGAGAUUCGCCCUUA	313
UUGCAAGGACACUUGAUUAb	125	GCAGCCCCUUAUUGUUAA	314
UAAUGAGCCUCGAUAACUAb	126	GCCCCUUAUUGUUAUACA	315
UGAAUGAGCCUCGAUAACAb	127	CCCCUUAUUGUUAUACGA	316
UGACAUUGUGUCAGGUUGAb	128	ACACAAUGCUCAGACGCA	317
UGAGAAUGAGCCUCGAUAAb	129	CACAAUGCUCAGACGCAA	318
UCCAUUUGGGUAGUAUUCAb	130	CCGAAAUCCAGAUCCUGA	319
UCACCAUUUGGGUAGUAUAb	131	CACGAUGCUCAGAUGCAA	320
UGACACCUGAUUCUGUUUAb	132	CCACACCAGCAUAGUCGA	321
UGGACACCUGAUUCUGUUAb	133	UAGUCGGACCCCAGAAAA	322
UUAACAAUAAGGGGCUGAbAb	134	CAGAUGCUGAGAUUCGCA	323

UGUAUAACAAUAAGGGGAbAb	135	AAUCAAGUGUCCUUGCAA	324
UCGUAUAACAAUAAGGGAbAb	136	AGUUAUCGAGGCUCAUUA	325
UGCGUCUGAGCAUUGUGAbAb	137	GUUAUCGAGGCUCAUUCA	326
UUGCGUCUGAGCAUUGUAbAb	138	CAACCUGACACAAUGUCA	327
UCAGGAUCUGGAUUUCGAbAb	139	UAUCGAGGCUCAUUCUCA	328
UUGCAUCUGAGCAUCGUAbAb	140	GAAUACUACCCAAAUGGA	329
UCGACUAUGCUGGUGUGAbAb	141	AUACUACCCAAAUGGUGA	330
UUUUCUGGGGUCCGACUAbAb	142	AAACAGAAUCAGGUGUCA	331
UGCGAAUCUCAGCAUCUAbAb	143	AACAGAAUCAGGUGUCCA	332
UUGCAAGGACACUUGAUAbAb	144	CAGCCCCUUAUUGUUAA	333
UAAUGAGCCUCGAUAACAbAb	145	CCCCUUAUUGUUAUACA	334
UGAAUGAGCCUCGAUAAAbAb	146	CCCUUAUUGUUAUACGA	335
UGACAUUGUGUCAGGUUAbAb	147	CACAAUGCUCAGACGCA	336
UGAGAAUGAGCCUCGAUAbAb	148	ACAAUGCUCAGACGCAA	337
UCCAUUUGGGUAGUAUUAbAb	149	CGAAAUCCAGAUCCUGA	338
UCACCAUUUGGGUAGUAAbAb	150	ACGAUGCUCAGAUGCAA	339
UGACACCUGAUUCUGUUAbAb	151	CACACCAGCAUAGUCGA	340
UGGACACCUGAUUCUGUAbAb	152	AGUCGGACCCCAGAAAA	341
UGAGAAUGAGCCUCGAUAACUCUUAU	153	AGAUGCUGAGAUUCGCA	342
UGACACCUGAUUCUGUUUCUGAGUAU	154	AUCAAGUGUCCUUGCAA	343
UGAGAAUGAGCCUCGAUAACUCTUAU	155	GUUAUCGAGGCUCAUUA	344
UCGUAUAACAAUAAGGGGCUGCCUAU	156	UUAUCGAGGCUCAUUCA	345
UGAGAAUGAGCCUCGAUAATT	157	AACCUGACACAAUGUCA	346
UCGUAUAACAAUAAGGCGCUGCCUAU	158	AUCGAGGCUCAUUCUCA	347
UGAGAAUGAGCCUCGATAbAb	159	AAUACUACCCAAAUGGA	348
UGACACCUGAUUCUGTTAbAb	160	UACUACCCAAAUGGUGA	349
UCGUAUAACAAUAAGGGGCUGAUU	161	AACAGAAUCAGGUGUCA	350
UCGUAUAACAAUAAGGGGCUGCUU	162	ACAGAAUCAGGUGUCCA	351
UGAGAAUGAGCCUCGAUAACUCUU	163	UAUAUCAGCGCCUUAUUGUUAUACGA	352
UCGUAUAACAAUAAGGGGCUU	164	ATCGAGGCUCAUUCUCA	353
UGUAUAACAAUAAGGGG	165	UCAGCCCCUUAUUGUUAUACGAUUAb	354
UCGUAUAACAAUAAGGG	166	UCAGCCCCUUAUUGUUAUACGAAb	355
UGAGAAUGAGCCUCGAT	167	UAGUUAUCGAGGCUCAUUCUCAUUAb	356
UGACACCUGAUUCUGTT	168	AbGCCCCUUAUUGUUAUACGAUUAb	357
TUCGUAUAACAAUAAGGGGCUGCCUA	169	AUAUCAGCCCCUUAUUGUUAUACGAT	358
UAUCGUAUAACAAUAAGGGGCUGCCU	170	UAUCAGCCCCUUAUUGUUAUACGAUT	359
TCCGUAUAACAAUAAGGGGCUGCCUA	171	AUAUAGUUAUCGAGGCUCAUUCUCAT	360
CUCCGUAUAACAAUAAGGGGCUGCCU	172	UAUAGUUAUCGAGGCUCAUUCUCAUT	361
TUGAGAAUGAGCCUCGAUAACUCUUA	173	AbUUAUCGAGGCUCAUUCUCAUUAb	362
UAUGAGAAUGAGCCUCGAUAACUCUU	174	UAUAUAAUUAUCGAGGCUCAUUCUCAAb	363
TGGAGAAUGAGCCUCGAUAACUCUUA	175	GGCAGCCCCUUAUUGUUAUACGATT	364
GUGGAGAAUGAGCCUCGAUAACUCUU	176	GGCAGCCCCUUAUUGUUAUACGAUUT	365
UGAGAAUGAGCCUCGAUAAUU	177	CAGCCCCUUAUUGUUAUACGATTTT	366
TCGUAUAACAAUAAGGGGCUU	178	GCGAUAGUUAUCGAGGCUCAUUCUCA	367
UGAGAAUGAGCCUCGAUAAUUAUAUA	179	UGAAUAGUUAUCGAGGCUCAUUCUCA	368
UCGUAUAACAAUAAGGGGCUGCC	180	AUCGUAGUUAUCGAGGCUCAUUCUCA	369

TUCGUAUAACAAUAAGGGGCUGCC	181	UAUAAAGUUAUCGAGGCUCAUUCUCA	370
TUCGUAUAACAAUAAGGGGCUG	182	AGCCCCUUAUUGUUAUACGAAb	371
UGAGAAUGAGCCUCGAUAACUAUCGC	183	AAGCCCCUUAUUGUUAUACGAAb	372
UGAGAAUGAGCCUCGAUAACUAUUCA	184	GCAGCCCCUUAUUGUUAUACGAAb	373
UGAGAAUGAGCCUCGAUAACUACGAU	185	UAUAUAGUUAUCGAGGCUCAUUCUCAAb	374
UCGUAUAACAAUAAGGGGCGU	186	ACGCCCCUUAUUGUUAUACGAAb	375
UCGUAUAACAAUAAGGGGCUGCCU	187	GCCCCUUAUUGUUAUACGAUUAb	376
UCGUAUAACAAUAAGGGGCUG	188	AGCCCCUUAUUGUUAUACGAUUAb	377
TCGUAUAACAAUAAGGGGCUGCUU	189	AAGCCCCUUAUUGUUAUACGAUUAb	378
TCGUAUAACAAUAAGGGGC	1242	UAUCAGCCCCUUAUUGUUAUACGA	379
UCGUAUAACAAUAAGGGG	1244	UAGCAGCCCCUUAUUGUUAUACGA	380
UCGUAUAACAAUAAGGG	1246	GCAGCCCCUUAUUGUUAUACGA	381
TGAGAAUGAGCCUCGAUAA	1248	AUAAGAGUUAUCGAGGCUCAUUCUCA	382
UGAGAAUGAGCCUCGAUA	1250	AUAGGCAGCCCCUUAUUGUUAUACGA	383
UGAGAAUGAGCCUCGAU	1252	CAGCCCCUUAUUGUUAUACGA	384
UGUAUAACAAUAAGGGG	1254	UAUAUCAGCCCCTUAUUGUUAUACGA	385
CGUAUAACAAUAAGGGGC	1280	AbGCCCCTUAUUGUUAUACGAUUAb	1241
GAGAAUGAGCCUCGAUAA	1281	GCCCCUUAUUGUUAUACGA	1243
UCGUAUAACAAUAAGGGGC	1282	CCCCUUAUUGUUAUACGA	1245
UGAGAAUGAGCCUCGAUAA	1283	CCCUUAUUGUUAUACGA	1247
		UUAUCGAGGCUCAUUCUCA	1249
		UAUCGAGGCUCAUUCUCA	1251
		AUCGAGGCUCAUUCUCA	1253
		CCCCUUAUUGUUAUACA	1255
		UUAUCGAGGCUCAUUCUCA	1258
		GCCCCUUAUUGUUAUACGA	1259
		ACAGCCCCUUAUUGUUAUACGA	1260
		AAAGCCCCUUAUUGUUAUACGA	1261
		GCCCCUUAUUGUUAUACG	1284
		UUAUCGAGGCUCAUUCUC	1285

Ab = abasic nucleotide

The LPA RNAi agents described herein are formed by annealing an antisense strand with a sense strand. A sense strand containing a sequence listed in Table 1 or Table 2B can be hybridized to any antisense strand containing a sequence listed in Table 1 or Table 2A provided the two sequences have a region of at least 90% complementarity over a contiguous 16, 17, 18, 19, 20, or 21 nucleotide sequence.

In some embodiments, an LPA RNAi agent antisense strand comprises a nucleotide sequence of any of the sequences in Table 1. In some embodiments, an LPA RNAi agent antisense strand comprises the sequence of nucleotides 1-17, 2-17, 1-18, 2-18, 1-19, 2-19, 1-20, 2-20, 1-21, 2-21, 1-22, 2-22, 1-23, 2-23, 1-24, 2-24, 1-25, 2-25, 1-26, or 2-26 of any of the sequences in

Table 1. In some embodiments, an LPA RNAi agent sense strand comprises the nucleotide sequence of any of the sequences in Tables 1. In some embodiments, an LPA RNAi agent sense strand comprises the sequence of nucleotides 1-17, 2-17, 1-18, 2-18, 1-19, 2-19, 1-20, 2-20, 1-21, 2-21, 1-22, 2-22, 1-23, 2-23, 1-24, 2-24, 1-25, 2-25, 1-26, or 2-26 of any of the sequences in Table 1.

In some embodiments, the sense and antisense strands of the RNAi agents described herein contain the same number of nucleotides. In some embodiments the sense and antisense strands of the RNAi agents described herein contain different numbers of nucleotides. In some embodiments, the sense strand 5′ end and the antisense strand 3′ end of an RNAi agent form a blunt end. In some embodiments, the sense strand 3′ end and the antisense strand 5′ end of an RNAi agent form a blunt end. In some embodiments, both ends of an RNAi agent form blunt ends. In some embodiments, neither end of an RNAi agent is blunt-ended. As used herein a blunt end refers to an end of a double stranded RNAi agent in which the terminal nucleotides of the two annealed strands are complementary (form a complementary base-pair). In some embodiments, the sense strand 5′ end and the antisense strand 3′ end of an RNAi agent form a frayed end. In some embodiments, the sense strand 3′ end and the antisense strand 5′ end of an RNAi agent form a frayed end. In some embodiments, both ends of an RNAi agent form a frayed end. In some embodiments, neither end of an RNAi agent is a frayed end. As used herein a frayed end refers to an end of a double stranded RNAi agent in which the terminal nucleotides of the two annealed strands from a pair (i.e. do not form an overhang) but are not complementary (i.e. form a non-complementary pair). As used herein, an overhang is a stretch of one or more unpaired nucleotides at the end of one strand of a double stranded RNAi agent. The unpaired nucleotides may be on the sense strand or the antisense strand, creating either 3' or 5' overhangs. In some embodiments the RNAi agent contains: a blunt end and a frayed end, a blunt end and 5′ overhang end, a blunt end and a 3′ overhang end, a frayed end and a 5′ overhang end, a frayed end and a 3′ overhang end, two 5′ overhang ends, two 3′ overhang ends, a 5′ overhang end and a 3′ overhang end, two frayed ends, or two blunt ends.

A nucleotide base (or nucleobase) is a heterocyclic pyrimidine or purine compound which is a constituent of all nucleic acids and includes adenine (A), guanine (G), cytosine (C), thymine (T), and uracil (U). As used herein, the term "nucleotide" can include a modified nucleotide or nucleotide mimic, abasic site (Ab or X), or a surrogate replacement moiety.

In some embodiments, an LPA RNAi agent is prepared or provided as a salt, mixed salt, or a free-acid.

Modified Nucleotides

In some embodiments, an LPA RNAi agent contains one or more modified nucleotides. As used herein, a "modified nucleotide" is a nucleotide other than a ribonucleotide (2′-hydroxyl nucleotide). In some embodiments, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or 100% of the nucleotides are modified. Modified nucleotides include, but are not limited to, deoxynucleotides, nucleotide mimics, abasic nucleotides (represented herein as X, Ab), 2′-modified nucleotides, 3′ to 3′ linkages (inverted) nucleotides (represented herein as invdN, invN, invn, invX, invAb, non-natural base-comprising nucleotides, bridged nucleotides, peptide nucleic acids (PNAs), 2′,3′-seco nucleotide mimics (unlocked nucleobase analogues, represented herein as N_{UNA} or NUNA), locked nucleotides (represented herein as N_{LNA} or NLNA), 3′-O-Methoxy (2′ internucleoside linked) nucleotides (represented herein as 3′-OMen), 2'-F-Arabino nucleotides (represented herein as NfANA or Nf_{ANA}), 5'-Me,2'-fluoro nucleotide (represented herein as 5Me-Nf), morpholino nucleotides, vinyl phosphonate deoxyribonucleotides (represented herein as vpdN), vinyl phosphonate containing nucleotides, and cyclopropyl phosphonate containing nucleotides (cPrpN). 2′-modified nucleotides (i.e. a nucleotide with a group other than a hydroxyl group at the 2′ position of the five-membered sugar ring) include, but are not limited to, 2′-O-methyl nucleotides (represented herein as a lower case letter 'n' in a nucleotide sequence), 2′-deoxy-2′-fluoro nucleotides (represented herein as Nf, also represented herein as 2′-fluoro nucleotide), 2′-deoxy nucleotides (represented herein as dN), 2′-methoxyethyl (2′-O-2-methoxylethyl) nucleotides (represented herein as NM or 2′-MOE), 2′-amino nucleotides, and 2′-alkyl nucleotides. It is not necessary for all positions in a given compound to be uniformly modified. Conversely, more than one modification may be incorporated in a single LPA RNAi agent or even in a single nucleotide thereof. The LPA RNAi agent sense strands and antisense strands may be synthesized and/or modified by methods known in the art. Modification at one nucleotide is independent of modification at another nucleotide.

Modified nucleotides also include nucleotides having modified nucleobases. Modified nucleobases include, but are not limited to, synthetic and natural nucleobases, 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and O-6 substituted purines, including 2-aminopropyladenine, 5-propynyluracil and 5-propynylcytosine, 5-methylcytosine (5-me-C),

5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2- thiocytosine, 5-halouracil and cytosine, 5-propynyl uracil and cytosine, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8- hydroxyl and other 8-substituted adenines and guanines, 5-halo particularly 5-bromo, 5- trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine and 7-methyladenine, 8-azaguanine and 8-azaadenine, 7-deazaguanine and 7-deazaadenine and 3-deazaguanine and 3-deazaadenine.

Modified Internucleoside Linkages

In some embodiments, one or more nucleotides of an LPA RNAi agent are linked by non-standard linkages or backbones (i.e. modified internucleoside linkages or modified backbones). In some embodiments, a modified internucleoside linkage is a non-phosphate-containing covalent internucleoside linkage. Modified internucleoside linkages or backbones include, but are not limited to, 5′-phosphorothioate group (represented herein as a lower case 's' before a nucleotide, as in sN, sn, sNf, or sdN), chiral phosphorothioates, thiophosphate, phosphorodithioates, phosphotriesters, aminoalkyl-phosphotriesters, methyl and other alkyl phosphonates including 3′-alkylene phosphonates and chiral phosphonates, phosphinates, phosphoramidates including 3′-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkyl-phosphonates, thionoalkylphosphotriesters, morpholino linkages, and boranophosphates having normal 3′-5′ linkages, 2′-5′ linked analogs of these, and those having inverted polarity wherein the adjacent pairs of nucleoside units are linked 3′-5′ to 5′-3′ or 2′-5′ to 5′-2′. In other embodiments, a modified internucleoside linkage or backbone lacks a phosphorus atom. Modified internucleoside linkages lacking a phosphorus atom include, but are not limited to, short chain alkyl or cycloalkyl inter-sugar linkages, mixed heteroatom and alkyl or cycloalkyl inter-sugar linkages, or one or more short chain heteroatomic or heterocyclic inter-sugar linkages. In some embodiments, modified internucleoside backbones include, but are not limited to, siloxane backbones, sulfide, sulfoxide and sulfone backbones; formacetyl and thioformacetyl backbones, methylene formacetyl and thioformacetyl backbones, alkene containing backbones, sulfamate backbones, methyleneimino and methylenehydrazino backbones, sulfonate and sulfonamide backbones, amide backbones; and others having mixed N, O, S, and CH_2 component parts.

In some embodiments, a sense strand of an LPA RNAi agent can contain 1, 2, 3, 4

phosphorothioate linkages, an antisense strand of an LPA RNAi agent can contain 1, 2, 3, or 4 phosphorothioate linkages, or both the sense strand and the antisense strand independently can contain 1, 2, 3, or 4 phosphorothioate linkages.

In some embodiments, an LPA RNAi agent sense strand contains two phosphorothioate internucleoside linkages. In some embodiments, the two phosphorothioate internucleoside linkages are between the nucleotides at positions 1-3 from the 3' end of the sense strand. In some embodiments, the two phosphorothioate internucleoside linkages are between the nucleotides at positions 1-3, 2-4, 3-5, 4-6, 4-5, or 6-8 from the 5' end of the sense strand. In some embodiments, an LPA RNAi agent antisense strand contains four phosphorothioate internucleoside linkages. In some embodiments, the four phosphorothioate internucleoside linkages are between the nucleotides at positions 1-3 from the 5' end of the sense strand and between the nucleotides at positions 19-21, 20-22, 21-23, 22-24, 23-25, or 24-26 from the 5' end. In some embodiments, an LPA RNAi agent contains two phosphorothioate internucleoside linkages in the sense strand and four phosphorothioate internucleoside linkages in the antisense strand.

In some embodiments, an LPA RNAi agent contains one or more modified nucleotides and one or more modified internucleoside linkages. In some embodiments, a 2′-modified nucleotide is combined with modified internucleoside linkage.

LPA RNAi Agents Having Modified Nucleotides

Examples of antisense strands containing modified nucleotides are provided in Table 2A. Examples of sense strands containing modified nucleotides are provided in Table 2B. In Tables 2A and 2B, the following notations are used to indicate modified nucleotides:

N	=	2′-OH (unmodified) ribonucleotide (capital letter without f or d indication)
n	=	2′-OMe modified nucleotide
Nf	=	2′-fluoro modified nucleotide
dN	=	2′-deoxy nucleotides
N_{UNA}	=	2′,3′-seco nucleotide mimics (unlocked nucleobase analogs)
N_{LNA}	=	locked nucleotide
Nf_{ANA}	=	2'-F-Arabino nucleotide
NM	=	2′-methoxyethyl nucleotide
Ab	=	abasic ribose

(invdN)	=	inverted deoxyribonucleotide (3′-3′ linked nucleotide)
(invAb)	=	inverted abasic nucleotide
(invn)	=	inverted 2′-OMe nucleotide
s	=	phosphorothioate linked nucleotide
p	=	phosphate
vpdN	=	vinyl phosphonate deoxyribonucleotide
(3'OMen)	=	3′-OMe nucleotide
(5Me-Nf)	=	5'-Me, 2'-fluoro nucleotide
cPrp	=	cyclopropyl phosphonate
epTcPr	=	see Table 4
epTM	=	see Table 4

In addition the following targeting groups and linking groups are listed in Tables 2A and 2B: (Alk-PEG5-C6), (C11-PEG3-NAG3), (C12), (C6-PEG4-NAG3), (C6-SS-Alk-Me), (Chol-TEG), (Dy540), (NAG13), (NAG18), (NAG24), (NAG25), (NAG26), (NAG27), (NAG28), (NAG29), (NAG30), (NAG31), (NAG32), (NAG33), (NAG34), (NAG35), (NAG36), (NAG37), (NAG4), (PAZ), (Sp18), (Steryl), (Alk-SMPT-C6). Each sense strand and/or antisense strand can have any of the above indicated targeting groups or linking groups, as well as other targeting or linking groups, conjugated to the 5′ and/or 3′ end of the sequence. The chemical structures for these groups are provided in Table 4.

Table 2A. LPA RNAi agent antisense strands having modified nucleotides.

Antisense Strand ID	Antisense strand sequence 5' → 3'	SEQ ID NO.	SEQ ID NO.
AM01240-AS	dTCfgGfcAfgUfcCfcUfuCfuGfcGfudTsdT	386	1
AM01241-AS	dTGfuAfgCfaCfuCfcUfgCfaCfcCfcdTsdT	387	2
AM01242-AS	dTAfaUfaAfgGfgGfcUfgCfcAfcAfgdTsdT	388	3
AM01243-AS	dTUfaAfcAfaUfaAfgGfgGfcUfgCfcdTsdT	389	4
AM01244-AS	dTGfuAfuAfaCfaAfuAfaGfgGfgCfudTsdT	390	5
AM01245-AS	dTCfgUfaUfaAfcAfaUfaAfgGfgGfcdTsdT	391	6
AM01246-AS	dTCfgUfcUfgAfgCfaUfuGfuGfuCfadTsdT	392	7
AM01247-AS	dTGfcGfuCfuGfaGfcAfuUfgUfgUfcdTsdT	393	8
AM01248-AS	dTUfgCfgUfcUfgAfgCfaUfuGfuGfudTsdT	394	9
AM01249-AS	dTUfcUfgCfgUfcUfgAfgCfaUfuGfudTsdT	395	10
AM01250-AS	dTGfgAfuCfuGfgAfuUfuCfgGfcAfgdTsdT	396	11
AM01251-AS	dTCfaGfgAfuCfuGfgAfuUfuCfgGfcdTsdT	397	12
AM01252-AS	dTCfaUfcUfgAfgCfaUfcGfuGfuCfadTsdT	398	13
AM01253-AS	dTGfcAfuCfuGfaGfcAfuCfgUfgUfcdTsdT	399	14
AM01254-AS	dTUfgCfaUfcUfgAfgCfaUfcGfuGfudTsdT	400	15
AM01255-AS	dTUfcUfgCfaUfcUfgAfgCfaUfcGfudTsdT	401	16
AM01256-AS	dTAfaAfgCfcUfcUfaGfgCfuUfgGfadTsdT	402	17

RECTIFIED SHEET (RULE 91) ISA/US

AM01257-AS	dTGfuAfcCfcCfgGfgGfgUfuUfcCfudTsdT	403	18
AM01258-AS	dTUfgUfaCfcCfcGfgGfgGfuUfuCfcdTsdT	404	19
AM01259-AS	dTCfuGfuAfcCfcCfgGfgGfgUfuUfcdTsdT	405	20
AM01260-AS	dTUfcCfaUfaAfuGfgUfaGfuAfgCfadTsdT	406	21
AM01261-AS	dTGfuCfcAfuAfaUfgGfuAfgUfaGfcdTsdT	407	22
AM01262-AS	dTCfuCfuGfuCfcAfuAfaUfgGfuAfgdTsdT	408	23
AM01263-AS	dTCfgAfcUfaUfgCfuGfgUfgUfgGfudTsdT	409	24
AM01264-AS	dTCfcGfaCfuAfuGfcUfgGfuGfuGfgdTsdT	410	25
AM01265-AS	dTUfcCfgAfcUfaUfgCfuGfgUfgUfgdTsdT	411	26
AM01266-AS	dTGfgUfcCfgAfcUfaUfgCfuGfgUfgdTsdT	412	27
AM01267-AS	dTUfuUfcUfgGfgGfuCfcGfaCfuAfudTsdT	413	28
AM01268-AS	dTUfuUfuCfuGfgGfgUfcCfgAfcUfadTsdT	414	29
AM01269-AS	dTGfcGfaAfuCfuCfaGfcAfuCfuGfgdTsdT	415	30
AM01270-AS	dTCfcAfaGfgGfcGfaAfuCfuCfaGfcdTsdT	416	31
AM01271-AS	dTAfcCfaAfgGfgCfgAfaUfcUfcAfgdTsdT	417	32
AM01272-AS	dTCfaCfcAfaGfgGfcGfaAfuCfuCfadTsdT	418	33
AM01273-AS	dTAfcAfcCfaAfgGfgCfgAfaUfcUfcdTsdT	419	34
AM01274-AS	dTCfcUfgAfcAfcUfgGfgAfuCfcAfudTsdT	420	35
AM01275-AS	dTUfgCfaAfgGfaCfaCfuUfgAfuUfcdTsdT	421	36
AM01276-AS	dTUfuGfcAfaGfgAfcAfcUfuGfaUfudTsdT	422	37
AM01277-AS	dTUfuGfcUfcCfgUfuGfgUfgCfuUfcdTsdT	423	38
AM01278-AS	dTAfaUfgAfgCfcUfcGfaUfaAfcUfcdTsdT	424	39
AM01279-AS	dTGfaAfuGfaGfcCfuCfgAfuAfaCfudTsdT	425	40
AM01280-AS	dTGfgAfuAfaUfaUfuCfuGfuUfgUfcdTsdT	426	41
AM01281-AS	dTCfcAfuGfgUfaUfaAfcAfcCfaAfgdTsdT	427	42
AM01282-AS	dTGfaUfcCfaUfgGfuAfuAfaCfaCfcdTsdT	428	43
AM01283-AS	dTAfuUfgGfgAfuCfcAfuGfgUfaUfadTsdT	429	44
AM01284-AS	dTCfaUfuGfgGfaUfcCfaUfgGfuAfudTsdT	430	45
AM01285-AS	dTAfcAfuUfgGfgAfuCfcAfuGfgUfadTsdT	431	46
AM01286-AS	dTGfaCfaUfuGfgGfaUfcCfaUfgGfudTsdT	432	47
AM01287-AS	dTGfaCfaUfuGfuGfuCfaGfgUfuGfcdTsdT	433	48
AM01288-AS	dTCfaCfuGfgAfcAfuUfgUfgUfcAfgdTsdT	434	49
AM01289-AS	dTAfcUfuGfaUfuCfuGfuCfaCfuGfgdTsdT	435	50
AM01290-AS	dTGfaGfaAfuGfaGfcCfuCfgAfuAfadTsdT	436	51
AM01291-AS	dTCfcAfuUfuGfgGfuAfgUfaUfuCfudTsdT	437	52
AM01292-AS	dTCfaCfcAfuUfuGfgGfuAfgUfaUfudTsdT	438	53
AM01293-AS	dTCfcAfcCfaUfuUfgGfgUfaGfuAfudTsdT	439	54
AM01294-AS	dTAfuAfaCfaCfcAfaGfgGfcGfaAfudTsdT	440	55
AM01295-AS	dTAfcUfgGfgAfuCfcAfuGfgUfaUfadTsdT	441	56
AM01296-AS	dTCfaCfuGfgGfaUfcCfaUfgGfuAfudTsdT	442	57
AM01297-AS	dTAfcCfaCfcGfuGfgGfaGfuUfgUfgdTsdT	443	58
AM01298-AS	dTCfaAfgAfcUfgAfcAfuGfuUfcUfudTsdT	444	59
AM01299-AS	dTGfgGfaGfuUfgUfgAfgGfaCfaCfudTsdT	445	60
AM01300-AS	dTUfcUfcAfgGfuGfgUfgCfuUfgUfudTsdT	446	61
AM01301-AS	dTCfaCfaGfgGfcUfuUfuCfuCfaGfgdTsdT	447	62
AM01302-AS	dTGfaUfgCfcAfgUfgUfgGfuAfuCfadTsdT	448	63
AM01303-AS	dTUfgAfuGfcCfaGfuGfuGfgUfaUfcdTsdT	449	64

AM01304-AS	dTGfaCfaCfcUfgAfuUfcUfgUfuUfcdTsdT	450	65
AM01305-AS	dTGfgAfcAfcCfuGfaUfuCfuGfuUfudTsdT	451	66
AM01306-AS	dTCfuAfgGfaCfaCfcUfgAfuUfcUfgdTsdT	452	67
AM01796-AS	dTAfuAfaGfgGfgCfuGfcCfaCfaGfgdTsdT	453	68
AM01798-AS	dTAfaCfaAfuAfaGfgGfgCfuGfcCfadTsdT	454	69
AM01800-AS	dTGfuCfcGfaCfuAfuGfcUfgGfuGfudTsdT	455	70
AM01802-AS	dTUfcUfcAfgCfaUfcUfgGfaUfuCfcdTsdT	456	71
AM01804-AS	dTCfgAfaUfcUfcAfgCfaUfcUfgGfadTsdT	457	72
AM01806-AS	dTAfaGfgGfcGfaAfuCfuCfaGfcAfudTsdT	458	73
AM01808-AS	dTUfgAfcAfcUfgGfgAfuCfcAfuGfgdTsdT	459	74
AM01810-AS	dTCfcGfuUfgGfuGfcUfuCfuUfcAfgdTsdT	460	75
AM01812-AS	dTCfuUfgAfuUfcUfgUfcAfcUfgGfadTsdT	461	76
AM01814-AS	dTCfaCfcGfuGfgGfaGfuUfgUfgAfgdTsdT	462	77
AM01816-AS	dTUfcUfaGfgAfcAfcCfuGfaUfuCfudTsdT	463	78
AM01818-AS	dTAfgUfcUfcUfaGfgAfcAfcCfuGfadTsdT	464	79
AM02003-AS	dTGfuAfuAfaCfaAfuaaGfgGfgCfudTsdT	465	5
AM02004-AS	dTGfuAfuA$_{UNA}$aCfaAfuaaGfgGfgCfudTsdT	466	5
AM02005-AS	dTGfuAfuAfA$_{UNA}$CfaAfuaaGfgGfgCfudTsdT	467	5
AM02007-AS	dTCfgUfaUfaAfcAfauaAfgGfgGfcdTsdT	468	6
AM02008-AS	dTCfgUfaU$_{UNA}$aAfcAfauaAfgGfgGfcdTsdT	469	6
AM02009-AS	dTCfgUfaUfA$_{UNA}$AfcAfauaAfgGfgGfcdTsdT	470	6
AM02011-AS	dTGfcGfuCfuGfaGfcauUfgUfgUfcdTsdT	471	8
AM02012-AS	dTGfcGfuC$_{UNA}$uGfaGfcauUfgUfgUfcdTsdT	472	8
AM02013-AS	dTGfcGfuCfU$_{UNA}$GfaGfcauUfgUfgUfcdTsdT	473	8
AM02015-AS	dTUfgCfgUfcUfgAfgcaUfuGfuGfudTsdT	474	9
AM02016-AS	dTUfgCfgU$_{UNA}$cUfgAfgcaUfuGfuGfudTsdT	475	9
AM02017-AS	dTUfgCfgUfC$_{UNA}$UfgAfgcaUfuGfuGfudTsdT	476	9
AM02019-AS	dTGfaGfaAfuGfaGfccuCfgAfuAfadTsdT	477	51
AM02020-AS	dTGfaGfaA$_{UNA}$uGfaGfccuCfgAfuAfadTsdT	478	51
AM02021-AS	dTGfaGfaAfU$_{UNA}$GfaGfccuCfgAfuAfadTsdT	479	51
AM02023-AS	dTGfaCfaCfcUfgAfuucUfgUfuUfcdTsdT	480	65
AM02024-AS	dTGfaCfaC$_{UNA}$cUfgAfuucUfgUfuUfcdTsdT	481	65
AM02025-AS	dTGfaCfaCfC$_{UNA}$UfgAfuucUfgUfuUfcdTsdT	482	65
AM02027-AS	dTGfuCfcGfaCfuAfugcUfgGfuGfudTsdT	483	70
AM02028-AS	dTGfuCfcG$_{UNA}$aCfuAfugcUfgGfuGfudTsdT	484	70
AM02029-AS	dTGfuCfcGfA$_{UNA}$CfuAfugcUfgGfuGfudTsdT	485	70
AM02031-AS	dTCfgAfaUfcUfcAfgcaUfcUfgGfadTsdT	486	72
AM02032-AS	dTCfgAfaU$_{UNA}$cUfcAfgcaUfcUfgGfadTsdT	487	72
AM02033-AS	dTCfgAfaUfC$_{UNA}$UfcAfgcaUfcUfgGfadTsdT	488	72
AM02035-AS	dTAfaGfgGfcGfaAfucuCfaGfcAfudTsdT	489	73
AM02036-AS	dTAfaGfgG$_{UNA}$cGfaAfucuCfaGfcAfudTsdT	490	73
AM02037-AS	dTAfaGfgGfC$_{UNA}$GfaAfucuCfaGfcAfudTsdT	491	73
AM02039-AS	dTUfgAfcAfcUfgGfgauCfcAfuGfgdTsdT	492	74
AM02040-AS	dTUfgAfcA$_{UNA}$cUfgGfgauCfcAfuGfgdTsdT	493	74
AM02041-AS	dTUfgAfcAfC$_{UNA}$UfgGfgauCfcAfuGfgdTsdT	494	74
AM02240-AS	dTCfaAfuAfaGfgGfgcuGfcCfaCfadTsdT	495	80
AM02241-AS	dTCfuGfcGfuCfuGfagcAfuUfgUfgdTsdT	496	81

AM02242-AS	dTAfcAfgGfaUfcUfggaUfuUfcGfgdTsdT	497	82
AM02243-AS	dTCfcGfgGfgGfuUfuccUfcAfgUfcdTsdT	498	83
AM02244-AS	dTUfgUfcCfaUfaAfuggUfaGfuAfgdTsdT	499	84
AM02245-AS	dTUfcUfgUfcCfaUfaauGfgUfaGfudTsdT	500	85
AM02246-AS	dTAfcUfcUfgUfcCfauaAfuGfgUfadTsdT	501	86
AM02247-AS	dTAfaCfuCfuGfuCfcauAfaUfgGfudTsdT	502	87
AM02248-AS	dTGfgGfcGfaAfuCfucaGfcAfuCfudTsdT	503	88
AM02249-AS	dTAfgGfgCfgAfaUfcucAfgCfaUfcdTsdT	504	89
AM02250-AS	dTAfaCfaCfcAfaGfggcGfaAfuCfudTsdT	505	90
AM02251-AS	dTAfgGfaCfaCfuUfgauUfcUfgUfcdTsdT	506	91
AM02252-AS	dTGfgAfcCfaAfgAfcugAfcAfuGfudTsdT	507	92
AM02253-AS	dTGfgUfcAfgGfcCfaccAfuUfuGfgdTsdT	508	93
AM02254-AS	dTAfuCfcAfuGfgUfauaAfcAfcCfadTsdT	509	94
AM02255-AS	dTGfgGfaUfcCfaUfgguAfuAfaCfadTsdT	510	95
AM02256-AS	dTUfgGfaCfaUfuGfuguCfaGfgUfudTsdT	511	96
AM02257-AS	dTAfuUfcUfgUfcAfcugGfaCfaUfudTsdT	512	97
AM02258-AS	dTGfgUfgCfuUfgUfucaGfaAfaCfadTsdT	513	98
AM02259-AS	dTGfgAfgAfaUfgAfgccUfcGfaUfadTsdT	514	99
AM02260-AS	dTGfuGfgAfgAfaUfgagCfcUfcGfadTsdT	515	100
AM02261-AS	dTCfcGfuGfgGfaGfuugUfgAfgGfadTsdT	516	101
AM02262-AS	dTGfgAfcCfaCfcGfuggGfaGfuUfgdTsdT	517	102
AM02263-AS	dTUfgCfuUfgUfuCfagaAfgGfaGfcdTsdT	518	103
AM02264-AS	dTCfuGfaUfgCfcAfgugUfgGfuAfudTsdT	519	104
AM02265-AS	dTUfaGfgAfcAfcCfugaUfuCfuGfudTsdT	520	105
AM02266-AS	dTCfuCfuAfgGfaCfaccUfgAfuUfcdTsdT	521	106
AM02267-AS	dTUfcUfcUfaGfgAfcacCfuGfaUfudTsdT	522	107
AM02268-AS	dTGfuCfuCfuAfgGfacaCfcUfgAfudTsdT	523	108
AM02404-AS	dTsGfsaGfaAfuGfaGfcCfuCfgAfuAfaCfuCfsusuAu	524	109
AM02406-AS	dTsGfsaGfaAfuGfaGfccUfCfgAfuAfaCfuCfsusuAu	525	109
AM02408-AS	dTsGfsaGfaAfuGfaGfccUfcgAfuAfaCfuCfsusuAu	526	109
AM02410-AS	dTsGfsaGfaAfuGfaGfcCfUfcGfaUfaAfcUfcsUfsuAu	527	109
AM02412-AS	dTsGfsaCfaCfcUfgAfuUfcUfgUfuUfcUfgAfsgsuAu	528	110
AM02414-AS	dTsGfsaCfaCfcUfgAfuuCfUfgUfuUfcUfgAfsgsuAu	529	110
AM02416-AS	dTsGfsaCfaCfcUfgAfuuCfugUfuUfcUfgAfsgsuAu	530	110
AM02418-AS	dTsGfsaCfaCfcUfgAfuUfCfuGfuUfuCfuGfasGfsuAu	531	110
AM02531-AS	dTsCfsgUfaUfaAfcAfauaAfgGfgGfcUfgCfscsuAu	532	111
AM02532-AS	dTsGfscGfuCfuGfaGfcauUfgUfgUfcAfgGfsusuAu	533	112
AM02533-AS	dTsUfsgCfgUfcUfgAfgcaUfuGfuGfuCfaGfsgsuAu	534	113
AM02534-AS 1532-AS00	dTsGfsaGfaAfuGfaGfccuCfgAfuAfaCfuCfsusuAu	535	109
AM02535-AS 1533-AS00	dTsGfsaCfaCfcUfgAfuucUfgUfuUfcUfgAfsgsuAu	536	110
AM02536-AS	dTsAfsaGfgGfcGfaAfucuCfaGfcAfuCfuGfsgsuAu	537	114
AM02755-AS	usUfsaAfcAfaUfaAfgGfgGfcUfgCfAbs(PAZ)	538	115
AM02756-AS	usGfsuAfuAfaCfaAfuAfaGfgGfgCfAbs(PAZ)	539	116
AM02757-AS	usCfsgUfaUfaAfcAfaUfaAfgGfgGfAbs(PAZ)	540	117
AM02758-AS	usGfscGfuCfuGfaGfcAfuUfgUfgUfAbs(PAZ)	541	118
AM02759-AS	usUfsgCfgUfcUfgAfgCfaUfuGfuGfAbs(PAZ)	542	119

AM02760-AS	usCfsaGfgAfuCfuGfgAfuUfuCfgGfAbs(PAZ)	543	120
AM02761-AS	usUfsgCfaUfcUfgAfgCfaUfcGfuGfAbs(PAZ)	544	121
AM02762-AS	usCfsgAfcUfaUfgCfuGfgUfgUfgGfAbs(PAZ)	545	122
AM02763-AS	usUfsuUfcUfgGfgGfuCfcGfaCfuAfAbs(PAZ)	546	123
AM02764-AS	usGfscGfaAfuCfuCfaGfcAfuCfuGfAbs(PAZ)	547	124
AM02765-AS	usUfsgCfaAfgGfaCfaCfuUfgAfuUfAbs(PAZ)	548	125
AM02766-AS	usAfsaUfgAfgCfcUfcGfaUfaAfcUfAbs(PAZ)	549	126
AM02767-AS	usGfsaAfuGfaGfcCfuCfgAfuAfaCfAbs(PAZ)	550	127
AM02768-AS	usGfsaCfaUfuGfuGfuCfaGfgUfuGfAbs(PAZ)	551	128
AM02769-AS	usGfsaGfaAfuGfaGfcCfuCfgAfuAfAbs(PAZ)	552	129
AM02770-AS	usCfscAfuUfuGfgGfuAfgUfaUfuCfAbs(PAZ)	553	130
AM02771-AS	usCfsaCfcAfuUfuGfgGfuAfgUfaUfAbs(PAZ)	554	131
AM02772-AS	usGfsaCfaCfcUfgAfuUfcUfgUfuUfAbs(PAZ)	555	132
AM02773-AS	usGfsgAfcAfcCfuGfaUfuCfuGfuUfAbs(PAZ)	556	133
AM02774-AS	usUfsaAfcAfaUfaAfgGfgGfcUfgAbAbs(PAZ)	557	134
AM02775-AS	usGfsuAfuAfaCfaAfuAfaGfgGfgAbAbs(PAZ)	558	135
AM02776-AS	usCfsgUfaUfaAfcAfaUfaAfgGfgAbAbs(PAZ)	559	136
AM02777-AS	usGfscGfuCfuGfaGfcAfuUfgUfgAbAbs(PAZ)	560	137
AM02778-AS	usUfsgCfgUfcUfgAfgCfaUfuGfuAbAbs(PAZ)	561	138
AM02779-AS	usCfsaGfgAfuCfuGfgAfuUfuCfgAbAbs(PAZ)	562	139
AM02780-AS	usUfsgCfaUfcUfgAfgCfaUfcGfuAbAbs(PAZ)	563	140
AM02781-AS	usCfsgAfcUfaUfgCfuGfgUfgUfgAbAbs(PAZ)	564	141
AM02782-AS	usUfsuUfcUfgGfgGfuCfcGfaCfuAbAbs(PAZ)	565	142
AM02783-AS	usGfscGfaAfuCfuCfaGfcAfuCfuAbAbs(PAZ)	566	143
AM02784-AS	usUfsgCfaAfgGfaCfaCfuUfgAfuAbAbs(PAZ)	567	144
AM02785-AS	usAfsaUfgAfgCfcUfcGfaUfaAfcAbAbs(PAZ)	568	145
AM02786-AS	usGfsaAfuGfaGfcCfuCfgAfuAfaAbAbs(PAZ)	569	146
AM02787-AS	usGfsaCfaUfuGfuGfuCfaGfgUfuAbAbs(PAZ)	570	147
AM02788-AS	usGfsaGfaAfuGfaGfcCfuCfgAfuAbAbs(PAZ)	571	148
AM02789-AS	usCfscAfuUfuGfgGfuAfgUfaUfuAbAbs(PAZ)	572	149
AM02790-AS	usCfsaCfcAfuUfuGfgGfuAfgUfaAbAbs(PAZ)	573	150
AM02791-AS	usGfsaCfaCfcUfgAfuUfcUfgUfuAbAbs(PAZ)	574	151
AM02792-AS	usGfsgAfcAfcCfuGfaUfuCfuGfuAbAbs(PAZ)	575	152
AM02857-AS 1532-AS14	usGfsaGfaAfuGfaGfccuCfgAfuAfaCfuCfsusuAu	576	153
AM02858-AS	usgsaGfaAfuGfaGfccuCfgAfuAfaCfuCfsusuAu	577	153
AM02859-AS	usgsaGfaAfuGfaGfccuCfgAfuAfaCfucsusuAu	578	153
AM02860-AS	usGfsaGfaAfuGfaGfccuCfgAfuAfaCfucsusuAu	579	153
AM02863-AS 1533-AS15	usGfsaCfaCfcUfgAfuucUfgUfuUfcUfgAfsgsuAu	580	154
AM02864-AS	usgsaCfaCfcUfgAfuucUfgUfuUfcUfgAfsgsuAu	581	154
AM02865-AS	usgsaCfaCfcUfgAfuucUfgUfuUfcUfgasgsuAu	582	154
AM02866-AS	usGfsaCfaCfcUfgAfuucUfgUfuUfcUfgasgsuAu	583	154
AM02943-AS	usgsagaAfugaGfccuCfgAfuaaCfuCfsusuAu	584	153
AM02944-AS	usgsagaauGfagccuCfgauAfaCfuCfsusuAu	585	153
AM02945-AS	usgsagaauGfagccuCfgauAfacucsusuAu	586	153
AM02950-AS	usgsaCfaCfcUfgAfuucUfgUfuucUfgasgsuAu	587	154
AM02951-AS	usgsaCfaCfcUfgAfuucUfguuUfcugasgsuAu	588	154

AM02952-AS	usgsacaccugAfuucUfgUfuucUfgasgsuAu	589	154
AM03040-AS	usGfsAfcAfcCfUfgAfuucUfgUfuUfcUfgAfsgsuAu	590	154
AM03041-AS	usGfsAfcAfccUfgAfuucUfgUfuUfcUfgAfsgsuAu	591	154
AM03043-AS	usGfsaCfaCfCfUfgAfuucUfgUfuUfcUfgAfsgsuAu	592	154
AM03065-AS 1533-AS18	dTsGfsaCfaCfcugauucUfgUfuUfcUfgAfsgsuAu	593	110
AM03066-AS 1533-AS03	usGfsaCfaCfcugauucUfgUfuUfcUfgAfsgsuAu	594	154
AM03067-AS	dTsGfsaCfaCfcugauucUfgUfuucugasgsuAu	595	110
AM03068-AS	usGfsaCfaCfcugauucUfgUfuucugasgsuAu	596	154
AM03069-AS 1533-AS14	dTsGfsaCfaCfcUfgAfuucUfgUfuucugasgsuAu	597	110
AM03070-AS 1533-AS29	usGfsaCfaCfcUfgAfuucUfgUfuucugasgsuAu	598	154
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AM03119-AS	usGfsaGfaAfuGfaGfccuCfgAfuAfaCfuCMsTMsuAu	601	155
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AM03121-AS	usGfsaGfaAfuGfaGfccuCfgAfuAfaCfucuuAu	603	153
AM03127-AS	usCfsgUfaUfaAfCfAfauaAfgGfgGfcUfgCfscsuAu	604	156
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AM03130-AS	usGfsaGfaAfuGfaGfCfcuCfgAfuAfaCfuCfsusuAu	606	153
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AM03255-AS 1532-AS26	usGfsaGfaAfugaGfccuCfgauaaCfuCfsusuAu	611	153
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AM03262-AS	usGfsagaaugagccUfCfgauaacuCfsusuAu	618	153
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AM03264-AS	usGfsagaaugagccUfCfgauaacucsusuAu	620	153
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AM03267-AS	usGfsagaaugagcCfuCfgauaacuCfsusuAu	623	153
AM03268-AS	usGfsagaaugagcCfuCfgauaaCfucsusuAu	624	153
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AM03272-AS	usGfsagaaugagCfcuCfgauaacuCfsusuAu	628	153
AM03273-AS	usGfsagaaugagCfcuCfgauaaCfucsusuAu	629	153
AM03274-AS	usGfsagaaugagCfcuCfgauaacucsusuAu	630	153
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AM03280-AS	usCfsgUfaUfaAfcAfauaAfggggcUfgCfscsuAu	632	156
AM03281-AS	usCfsguauaAfcAfauaAfgGfgGfcUfgCfscsuAu	633	156
AM03282-AS	usCfsgUfaUfaAfcAfauaAfgGfgGfcugcscsuAu	634	156
AM03283-AS	usCfsgUfaUfaacaauaAfgGfgGfcugcscsuAu	635	156
AM03284-AS	usCfsguauaAfcAfauaAfggggcUfgCfscsuAu	636	156
AM03300-AS	usCfsgUfaUfaacaaUfaAfgGfgGfcUfgCfscsuAu	637	156
AM03301-AS	usCfsguauaAfcAfaUfaAfggggcUfgCfscsuAu	638	156
AM03331-AS	usGfsaGfaAfuGfaGfcCfuCfgAfuAfasdTsdT	639	157
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AM03376-AS	usCfsguauaacaauaAfggggcugcscsuAu	641	156
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AM03487-AS	vpdTsGfsaGfaAfuGfaGfccuCfgAfuAfaCfucsusuAu	645	109
AM03488-AS	dTsGfsaGfaAfuGfaGfccuCfgAfuAfaCfucsusuAu	646	109
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AM03661-AS	usGfsagaaugaGfccuCfgauaacucsusuAu	655	153
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AM03672-AS	usCfsgUfaUfaAfcAfauaAfggggCfugCfscsuAu	657	156
AM03673-AS	usCfsgUfaUfaAfcAfauaAfggggcugcscsuAu	658	156
AM03674-AS	usCfsGfuauaAfcAfauaAfggggcugcscsuAu	659	156
AM03675-AS	usCfsgUfaUfaAfcaauaAfggggcugcscsuAu	660	156
AM03676-AS	usCfsgUfaUfaaCfaauaAfggggcugcscsuAu	661	156
AM03677-AS	usCfsGfuauAfaCfaauaAfggggcugcscsuAu	662	156
AM03678-AS	usGfsaGfaAfuGfaGfccuCfgauaacucsusuAu	663	153
AM03679-AS	usGfsAfgaAfuGfaGfccuCfgauaacucsusuAu	664	153
AM03680-AS	usGfsAfgAfauGfaGfcCfuCfgauaacucsusuAu	665	153
AM03681-AS	usGfsAfgAfauGfagCfCfuCfgauaacucsusuAu	666	153
AM03682-AS	usGfsaGfaAfuGfagccuCfgauaacucsusuAu	667	153
AM03744-AS	usGfsuauaaCfaAfuaaGfgggAbAbs(PAZ)	668	135
AM03745-AS	usGfsuAfuAfaCfaAfuAfaGfgGMGMAbAbs(PAZ)	669	135
AM03749-AS	usCfsguauaAfcAfauaAfgggAbAbs(PAZ)	670	136
AM03750-AS	usCfsgUfaUfaAfcAfaUfaAfgGMGMAbAbs(PAZ)	671	136
AM03754-AS	usGfsagaauGfaGfccuCfgauAbAbs(PAZ)	672	148
AM03755-AS	usGfsagaaugagcCfuCfgauAbAbs(PAZ)	673	148
AM03756-AS	usGfsaGfaAfuGfaGfcCfuCfgAMTMAbAbs(PAZ)	674	159
AM03760-AS	usGfsacaccUfgAfuucUfguuAbAbs(PAZ)	675	151
AM03761-AS	usGfsaCfaCfcugauucUfguuAbAbs(PAZ)	676	151
AM03762-AS	usGfsaCfaCfcUfgAfuUfcUfgTMTMAbAbs(PAZ)	677	160
AM03823-AS	usCf$_{ANA}$sgUfaUfaAfCfAfauaAfgGfgGfcUfgcscsuAu	678	156
AM03824-AS	usCfsgUf$_{ANA}$aUfaAfCfAfauaAfgGfgGfcUfgcscsuAu	679	156

AM03825-AS	usCfsgUfaUf$_{ANA}$aAfCfAfauaAfgGfgGfcUfgcscsuAu	680	156
AM03826-AS	usCfsgUfaUfaAf$_{ANA}$CfAfauaAfgGfgGfcUfgcscsuAu	681	156
AM03827-AS	usGf$_{ANA}$sagaauGfaGfccuCfgauaacucsusuAu	682	153
AM03828-AS	usGfsagaauGf$_{ANA}$aGfccuCfgauaacucsusuAu	683	153
AM03856-AS	TMsGfsagaauGfaGfccuCfgauaacucsusuAu	684	109
AM03857-AS	TMsCfsgUfaUfaAfCfAfauaAfgGfgGfcUfgcscsuAu	685	111
AM03862-AS	TMsGfsagaaugagccuCfgauaacucsusuAu	686	109
AM03866-AS	usCfsgUfaUfaacaauaAfggggcugcscsuAu	687	156
AM03867-AS	usCfsgUfauaAfcaauaAfggggcugcscsuAu	688	156
AM03868-AS	usCfsgUfauaacAfauaAfggggcugcscsuAu	689	156
AM03869-AS	usCfsgUfauaacaaUfaAfggggcugcscsuAu	690	156
AM03870-AS	usCfsguaUfaAfcaauaAfggggcugcscsuAu	691	156
AM03871-AS	usCfsguaUfaacAfauaAfggggcugcscsuAu	692	156
AM03872-AS	usCfsguaUfaacaaUfaAfggggcugcscsuAu	693	156
AM03873-AS	usCfsguauaAfcaaUfaAfggggcugcscsuAu	694	156
AM03874-AS	usCfsguauaacAfaUfaAfggggcugcscsuAu	695	156
AM03875-AS	usCfsgUfaUfaAfcAfaUfaAfgggGfcUfgCfscsuAu	696	156
AM03876-AS	usCfsgUfaUfaAfcAfaUfaAfgGfggcUfgCfscsuAu	697	156
AM03877-AS	usCfsgUfaUfaAfcAfaUfaAfgGfgGfcugCfscsuAu	698	156
AM03878-AS	usCfsgUfaUfaAfcAfaUfaAfgGfgGfcUfgcscsuAu	699	156
AM03883-AS	vpusCfsgsUfaUfaAfCfAfauaAfgGfgGfcUfgasusu	700	161
AM03884-AS	vpusCfsgsUfaUfaAfCfAfauaAfgGfgGfcUfgcsusu	701	162
AM03885-AS	vpusGfsasgaauGfaGfccuCfgauaacucsusu	702	163
AM03929-AS	usCfsguaUfaAfcaauaAfgGfggcugcscsuAu	703	156
AM03930-AS	usCfsguaUfaAfCfaauaAfgGfggcugcscsuAu	704	156
AM03932-AS	usGfsagaAfuGfagccuCfgAfuaacucsusuAu	705	153
AM03933-AS	usGfsagaAfuGfAfgccuCfgAfuaacucsusuAu	706	153
AM03969-AS	vpusCfsgUfaUfaAfCfAfauaAfgGfgGfcUfgcscsuAu	707	156
AM03971-AS	vpusCfsgsUfaUfaAfCfAfauaAfgGfgGfcusu	708	164
AM03972-AS	usCfsgsUfaUfaAfCfAfauaAfgGfgGfcusu	709	164
AM03973-AS	U$_{UNA}$sCfsgsUfaUfaAfCfAfauaAfgGfgGfcusu	710	164
AM04132-AS	usGfsaGfaAfuGfaGfccuCfgAfuAfaCfucsusuau	711	153
AM04133-AS	usGfsagaauGfaGfccuCfgauaacucsusuau	712	153
AM04134-AS	usGfsaGfaAfuGfAfGfccuCfgAfuAfaCfucsusuau	713	153
AM04135-AS	usGfsagaauGfAfGfccuCfgauaacucsusuau	714	153
AM04136-AS	usGfsaGfaAfuGfAfgccuCfgAfuAfaCfucsusuau	715	153
AM04137-AS	usGfsagaauGfAfgccuCfgauaacucsusuau	716	153
AM04150-AS	usGfsagaauGfaGfccuCfgauaacucsusuau(Dy540)	717	153
AM04215-AS	usCfsgUfaUfaaCfaaUfaAfgGfgGfcUfgCfscsuAu	718	156
AM04216-AS	usCfsguauaAfcaaUfaAfggggcugCfscsuAu	719	156
AM04217-AS	usCfsguauaaCfaaUfaAfggggcugCfscsuAu	720	156
AM04218-AS	usCfsguauaaCfaaUfaAfggggCfugCfscsuAu	721	156
AM04219-AS	usCfsguaUfaaCfaaUfaAfggggCfugCfscsuAu	722	156
AM04250-AS	usGfsuAfuAfaCfaAfuAfaGfgGMGMsAbsAbs(PAZ)	723	135
AM04251-AS	usGfsuAfuAfaCfaAfuAfaGfgGMGM(Sp18)s(PAZ)	724	165
AM04252-AS	usGfsuAfuAfaCfaAfuAfaGfgGMGM(C12)s(PAZ)	725	165
AM04253-AS	usCfsgUfaUfaAfcAfaUfaAfgGMGMsAbsAbs(PAZ)	726	136

AM04254-AS	usCfsgUfaUfaAfcAfaUfaAfgGMGM(Sp18)s(PAZ)	727	166
AM04255-AS	usCfsgUfaUfaAfcAfaUfaAfgGMGM(C12)s(PAZ)	728	166
AM04256-AS	usGfsaGfaAfuGfaGfcCfuCfgAMTMsAbsAbs(PAZ)	729	159
AM04257-AS	usGfsaGfaAfuGfaGfcCfuCfgAMTM(Sp18)s(PAZ)	730	167
AM04258-AS	usGfsaGfaAfuGfaGfcCfuCfgAMTM(C12)s(PAZ)	731	167
AM04259-AS	usGfsaCfaCfcUfgAfuUfcUfgTMTMsAbsAbs(PAZ)	732	160
AM04260-AS	usGfsaCfaCfcUfgAfuUfcUfgTMTM(Sp18)s(PAZ)	733	168
AM04261-AS	usGfsaCfaCfcUfgAfuUfcUfgTMTM(C12)s(PAZ)	734	168
AM04377-AS	dTusCfsgUfaUfaacaaUfaAfgGfgGfcUfgCfscsua	735	169
AM04378-AS	uAusCfsgUfaUfaacaaUfaAfgGfgGfcUfgCfscsu	736	170
AM04379-AS	dTcsCfsgUfaUfaacaaUfaAfgGfgGfcUfgCfscsua	737	171
AM04380-AS	cUcsCfsgUfaUfaacaaUfaAfgGfgGfcUfgCfscsu	738	172
AM04383-AS	dTusGfsaGfaAfuGfaGfccuCfgAfuAfaCfucsusua	739	173
AM04384-AS	uAusGfsaGfaAfuGfaGfccuCfgAfuAfaCfucsusu	740	174
AM04385-AS	dTgsGfsaGfaAfuGfaGfccuCfgAfuAfaCfucsusua	741	175
AM04386-AS	gUgsGfsaGfaAfuGfaGfccuCfgAfuAfaCfucsusu	742	176
AM04387-AS	dTusGfsagaauGfaGfccuCfgauaacucsusua	743	173
AM04388-AS	uAusGfsagaauGfaGfccuCfgauaacucsusu	744	174
AM04389-AS	dTgsGfsagaauGfaGfccuCfgauaacucsusua	745	175
AM04390-AS	gUgsGfsagaauGfaGfccuCfgauaacucsusu	746	176
AM04413-AS	usCfsgsUfaUfaacaaUfaAfgGfgGfcusu	747	164
AM04415-AS	usGfsasGfaAfuGfaGfccuCfgAfuAfausu	748	177
AM04437-AS	usGfsuAfuAfaCfaAfuAfaGfgGMGMs(C12)s(PAZ)	749	165
AM04438-AS	usCfsgUfaUfaAfcAfaUfaAfgGMGMs(C12)s(PAZ)	750	166
AM04439-AS	usGfsaGfaAfuGfaGfcCfuCfgAMTMs(C12)s(PAZ)	751	167
AM04440-AS	usGfsaCfaCfcUfgAfuUfcUfgTMTMs(C12)s(PAZ)	752	168
AM04501-AS	cPrpTMsCfsgsUfaUfaAfCfAfauaAfgGfgGfcusu	753	178
AM04507-AS	usGfsasGfaAfuGfaGfccuCfgAfuAfausuAUAUA	754	179
AM04539-AS	usCfsgUfaUfaacaaUfaAfgGfgGfcUfgsCfscuAu	755	156
AM04540-AS	usCfsgUfaUfaacaaUfaAfgGfgGfcUfgsCfcuAu	756	156
AM04541-AS	usGfsaGfaAfuGfaGfccuCfgAfuAfaCfuscsuuAu	757	153
AM04542-AS	usGfsaGfaAfuGfaGfccuCfgAfuAfaCfuscuuAu	758	153
AM04544-AS	usCfsgsUfaUfaAfCfAfauaAfgGfgGfcUfgcsusu	759	162
AM04545-AS	usCfsgsUfaUfaAfCfAfauaagGfgGfcusu	760	164
AM04546-AS	usCfsgsUfaUfaAfCfAfaUfaagGfgGfcusu	761	164
AM04582-AS	usCfsgUfaUfaacaaUfaAfgGfgGfcUfgsCfsc	762	180
AM04583-AS	dTusCfsgUfaUfaacaaUfaAfgGfgGfcUfgsCfsc	763	181
AM04584-AS	dTusCfsgUfaUfaacaaUfaAfgGfgGfcUfgscsc	764	181
AM04585-AS	dTusCfsgsUfaUfaacaaUfaAfgGfgGfcUfgscsc	765	181
AM04586-AS	dTusCfsgsUfaUfaacaaUfaAfgGfgGfcUfgcsc	766	181
AM04587-AS	dTusCfsgsUfaUfaacaaUfaAfgGfgGfcusg	767	182
AM04609-AS	epTcPrsCfsgsUfaUfaAfCfAfauaAfgGfgGfcusu	768	178
AM04610-AS	epTMsCfsgsUfaUfaAfCfAfauaAfgGfgGfcusu	769	178
AM04677-AS	usGfsaGfaAfuGfaGfccuCfgAfuAfaCfsuscuuAu	770	153
AM04678-AS	usGfsaGfaAfuGfaGfccuCfgAfuAfasCfsucuuAu	771	153
AM04679-AS	usGfsaGfaAfuGfaGfccuCfgAfuAfaCfuasuscGc	772	183
AM04680-AS	usGfsaGfaAfuGfaGfccuCfgAfuAfaCfuasusuCa	773	184
AM04681-AS	usGfsaGfaAfuGfaGfccuCfgAfuAfaCfuascsgAu	774	185

AM04733-AS	us(5Me-Gf)saGfaAfuGfaGfccuCfgAfuAfaCfucsusuAu	775	153
AM04734-AS	usGfsa(5Me-Gf)aAfuGfaGfccuCfgAfuAfaCfucsusuAu	776	153
AM04735-AS	usGfsaGfaAfu(5Me-Gf)aGfccuCfgAfuAfaCfucsusuAu	777	153
AM04736-AS	usGfsaGfaAfuGfa(5Me-Gf)ccuCfgAfuAfaCfucsusuAu	778	153
AM04805-AS	vpusCfsgsUfaUfaAfCfAfauaAfgGfgGfcgsu	779	186
AM04821-AS	usCfsgUfaUfaacaaUfaAfgGfgGfcUfgCfscsu	780	187
AM04822-AS	usCfsgUfaUfaacaaUfaAfgGfgGfcUfgCfsusu	781	162
AM04823-AS	vpusCfsgUfaUfaacaaUfaAfgGfgGfcUfgCfscsu	782	187
AM04824-AS	vpusCfsgUfaUfaacaaUfaAfgGfgGfcUfgCfsusu	783	162
AM04871-AS	usGfsaGfaAfuGfAfgccuCfgAfuAfaCfusCfsuuAu	784	153
AM04872-AS	cPrpusGfsaGfaAfuGfaGfccuCfgAfuAfaCfucsusuAu	785	153
AM04873-AS	cPrpusCfsgUfaUfaacaaUfaAfgGfgGfcUfgCfscsuAu	786	156
AM04874-AS	usCfsgUfaUfaacaaUfaAfgGfgGfcsusu	787	164
AM04875-AS	cPrpusCfsgUfaUfaacaaUfaAfgGfgGfcsusu	788	164
AM04876-AS	usCfsgUfaUfaacaaUfaAfgGfgGfcsusg	789	188
AM04877-AS	usCfsgUfaUfaacaaUfaAfgGfgGfcsUfsg	790	188
AM04878-AS	cPrpusCfsgUfaUfaacaaUfaAfgGfgGfcUfgCfsusu	791	162
AM04879-AS	usGfsaGfaAfuGfaGfcCfuCfgAfuAfaCfucsusuAu	792	153
AM04880-AS	cPrpusGfsaGfaAfuGfaGfcCfuCfgAfuAfaCfucsusuAu	793	153
AM04969-AS	cPrpTMsGfsaGfaAfuGfaGfcCfuCfgAfuAfaCfucsusuAu	794	109
AM04970-AS	cPrpTMsCfsgUfaUfaacaaUfaAfgGfgGfcUfgCfscsuAu	795	111
AM04971-AS	cPrpTMsCfsgUfaUfaacaaUfaAfgGfgGfcsusu	796	178
AM04972-AS	cPrpTMsCfsgUfaUfaacaaUfaAfgGfgGfcUfgCfsusu	797	189
AM04979-AS	usCfsgsUfaUfaAfcAfaUfaAfgGfgGfcusu	798	164
1532-AS01	usgsagaaugaGfccuCfgAfuAfaCfuCfsusuAu	799	153
1532-AS02	usgsagaauGfagccuCfgAfuAfaCfuCfsusuAu	800	153
1532-AS03	usgsagaAfugagccuCfgAfuAfaCfuCfsusuAu	801	153
1532-AS04	usgsaGfaaugagccuCfgAfuAfaCfuCfsusuAu	802	153
1532-AS05	usGfsagaaugagccuCfgAfuAfaCfuCfsusuAu	803	153
1532-AS06	dTsgsagaaugagccuCfgAfuAfaCfuCfsusuAu	804	109
1532-AS07	dTsGfsaGfaAfugagccuCfgAfuAfaCfuCfsusuAu	805	109
1532-AS08	dTsGfsaGfaAfugaGfccuCfgauAfaCfuCfsusuAu	806	109
1532-AS09	dTsGfsaGfaAfuGfagccuCfgauAfaCfuCfsusuAu	807	109
1532-AS10	dTsGfsaGfaAfugagccuCfgauAfaCfuCfsusuAu	808	109
1532-AS11	dTsGfsaGfaAfugagccuCfgAfuaaCfuCfsusuAu	809	109
1532-AS12	dTsGfsaGfaAfugaGfccuCfgauaaCfuCfsusuAu	810	109
1532-AS13	dTsGfsaGfaAfuGfagccuCfgauaaCfuCfsusuAu	811	109
1532-AS15	dTsgsagaaugaGfccuCfgAfuAfaCfuCfsusuAu	812	109
1532-AS16	dTsgsagaauGfagccuCfgAfuAfaCfuCfsusuAu	813	109
1532-AS17	dTsgsagaAfugagccuCfgAfuAfaCfuCfsusuAu	814	109
1532-AS18	dTsgsaGfaaugagccuCfgAfuAfaCfuCfsusuAu	815	109
1532-AS19	dTsGfsagaaugagccuCfgAfuAfaCfuCfsusuAu	816	109
1532-AS20	usgsagaaugagccuCfgAfuAfaCfuCfsusuAu	817	153
1532-AS21	usGfsaGfaAfugagccuCfgAfuAfaCfuCfsusuAu	818	153
1532-AS22	usGfsaGfaAfugaGfccuCfgauAfaCfuCfsusuAu	819	153
1532-AS23	usGfsaGfaAfuGfagccuCfgauAfaCfuCfsusuAu	820	153
1532-AS24	usGfsaGfaAfugagccuCfgauAfaCfuCfsusuAu	821	153

1532-AS25	usGfsaGfaAfugagccuCfgAfuaaCfuCfsusuAu	822	153
1532-AS27	usGfsaGfaAfuGfagccuCfgauaaCfuCfsusuAu	823	153
1533-AS01	usgsaCfaCfcugAfuucUfgUfuUfcUfgAfsgsuAu	824	154
1533-AS02	usgsaCfaCfcUfgauucUfgUfuUfcUfgAfsgsuAu	825	154
1533-AS04	dTsgsaCfaCfcugauucUfgUfuUfcUfgAfsgsuAu	826	110
1533-AS05	dTsGfsaCfaCfcugAfuucUfguuUfcUfgAfsgsuAu	827	110
1533-AS06	dTsGfsaCfaCfcUfgauucUfguuUfcUfgAfsgsuAu	828	110
1533-AS07	dTsGfsaCfaCfcUfgauucUfgUfuucUfgAfsgsuAu	829	110
1533-AS08	dTsGfsaCfaCfcUfgAfuucUfguuucUfgAfsgsuAu	830	110
1533-AS09	dTsGfsaCfaCfcUfgAfuucUfguuUfcugAfsgsuAu	831	110
1533-AS10	dTsGfsaCfaCfcUfgAfuucUfgUfuucugAfsgsuAu	832	110
1533-AS11	dTsGfsaCfaCfcUfgAfuucUfguuucugAfsgsuAu	833	110
1533-AS12	dTsGfsaCfaCfcUfgAfuucUfguuucUfgasgsuAu	834	110
1533-AS13	dTsGfsaCfaCfcUfgAfuucUfguuUfcugasgsuAu	835	110
1533-AS16	dTsgsaCfaCfcugAfuucUfgUfuUfcUfgAfsgsuAu	836	110
1533-AS17	dTsgsaCfaCfcUfgauucUfgUfuUfcUfgAfsgsuAu	837	110
1533-AS19	usgsaCfaCfcugauucUfgUfuUfcUfgAfsgsuAu	838	154
1533-AS20	usGfsaCfaCfcugAfuucUfguuUfcUfgAfsgsuAu	839	154
1533-AS21	usGfsaCfaCfcUfgauucUfguuUfcUfgAfsgsuAu	840	154
1533-AS22	usGfsaCfaCfcUfgauucUfgUfuucUfgAfsgsuAu	841	154
1533-AS23	usGfsaCfaCfcUfgAfuucUfguuucUfgAfsgsuAu	842	154
1533-AS24	usGfsaCfaCfcUfgAfuucUfguuUfcugAfsgsuAu	843	154
1533-AS25	usGfsaCfaCfcUfgAfuucUfgUfuucugAfsgsuAu	844	154
1533-AS26	usGfsaCfaCfcUfgAfuucUfguuucugAfsgsuAu	845	154
1533-AS27	usGfsaCfaCfcUfgAfuucUfguuucUfgasgsuAu	846	154
1533-AS28	usGfsaCfaCfcUfgAfuucUfguuUfcugasgsuAu	847	154
1533-CfinAS	dTsGfsacaccUfgAfuucUfgUfuUfcUfgAfsgsuAu	848	110
AM05490-AS	usGfsasGfaAfuGfaGfcCfuCfgAfuAfausu	1262	177
AM05492-AS	cPrpTMsCfsgsUfaUfaAfCfAfaUfaAfgGfgGfcusu	1263	178
AM05493-AS	cPrpTMsCfsgsUfaUfaAfcAfaUfaAfgGfgGfcusu	1264	178
AM05495-AS	usCfsguauaaCfaaUfaAfgggGfcugCfscsuAu	1265	156
AM05496-AS	usCfsguaUfaaCfaaUfaAfgggGfcugCfscsuAu	1266	156
AM05497-AS	usCfsgUfaUfaacaaUfaAfgGfgGfcsUfsu	1267	164
AM05498-AS	usCfsgsUfaUfaAfCfAfaUfaAfgGfgGfcusu	1268	164

Table 2B. LPA RNAi agent sense strands having modified nucleotides.

Sense Strand ID	SS Sequence 5' → 3'	SEQ ID NO.	SEQ ID NO.
AM01173-SS	AfcGfcAfgAfaGfgGfaCfuGfcCfgAf(invdT)	849	190
AM01174-SS	GfgGfgUfgCfaGfgAfgUfgCfuAfcAf(invdT)	850	191
AM01175-SS	CfuGfuGfgCfaGfcCfcCfuUfaUfuAf(invdT)	851	192
AM01176-SS	GfgCfaGfcCfcCfuUfaUfuGfuUfaAf(invdT)	852	193
AM01177-SS	AfgCfcCfcUfuAfuUfgUfuAfuAfcAf(invdT)	853	194
AM01178-SS	GfcCfcCfuUfaUfuGfuUfaUfaCfgAf(invdT)	854	195
AM01179-SS	UfgAfcAfcAfaUfgCfuCfaGfaCfgAf(invdT)	855	196

AM01180-SS	GfaCfaCfaAfuGfcUfcAfgAfcGfcAf(invdT)	856	197
AM01181-SS	AfcAfcAfaUfgCfuCfaGfaCfgCfaAf(invdT)	857	198
AM01182-SS	AfcAfaUfgCfuCfaGfaCfgCfaGfaAf(invdT)	858	199
AM01183-SS	CfuGfcCfgAfaAfuCfcAfgAfuCfcAf(invdT)	859	200
AM01184-SS	GfcCfgAfaAfuCfcAfgAfuCfcUfgAf(invdT)	860	201
AM01185-SS	UfgAfcAfcGfaUfgCfuCfaGfaUfgAf(invdT)	861	202
AM01186-SS	GfaCfaCfgAfuGfcUfcAfgAfuGfcAf(invdT)	862	203
AM01187-SS	AfcAfcGfaUfgCfuCfaGfaUfgCfaAf(invdT)	863	204
AM01188-SS	AfcGfaUfgCfuCfaGfaUfgCfaGfaAf(invdT)	864	205
AM01189-SS	UfcCfaAfgCfcUfaGfaGfgCfuUfuAf(invdT)	865	206
AM01190-SS	AfgGfaAfaCfcCfcCfgGfgGfuAfcAf(invdT)	866	207
AM01191-SS	GfgAfaAfcCfcCfcGfgGfgUfaCfaAf(invdT)	867	208
AM01192-SS	GfaAfaCfcCfcCfgGfgGfuAfcAfgAf(invdT)	868	209
AM01193-SS	UfgCfuAfcUfaCfcAfuUfaUfgGfaAf(invdT)	869	210
AM01194-SS	GfcUfaCfuAfcCfaUfuAfuGfgAfcAf(invdT)	870	211
AM01195-SS	CfuAfcCfaUfuAfuGfgAfcAfgAfgAf(invdT)	871	212
AM01196-SS	AfcCfaCfaCfcAfgCfaUfaGfuCfgAf(invdT)	872	213
AM01197-SS	CfcAfcAfcCfaGfcAfuAfgUfcGfgAf(invdT)	873	214
AM01198-SS	CfaCfaCfcAfgCfaUfaGfuCfgGfaAf(invdT)	874	215
AM01199-SS	CfaCfcAfgCfaUfaGfuCfgGfaCfcAf(invdT)	875	216
AM01200-SS	AfuAfgUfcGfgAfcCfcCfaGfaAfaAf(invdT)	876	217
AM01201-SS	UfaGfuCfgGfaCfcCfcAfgAfaAfaAf(invdT)	877	218
AM01202-SS	CfcAfgAfuGfcUfgAfgAfuUfcGfcAf(invdT)	878	219
AM01203-SS	GfcUfgAfgAfuUfcGfcCfcUfuGfgAf(invdT)	879	220
AM01204-SS	CfuGfaGfaUfuCfgCfcCfuUfgGfuAf(invdT)	880	221
AM01205-SS	UfgAfgAfuUfcGfcCfcUfuGfgUfgAf(invdT)	881	222
AM01206-SS	GfaGfaUfuCfgCfcCfuUfgGfuGfuAf(invdT)	882	223
AM01207-SS	AfuGfgAfuCfcCfaGfuGfuCfaGfgAf(invdT)	883	224
AM01208-SS	GfaAfuCfaAfgUfgUfcCfuUfgCfaAf(invdT)	884	225
AM01209-SS	AfaUfcAfaGfuGfuCfcUfuGfcAfaAf(invdT)	885	226
AM01210-SS	GfaAfgCfaCfcAfaCfgGfaGfcAfaAf(invdT)	886	227
AM01211-SS	GfaGfuUfaUfcGfaGfgCfuCfaUfuAf(invdT)	887	228
AM01212-SS	AfgUfuAfuCfgAfgGfcUfcAfuUfcAf(invdT)	888	229
AM01213-SS	GfaCfaAfcAfgAfaUfaUfuAfuCfcAf(invdT)	889	230
AM01214-SS	CfuUfgGfuGfuUfaUfaCfcAfuGfgAf(invdT)	890	231
AM01215-SS	GfgUfgUfuAfuAfcCfaUfgGfaUfcAf(invdT)	891	232
AM01216-SS	UfaUfaCfcAfuGfgAfuCfcCfaAfuAf(invdT)	892	233
AM01217-SS	AfuAfcCfaUfgGfaUfcCfcAfaUfgAf(invdT)	893	234
AM01218-SS	UfaCfcAfuGfgAfuCfcCfaAfuGfuAf(invdT)	894	235
AM01219-SS	AfcCfaUfgGfaUfcCfcAfaUfgUfcAf(invdT)	895	236
AM01220-SS	GfcAfaCfcUfgAfcAfcAfaUfgUfcAf(invdT)	896	237
AM01221-SS	CfuGfaCfaCfaAfuGfuCfcAfgUfgAf(invdT)	897	238
AM01222-SS	CfcAfgUfgAfcAfgAfaUfcAfaGfuAf(invdT)	898	239
AM01223-SS	UfuAfuCfgAfgGfcUfcAfuUfcUfcAf(invdT)	899	240
AM01224-SS	AfgAfaUfaCfuAfcCfcAfaAfuGfgAf(invdT)	900	241
AM01225-SS	AfaUfaCfuAfcCfcAfaAfuGfgUfgAf(invdT)	901	242

AM01226-SS	AfuAfcUfaCfcCfaAfaUfgGfuGfgAf(invdT)	902	243
AM01227-SS	AfuUfcGfcCfcUfuGfgUfgUfuAfuAf(invdT)	903	244
AM01228-SS	UfaUfaCfcAfuGfgAfuCfcCfaGfuAf(invdT)	904	245
AM01229-SS	AfuAfcCfaUfgGfaUfcCfcAfgUfgAf(invdT)	905	246
AM01230-SS	CfaCfaAfcUfcCfcAfcGfgUfgGfuAf(invdT)	906	247
AM01231-SS	AfaGfaAfcAfuGfuCfaGfuCfuUfgAf(invdT)	907	248
AM01232-SS	AfgUfgUfcCfuCfaCfaAfcUfcCfcAf(invdT)	908	249
AM01233-SS	AfaCfaAfgCfaCfcAfcCfuGfaGfaAf(invdT)	909	250
AM01234-SS	CfcUfgAfgAfaAfaGfcCfcUfgUfgAf(invdT)	910	251
AM01235-SS	UfgAfuAfcCfaCfaCfuGfgCfaUfcAf(invdT)	911	252
AM01236-SS	GfaUfaCfcAfcAfcUfgGfcAfuCfaAf(invdT)	912	253
AM01237-SS	GfaAfaCfaGfaAfuCfaGfgUfgUfcAf(invdT)	913	254
AM01238-SS	AfaAfcAfgAfaUfcAfgGfuGfuCfcAf(invdT)	914	255
AM01239-SS	CfaGfaAfuCfaGfgUfgUfcCfuAfgAf(invdT)	915	256
AM01795-SS	CfcUfgUfgGfcAfgCfcCfcUfuAfuAf(invdT)	916	257
AM01797-SS	UfgGfcAfgCfcCfcUfuAfuUfgUfuAf(invdT)	917	258
AM01799-SS	AfcAfcCfaGfcAfuAfgUfcGfgAfcAf(invdT)	918	259
AM01801-SS	GfgAfaUfcCfaGfaUfgCfuGfaGfaAf(invdT)	919	260
AM01803-SS	UfcCfaGfaUfgCfuGfaGfaUfuCfgAf(invdT)	920	261
AM01805-SS	AfuGfcUfgAfgAfuUfcGfcCfcUfuAf(invdT)	921	262
AM01807-SS	CfcAfuGfgAfuCfcCfaGfuGfuCfaAf(invdT)	922	263
AM01809-SS	CfuGfaAfgAfaGfcAfcCfaAfcGfgAf(invdT)	923	264
AM01811-SS	UfcCfaGfuGfaCfaGfaAfuCfaAfgAf(invdT)	924	265
AM01813-SS	CfuCfaCfaAfcUfcCfcAfcGfgUfgAf(invdT)	925	266
AM01815-SS	AfgAfaUfcAfgGfuGfuCfcUfaGfaAf(invdT)	926	267
AM01817-SS	UfcAfgGfuGfuCfcUfaGfaGfaCfuAf(invdT)	927	268
AM02006-SS	(Chol-TEG)uAuAfgCfcCfcUfUfAfuUfgUfuAfuAfcAf(invdT)	928	269
AM02010-SS	(Chol-TEG)uAuGfcCfcCfuUfAfUfuGfuUfaUfaCfgAf(invdT)	929	270
AM02014-SS	(Chol-TEG)uAuGfaCfaCfaAfUfGfcUfcAfgAfcGfcAf(invdT)	930	271
AM02018-SS	(Chol-TEG)uAuAfcAfcAfaUfGfCfuCfaGfaCfgCfaAf(invdT)	931	272
AM02022-SS	(Chol-TEG)uAuUfuAfuCfgAfGfGfcUfcAfuUfcUfcAf(invdT)	932	273
AM02026-SS	(Chol-TEG)uAuGfaAfaCfaGfAfAfuCfaGfgUfgUfcAf(invdT)	933	274
AM02030-SS	(Chol-TEG)uAuAfcAfcCfaGfCfAfuAfgUfcGfgAfcAf(invdT)	934	275
AM02034-SS	(Chol-TEG)uAuUfcCfaGfaUfGfCfuGfaGfaUfuCfgAf(invdT)	935	276
AM02038-SS	(Chol-TEG)uAuAfuGfcUfgAfgAfuUfcGfcCfcUfuAf(invdT)	936	277
AM02042-SS	(Chol-TEG)uAuCfcAfuGfgAfUfCfcCfaGfuGfuCfaAf(invdT)	937	278
AM02211-SS	UfgUfgGfcAfGfCfcCfcUfuAfuUfgAf(invdT)	938	279
AM02212-SS	CfaCfaAfuGfCfUfcAfgAfcGfcAfgAf(invdT)	939	280
AM02213-SS	CfcGfaAfaUfCfCfaGfaUfcCfuGfuAf(invdT)	940	281
AM02214-SS	GfaCfuGfaGfGfAfaAfcCfcCfcGfgAf(invdT)	941	282
AM02215-SS	CfuAfcUfaCfCfAfuUfaUfgGfaCfaAf(invdT)	942	283
AM02216-SS	AfcUfaCfcAfUfUfaUfgGfaCfaGfaAf(invdT)	943	284
AM02217-SS	UfaCfcAfuUfAfUfgGfaCfaGfaGfuAf(invdT)	944	285
AM02218-SS	AfcCfaUfuAfUfGfgAfcAfgAfgUfuAf(invdT)	945	286
AM02219-SS	AfgAfuGfcUfGfAfgAfuUfcGfcCfcAf(invdT)	946	287
AM02220-SS	GfaUfgCfuGfAfGfaUfuCfgCfcCfuAf(invdT)	947	288

AM02221-SS	AfgAfuUfcGfCfCfcUfuGfgUfgUfuAf(invdT)	948	289
AM02222-SS	GfaCfaGfaAfUfCfaAfgUfgUfcCfuAf(invdT)	949	290
AM02223-SS	AfcAfuGfuCfAfGfuCfuUfgGfuCfcAf(invdT)	950	291
AM02224-SS	CfcAfaAfuGfGfUfgGfcCfuGfaCfcAf(invdT)	951	292
AM02225-SS	UfgGfuGfuUfAfUfaCfcAfuGfgAfuAf(invdT)	952	293
AM02226-SS	UfgUfuAfuAfCfCfaUfgGfaUfcCfcAf(invdT)	953	294
AM02227-SS	AfaCfcUfgAfCfAfcAfaUfgUfcCfaAf(invdT)	954	295
AM02228-SS	AfaUfgUfcCfAfGfuGfaCfaGfaAfuAf(invdT)	955	296
AM02229-SS	UfgUfuUfcUfGfAfaCfaAfgCfaCfcAf(invdT)	956	297
AM02230-SS	UfaUfcGfaGfGfCfuCfaUfuCfuCfcAf(invdT)	957	298
AM02231-SS	UfcGfaGfgCfUfCfaUfuCfuCfcAfcAf(invdT)	958	299
AM02232-SS	UfcCfuCfaCfAfAfcUfcCfcAfcGfgAf(invdT)	959	300
AM02233-SS	CfaAfcUfcCfCfAfcGfgUfgGfuCfcAf(invdT)	960	301
AM02234-SS	GfcUfcCfuUfCfUfgAfaCfaAfgCfaAf(invdT)	961	302
AM02235-SS	AfuAfcCfaCfAfCfuGfgCfaUfcAfgAf(invdT)	962	303
AM02236-SS	AfcAfgAfaUfCfAfgGfuGfuCfcUfaAf(invdT)	963	304
AM02237-SS	GfaAfuCfaGfGfUfgUfcCfuAfgAfgAf(invdT)	964	305
AM02238-SS	AfaUfcAfgGfUfGfuCfcUfaGfaGfaAf(invdT)	965	306
AM02239-SS	AfuCfaGfgUfGfUfcCfuAfgAfgAfcAf(invdT)	966	307
AM02441-SS	uAuAusAfsgUfuAfuCfgAfgGfcUfcAfuUfcUfcAf(C6-SS-Alk-Me)	967	308
AM02442-SS	uAuAusAfsgUfuAfuCfgaGfGfcUfcAfuUfcUfcAf(C6-SS-Alk-Me)	968	308
AM02443-SS	uAuAusAfsgUfuAfuCfGfaGfGfcUfcAfuUfcUfcAf(C6-SS-Alk-Me)	969	308
AM02444-SS	uAuAusasGfuUfaUfcGfaGfGfcUfcAfuUfcUfcAf(C6-SS-Alk-Me)	970	308
AM02445-SS	uAuAusCfsaGfaAfaCfaGfaAfuCfaGfgUfgUfcAf(C6-SS-Alk-Me)	971	309
AM02446-SS	uAuAusCfsaGfaAfaCfagAfAfuCfaGfgUfgUfcAf(C6-SS-Alk-Me)	972	309
AM02447-SS	uAuAusCfsaGfaAfaCfAfgAfAfuCfaGfgUfgUfcAf(C6-SS-Alk-Me)	973	309
AM02448-SS	uAuAuscsAfgAfaAfcAfgAfAfuCfaGfgUfgUfcAf(C6-SS-Alk-Me)	974	309
AM02537-SS	uAuAusCfsaGfcCfcCfuUfAfUfuGfuUfaUfaCfgAf(C11-PEG3-NAG3)	975	310
AM02538-SS	uAuAusCfsuGfaCfaCfaAfUfGfcUfcAfgAfcGfcAf(C11-PEG3-NAG3)	976	311
AM02539-SS	uAuAusUfsgAfcAfcAfaUfGfCfuCfaGfaCfgCfaAf(C11-PEG3-NAG3)	977	312
AM02540-SS	uAuAusAfsgUfuAfuCfgAfGfGfcUfcAfuUfcUfcAf(C11-PEG3-NAG3)	978	308
AM02541-SS	uAuAusCfsaGfaAfaCfaGfAfAfuCfaGfgUfgUfcAf(C11-PEG3-NAG3)	979	309
AM02542-SS	uAuAusAfsgAfuGfcUfgAfGfAfuUfcGfcCfcUfuAf(C11-PEG3-NAG3)	980	313
AM02793-SS	gsCfsaGfcCfcCfuUfaUfuGfuUfa(invdA)	981	314
AM02794-SS	gsCfscCfcUfuAfuUfgUfuAfuAfc(invdA)	982	315
AM02795-SS	csCfscCfuUfaUfuGfuUfaUfaCfg(invdA)	983	316
AM02796-SS	asCfsaCfaAfuGfcUfcAfgAfcGfc(invdA)	984	317
AM02797-SS	csAfscAfaUfgCfuCfaGfaCfgCfa(invdA)	985	318
AM02798-SS	csCfsgAfaAfuCfcAfgAfuCfcUfg(invdA)	986	319
AM02799-SS	csAfscGfaUfgCfuCfaGfaUfgCfa(invdA)	987	320
AM02800-SS	csCfsaCfaCfcAfgCfaUfaGfuCfg(invdA)	988	321
AM02801-SS	usAfsgUfcGfgAfcCfcCfaGfaAfa(invdA)	989	322
AM02802-SS	csAfsgAfuGfcUfgAfgAfuUfcGfc(invdA)	990	323
AM02803-SS	asAfsuCfaAfgUfgUfcCfuUfgCfa(invdA)	991	324
AM02804-SS	asGfsuUfaUfcGfaGfgCfuCfaUfu(invdA)	992	325
AM02805-SS	gsUfsuAfuCfgAfgGfcUfcAfuUfc(invdA)	993	326

AM02806-SS	csAfsaCfcUfgAfcAfcAfaUfgUfc(invdA)	994	327
AM02807-SS	usAfsuCfgAfgGfcUfcAfuUfcUfc(invdA)	995	328
AM02808-SS	gsAfsaUfaCfuAfcCfcAfaAfuGfg(invdA)	996	329
AM02809-SS	asUfsaCfuAfcCfcAfaAfuGfgUfg(invdA)	997	330
AM02810-SS	asAfsaCfaGfaAfuCfaGfgUfgUfc(invdA)	998	331
AM02811-SS	asAfscAfgAfaUfcAfgGfuGfuCfc(invdA)	999	332
AM02812-SS	CfsasGfcCfcCfuUfaUfuGfuUfa(invdA)	1000	333
AM02813-SS	CfscsCfcUfuAfuUfgUfuAfuAfc(invdA)	1001	334
AM02814-SS	CfscsCfuUfaUfuGfuUfaUfaCfg(invdA)	1002	335
AM02815-SS	CfsasCfaAfuGfcUfcAfgAfcGfc(invdA)	1003	336
AM02816-SS	AfscsAfaUfgCfuCfaGfaCfgCfa(invdA)	1004	337
AM02817-SS	CfsgsAfaAfuCfcAfgAfuCfcUfg(invdA)	1005	338
AM02818-SS	AfscsGfaUfgCfuCfaGfaUfgCfa(invdA)	1006	339
AM02819-SS	CfsasCfaCfcAfgCfaUfaGfuCfg(invdA)	1007	340
AM02820-SS	AfsgsUfcGfgAfcCfcCfaGfaAfa(invdA)	1008	341
AM02821-SS	AfsgsAfuGfcUfgAfgAfuUfcGfc(invdA)	1009	342
AM02822-SS	AfsusCfaAfgUfgUfcCfuUfgCfa(invdA)	1010	343
AM02823-SS	GfsusUfaUfcGfaGfgCfuCfaUfu(invdA)	1011	344
AM02824-SS	UfsusAfuCfgAfgGfcUfcAfuUfc(invdA)	1012	345
AM02825-SS	AfsasCfcUfgAfcAfcAfaUfgUfc(invdA)	1013	346
AM02826-SS	AfsusCfgAfgGfcUfcAfuUfcUfc(invdA)	1014	347
AM02827-SS	AfsasUfaCfuAfcCfcAfaAfuGfg(invdA)	1015	348
AM02828-SS	UfsasCfuAfcCfcAfaAfuGfgUfg(invdA)	1016	349
AM02829-SS	AfsasCfaGfaAfuCfaGfgUfgUfc(invdA)	1017	350
AM02830-SS	AfscsAfgAfaUfcAfgGfuGfuCfc(invdA)	1018	351
AM02861-SS	uAuAusAfsgUfuauCfgAfGfGfcUfcAfuUfcUfcAf(C11-PEG3-NAG3)	1019	308
AM02941-SS	uAuAusasguuaucgAfgGfcucauucuca(C11-PEG3-NAG3)	1020	308
AM02942-SS	uAuAusasguuaucgaGfGfcucauucuca(C11-PEG3-NAG3)	1021	308
AM02946-SS	uAuAuscsagaaaCfagAfAfuCfagguguca(C11-PEG3-NAG3)	1022	309
AM02947-SS	uAuAuscsagaaaCfaGfaAfuCfagguguca(C11-PEG3-NAG3)	1023	309
AM02948-SS	uAuAuscsagaaacaGfaAfucagguguca(C11-PEG3-NAG3)	1024	309
AM02949-SS	uAuAuscsagaaacagAfAfucagguguca(C11-PEG3-NAG3)	1025	309
AM03030-SS	(Stearyl)uAuAusCfsaGfaAfaCfaGfAfAfuCfaGfgUfgUfcAf(C11-PEG3-NAG3)	1026	309
AM03036-SS	uAuAusCfsagaAfaCfaGfAfAfuCfaGfgUfgUfcAf(C11-PEG3-NAG3)	1027	309
AM03037-SS	uAuAusCfsagaaaCfaGfAfAfuCfaGfgUfgUfcAf(C11-PEG3-NAG3)	1028	309
AM03038-SS	uAuAusCfsagaaaCfagaAfuCfaggUfgUfcAf(C11-PEG3-NAG3)	1029	309
AM03039-SS	uAuAusCfsaGfaAfaCfaGfAfAfuCfagGfuGfucAf(C11-PEG3-NAG3)	1030	309
AM03042-SS	uAuAusCfsaGfaAfaCfaGfAfAfucagguguca(C11-PEG3-NAG3)	1031	309
AM03060-SS	uAuAusCfsaGfaAfaCfaGfAfAfuCfaggugUfca(C11-PEG3-NAG3)	1032	309
AM03061-SS	uAuAusCfsaGfaAfaCfaGfAfAfuCfagguguca(C11-PEG3-NAG3)	1033	309
AM03062-SS	uAuAusCfsagaaaCfaGfAfAfuCfaggugUfca(C11-PEG3-NAG3)	1034	309
AM03064-SS	uAuAusCfsaGfaAfaCfaGfaAfuCfaGfgugucAf(C11-PEG3-NAG3)	1035	309
AM03122-SS	uAuAusAfsgUfuAfuCfgAfGfGfcUfcAfuUfcUfCMAM(C11-PEG3-NAG3)	1036	308
AM03123-SS	uAuAU$_{UNA}$AfsgsUfuAfuCfgAfGfGfcUfcAfuUfcUfcAf(C11-PEG3-NAG3)	1037	308
AM03124-SS	uAuAuAfsgsUfuAfuCfgAfGfGfcUfcAfuUfcUfcAf(C11-PEG3-NAG3)	1038	308
AM03125-SS	uAuAusCfsaGfcCfcCfuUfAfUfuGfuUfaUfaCfga(C11-PEG3-NAG3)	1039	310

AM03126-SS	uAuAuscsaGfcCfcCfuUfAfUfuGfuUfaUfaCfgAf(C11-PEG3-NAG3)	1040	310
AM03128-SS	uAuAuscsaGfcCfcCfuUfAfUfuGfuUfaUfaCfga(C11-PEG3-NAG3)	1041	310
AM03144-SS	uAuAusAfsgUfuAfuCfgAfGfGfcUfcAfuUfcUfcAf(C6-PEG4-NAG3)	1042	308
AM03220-SS 1532-SS01	uAuAusAfsgUfuAfuCfgAfGfGfcUfcauucuca	1043	308
AM03221-SS	uAuAusAfsgUfuAfuCfgAfGfGfcucauucuca	1044	308
AM03222-SS	uAuAusAfsguuauCfgAfGfGfcUfcauucuca	1045	308
AM03223-SS	uAuAusAfsguuauCfgAfGfGfcucauucuca	1046	308
AM03224-SS	uAuAusasguuauCfgAfGfGfcucauucuca	1047	308
AM03225-SS	uAuAusasguuaucgAfGfGfcucauucuca	1048	308
AM03226-SS	uAuAusAfsgUfuAfuCfgAfGfdGcUfcauucuca	1049	308
AM03227-SS	uAuAusAfsgUfuAfuCfgAfGfdGcucauucuca	1050	308
AM03228-SS	uAuAusAfsguuauCfgAfGfdGcUfcauucuca	1051	308
AM03229-SS	uAuAusAfsguuauCfgAfGfdGcucauucuca	1052	308
AM03230-SS	uAuAusasguuauCfgAfGfdGcucauucuca	1053	308
AM03231-SS	uAuAusasguuaucgAfGfdGcucauucuca	1054	308
AM03232-SS	uAuAusAfsgUfuAfuCfgaGfGfcUfcauucuca	1055	308
AM03233-SS	uAuAusAfsgUfuAfuCfgaGfGfcucauucuca	1056	308
AM03234-SS	uAuAusAfsguuauCfgaGfGfcUfcauucuca	1057	308
AM03235-SS	uAuAusAfsguuauCfgaGfGfcucauucuca	1058	308
AM03236-SS	uAuAusasguuauCfgaGfGfcucauucuca	1059	308
AM03237-SS	uAuAusasguuaucgaGfGfcucauucuca	1060	308
AM03238-SS	uAuAusAfsgUfuAfuCfgAfGfGfcUfcauucuca(C11-PEG3-NAG3)	1061	308
AM03240-SS	uAuAusAfsguuauCfgAfGfGfcUfcauucuca(C11-PEG3-NAG3)	1062	308
AM03330-SS 1532-SS00	uAuAusAfsgUfuAfuCfgAfGfGfcUfcAfuUfcUfcAf	1063	308
AM03291-SS	uAuAusCfsaGfcCfcCfuUfAfUfuGfuUfaUfaCfgAf	1064	310
AM03292-SS	uAuAusCfsagcCfcCfuUfaUfuguUfaUfaCfga	1065	310
AM03293-SS	uAuAusCfsagcCfcCfuUfaUfuguuauaCfga	1066	310
AM03294-SS	uAuAuscsagccccuUfaUfuguuauacga	1067	310
AM03295-SS	uAuAuscsagccccuuAfUfuguuauacga	1068	310
AM03296-SS	uAuAusCfsagcCfcCfuUfAfUfuguUfaUfaCfga	1069	310
AM03297-SS	uAuAusCfsagcCfcCfuUfAfUfuguuauaCfga	1070	310
AM03298-SS	uAuAuscsagccccuUfAfUfuguuauacga	1071	310
AM03299-SS	uAuAusCfsagcCfcCfuuAfUfuguuauaCfga	1072	310
AM03277-SS	uAuAuscsagccccuUfaUfuguuauacga(C11-PEG3-NAG3)	1073	310
AM03275-SS	uAuAusCfsagcCfcCfuUfaUfuguUfaUfaCfga(C11-PEG3-NAG3)	1074	310
AM03276-SS	uAuAusCfsagcCfcCfuUfaUfuguuauaCfga(C11-PEG3-NAG3)	1075	310
AM03278-SS	uAuAuscsagccccuuAfUfuguuauacga(C11-PEG3-NAG3)	1076	310
AM03287-SS	uAuAusCfsagcCfcCfuUfAfUfuguUfaUfaCfga(C11-PEG3-NAG3)	1077	310
AM03288-SS	uAuAusCfsagcCfcCfuUfAfUfuguuauaCfga(C11-PEG3-NAG3)	1078	310
AM03289-SS	uAuAuscsagccccuUfAfUfuguuauacga(C11-PEG3-NAG3)	1079	310
AM03290-SS	uAuAusCfsagcCfcCfuuAfUfuguuauaCfga(C11-PEG3-NAG3)	1080	310
AM03243-SS	uAuAusasguuaucgAfGfGfcucauucuca(C11-PEG3-NAG3)	1081	308
AM03424-SS	(Chol-TEG)uAuAusasguuaucgaGfGfcucauucuc(invdA)	1082	308
AM03425-SS	(Chol-TEG)uAuAusasguuaucgaGfGfcucauucuca	1083	308

AM03426-SS	(Chol-TEG)uAuAusAfgUfuAfuCfgAfGfGfcUfcAfuUfcUfc(invdA)	1084	308
AM03457-SS	CfscsCfcUfuAfuUfgUfuAfuAfca(NAG13)	1085	334
AM03458-SS	CfscsCfuUfaUfuGfuUfaUfaCfga(NAG13)	1086	335
AM03459-SS	AfsgsAfuGfcUfgAfgAfuUfcGfca(NAG13)	1087	342
AM03460-SS	GfsusUfaUfcGfaGfgCfuCfaUfua(NAG13)	1088	344
AM03461-SS	AfsusCfgAfgGfcUfcAfuUfcUfca(NAG13)	1089	347
AM03462-SS	AfsasCfaGfaAfuCfaGfgUfgUfca(NAG13)	1090	350
AM03489-SS	uAuAusasguuaucgaGfGfcucauucuca(NAG13)	1091	308
AM03492-SS	uAuAusCfsaGfcCfcCfuUfAfUfuGfuUfaUfaCfga(NAG13)	1092	310
AM03544-SS	uAuAuscsagcccCfuUfaUfuguuauacga(NAG13)	1093	310
AM03545-SS	uAuAuscsagccccuuAfUfuGfuuauacga(NAG13)	1094	310
AM03546-SS	uAuAuscsagccccuUfAfUfuguuauacga(NAG13)	1095	310
AM03547-SS	uAuAusAfsgUfuAfuCfgAfGfGfcUfcAfuUfcUfcAf(NAG13)	1096	308
AM03650-SS	uAuAusasguuaucgAfGfGfcucauucuca(NAG13)	1097	308
AM03651-SS	uAuAuscsaGfcCfcCfuUfAfUfuGfuUfaUfaCfga(NAG13)	1098	310
AM03670-SS	uAuAuscsagcgccuUfAfUfuguuauacga(NAG13)	1099	352
AM03683-SS	uAuAuscsaGfcCfcCfuUfAfUfuGfuUfaUfaCfga	1100	310
AM03741-SS	cscsccUfUfAfuuguuauaca(NAG13)	1101	334
AM03742-SS	cscsccUfUfAfuuguuauaCMAM(NAG13)	1102	334
AM03743-SS	CMsCMsccUfUfAfuuguuauaCMAM(NAG13)	1103	334
AM03746-SS	cscscuUfAfUfuguuauacga(NAG13)	1104	335
AM03747-SS	cscscuUfAfUfuguuauacGMAM(NAG13)	1105	335
AM03748-SS	CMsCMscuUfAfUfuguuauacGMAM(NAG13)	1106	335
AM03751-SS	asuscgAfGfGfcucauucuca(NAG13)	1107	347
AM03752-SS	asuscgAfGfGfcucauucuCMAM(NAG13)	1108	347
AM03753-SS	AMsTMscgAfGfGfcucauucuCMAM(NAG13)	1109	353
AM03757-SS	asascaGfAfAfucagguguca(NAG13)	1110	350
AM03758-SS	asascaGfAfAfucagguguCMAM(NAG13)	1111	350
AM03759-SS	AMsAMscaGfAfAfucagguguCMAM(NAG13)	1112	350
AM03859-SS	(NAG18)uauausasguuaucgAfGfGfcucauucuc(invdA)	1113	308
AM03861-SS	(NAG18)uauauscsaGfcCfcCfuUfAfUfuGfuUfaUfaCfg(invdA)	1114	310
AM03879-SS	(NAG4)uscaGfcCfcCfuUfAfUfuGfuUfaUfaCfgausu(invAb)	1115	354
AM03880-SS	(NAG4)uscaGfcCfcCfuUfAfUfuGfuUfaUfaCfgsa(invAb)	1116	355
AM03881-SS	(NAG24)uscaGfcCfcCfuUfAfUfuGfuUfaUfaCfgausu(invAb)	1117	354
AM03882-SS	(NAG4)usaguuaucgAfGfGfcucauucucausu(invAb)	1118	356
AM03928-SS	uAuAuscsagcccCfuUfAfUfuguuauacga(NAG13)	1119	310
AM03931-SS	uAuAusasguuauCfgAfGfGfcucauucuca(NAG13)	1120	308
AM03968-SS	(NAG4)uauauscaGfcCfcCfuUfAfUfuGfuUfaUfaCfgs(invdA)	1121	310
AM03970-SS	(NAG4)(invAb)GfcCfcCfuUfAfUfuGfuUfaUfaCfgausu(invAb)	1122	357
AM04138-SS	(NAG25)uauausasguuaucgAfGfGfcucauucuc(invdA)	1123	308
AM04152-SS	(Alk-PEG5-C6)uauausasguuaucgAfGfGfcucauucuCM(invdA)	1124	308
AM04214-SS	(Alk-SMPT-C6)uauausasguuaucgAfGfGfcucauucuCM(invdA)	1125	308
AM04233-SS	(NAG26)uauausasguuaucgAfGfGfcucauucuCM(invdA)	1126	308
AM04372-SS	(NAG27)uauausasguuaucgAfGfGfcucauucuCM(invdA)	1127	308
AM04381-SS	(NAG25)auauscsagccccuUfAfUfuguuauacga(invdT)	1128	358
AM04382-SS	(NAG25)uauscsagccccuUfAfUfuguuauacgau(invdT)	1129	359

AM04391-SS	(NAG25)auausasguuaucgAfGfGfcucauucuca(invdT)	1130	360
AM04392-SS	(NAG25)uausasguuaucgAfGfGfcucauucucau(invdT)	1131	361
AM04412-SS	(NAG25)uauauscsagccccuUfAfUfuguuauacg(invdA)	1132	310
AM04414-SS	(NAG25)(invAb)gccccuUfAfUfuguuauacgauus(invAb)	1133	357
AM04416-SS	(NAG25)(invAb)uuaucgAfGfGfcucauucucausu(invAb)	1134	362
AM04496-SS	(NAG25)(invAb)GfcCfcCfuUfAfUfuGfuUfaUfaCfgausu(invAb)	1135	357
AM04497-SS	(NAG29)uauausasguuaucgAfGfGfcucauucuc(invdA)	1136	308
AM04499-SS	(NAG28)(invAb)GfcCfcCfuUfAfUfuGfuUfaUfaCfgausu(invAb)	1137	357
AM04498-SS	(NAG29)uauauaasuuaucgaGfGfcucauucucsa(invAb)	1138	363
AM04500-SS	(NAG30)(invAb)GfcCfcCfuUfAfUfuGfuUfaUfaCfgausu(invAb)	1139	357
AM04502-SS	(NAG25)uauauaasuuaucgaGfGfcucauucucsa(invAb)	1140	363
AM04535-SS	(NAG25)uauaucsasgccccuUfAfUfuguuauacg(invdA)	1141	310
AM04536-SS	(NAG25)uauaucasgccccuUfAfUfuguuauacg(invdA)	1142	310
AM04537-SS	(NAG25)uauauasgsuuaucgAfGfGfcucauucuc(invdA)	1143	308
AM04538-SS	(NAG25)uauauagsuuaucgAfGfGfcucauucuc(invdA)	1144	308
AM04543-SS	(NAG30)uscaGfcCfcCfuUfAfUfuGfuUfaUfaCfgsa(invAb)	1145	355
AM04578-SS	(NAG25)ggcsagccccuUfAfUfuguuauacgAMs(invdT)dT	1146	364
AM04588-SS	(NAG25)ggcsagccccuUfAfUfuguuauacgAMsuu(invdT)	1147	365
AM04579-SS	(NAG25)G_{UNA}gcsagccccuUfAfUfuguuauacgAMs(invdT)dT	1148	364
AM04580-SS	(NAG25)ggcs(invdA)gccccuUfAfUfuguuauacgAMs(invdT)dT	1149	364
AM04581-SS	(NAG25)csagccccuUfAfUfuguuauacgAMs(invdT)dTdTdT	1150	366
AM04611-SS	(NAG31)(invAb)GfcCfcCfuUfAfUfuGfuUfaUfaCfgausu(invAb)	1151	357
AM04612-SS	(NAG32)(invAb)GfcCfcCfuUfAfUfuGfuUfaUfaCfgausu(invAb)	1152	357
AM04669-SS	(NAG25)uauauagsusuaucgAfGfGfcucauucuc(invdA)	1153	308
AM04670-SS	(NAG25)uauauagususaucgAfGfGfcucauucuc(invdA)	1154	308
AM04671-SS	(NAG25)gcgausasguuaucgAfGfGfcucauucuc(invdA)	1155	367
AM04672-SS	(NAG25)ugaausasguuaucgAfGfGfcucauucuc(invdA)	1156	368
AM04673-SS	(NAG25)aucgusasguuaucgAfGfGfcucauucuc(invdA)	1157	369
AM04674-SS	(NAG25)u(invdA)uausasguuaucgAfGfGfcucauucuc(invdA)	1158	308
AM04675-SS	(NAG25)uaua(invdA)sasguuaucgAfGfGfcucauucuc(invdA)	1159	370
AM04676-SS	(NAG25)uauaus(invdA)sguuaucgAfGfGfcucauucuc(invdA)	1160	308
AM04726-SS	(NAG30)aGfcCfcCfuUfAfUfuGfuUfaUfaCfgsa(invAb)	1161	371
AM04727-SS	(NAG30)aaGfcCfcCfuUfAfUfuGfuUfaUfaCfgsa(invAb)	1162	372
AM04728-SS	(NAG30)sasGfcCfcCfuUfAfUfuGfuUfaUfaCfgas(invAb)	1163	371
AM04729-SS	(NAG30)gscaGfcCfcCfuUfAfUfuGfuUfaUfaCfgsa(invAb)	1164	373
AM04737-SS	(NAG25)uauauagsuuaucgaGfGfcucauucucsa(invAb)	1165	374
AM04741-SS	(NAG30)sgscaGfcCfcCfuUfAfUfuGfuUfaUfaCfgsa(invAb)	1166	373
AM04742-SS	(NAG33)(invAb)GfcCfcCfuUfAfUfuGfuUfaUfaCfgausu(invAb)	1167	357
AM04743-SS	(NAG34)(invAb)GfcCfcCfuUfAfUfuGfuUfaUfaCfgausu(invAb)	1168	357
AM04744-SS	(NAG35)(invAb)GfcCfcCfuUfAfUfuGfuUfaUfaCfgausu(invAb)	1169	357
AM04803-SS	(NAG30)acGfcCfcCfuUfAfUfuGfuUfaUfaCfgsa(invAb)	1170	375
AM04804-SS	(NAG30)sasaGfcCfcCfuUfAfUfuGfuUfaUfaCfgas(invAb)	1171	372
AM04807-SS	(NAG30)sascGfcCfcCfuUfAfUfuGfuUfaUfaCfgas(invAb)	1172	375
AM04806-SS	(NAG30)sgscaGfcCfcCfuUfAfUfuGfuUfaUfaCfgas(invAb)	1173	373
AM04808-SS	(NAG31)sGfcCfcCfuUfAfUfuGfuUfaUfaCfgausu(invAb)	1174	376
AM04809-SS	(NAG31)saGfcCfcCfuUfAfUfuGfuUfaUfaCfgausu(invAb)	1175	377

AM04810-SS	(NAG31)sasaGfcCfcCfuUfAfUfuGfuUfaUfaCfgas(invAb)	1176	372
AM04811-SS	(NAG31)sasaGfcCfcCfuUfAfUfuGfuUfaUfaCfgausu(invAb)	1177	378
AM04812-SS	(NAG31)sasaGfcCfcCfuUfAfUfuGfuUfaUfaCfg(invdA)usu(invAb)	1178	378
AM04813-SS	(NAG31)uauausasguuaucgAfGfGfcucauucuc(invdA)	1179	308
AM04816-SS	(NAG31)uauscsagccccuUfAfUfuguuauacgs(invdA)	1180	379
AM04817-SS	(NAG31)uagscsagccccuUfAfUfuguuauacgs(invdA)	1181	380
AM04835-SS	(NAG31)uaucagccccuUfAfUfuguuauacgs(invdA)	1182	379
AM04819-SS	(NAG31)sgscagccccuUfAfUfuguuauacgs(invdA)	1183	381
AM04820-SS	(NAG31)sgscagccccuUfAfUfuguuauacgsa(invAb)	1184	373
AM04862-SS	(NAG25)auaagasguuaucgAfGfGfcucauucuc(invdA)	1185	382
AM04863-SS	(NAG25)auaagsasguuaucgAfGfGfcucauucuc(invdA)	1186	382
AM04864-SS	(NAG25)auaggcsagccccuUfAfUfuguuauacg(invdA)	1187	383
AM04865-SS	(NAG25)auaggscsagccccuUfAfUfuguuauacg(invdA)	1188	383
AM04866-SS	(NAG25)scsagccccuUfAfUfuguuauacgs(invdA)	1189	384
AM04867-SS	(NAG31)scsagccccuUfAfUfuguuauacgs(invdA)	1190	384
AM04868-SS	(NAG25)sgsccccuUfAfUfuguuauacgauus(invAb)	1191	376
AM04869-SS	(NAG31)sgsccccuUfAfUfuguuauacgauus(invAb)	1192	376
AM04870-SS	(NAG25)sGfsccccuUfAfUfuguuauacgauus(invAb)	1193	376
AM04978-SS	(NAG31)sGfscCfcCfuUfAfUfuGfuUfaUfaCfgauus(invAb)	1194	376
AM05070-SS	(NAG25)uauauscsagcccc(NOTA-dT)UfAfUfuguuauacg(invdA)	1195	385
AM05072-SS	(NAG25)(invAb)GfcCfcCf(NOTA-dT)UfAfUfuGfuUfaUfaCfgausu(invAb)	1196	1241
1532-SS02	uAuAusAfsgUfuAfuCfgAfGfGfcucAfuucuca	1197	308
1532-SS03	uAuAusAfsgUfuAfuCfgAfGfGfcucauUfcuca	1198	308
1532-SS04	uAuAusAfsgUfuAfuCfgAfGfGfcucauucUfca	1199	308
1532-SS05	uAuAusAfsgUfuAfuCfgAfGfGfcucauucucAf	1200	308
1532-SS06	uAuAusAfsgUfuAfuCfgAfgGfcUfcauucucAf	1201	308
1532-SS07	uAuAusAfsgUfuAfuCfgAfgGfcucAfuucucAf	1202	308
1532-SS08	uAuAusAfsgUfuAfuCfgAfgGfcucauUfcucAf	1203	308
1532-SS09	uAuAusAfsgUfuAfuCfgAfgGfcucauucUfcAf	1204	308
1532-SS10	uAuAusAfsgUfuAfuCfgAfgGfcucauucucAf	1205	308
1532-SS11	uAuAusAfsgUfuAfuCfgaGfGfcucauucucAf	1206	308
1532-SS12	uAuAusAfsgUfuAfuCfgagGfcUfcauucucAf	1207	308
1532-SS13	uAuAusAfsgUfuAfuCfgagGfcucAfuucucAf	1208	308
1532-SS14	uAuAusAfsgUfuAfuCfgagGfcucauUfcucAf	1209	308
1532-SS15	uAuAusAfsgUfuAfuCfgagGfcucauucUfcAf	1210	308
1532-SS16	uAuAusAfsgUfuAfuCfgagGfcucauUfcUfcAf	1211	308
1532-SS17	uAuAusAfsgUfuauCfgAfgGfcucauUfcUfcAf	1212	308
1532-SS18	uAuAusAfsgUfuauCfgaGfGfcucauUfcUfcAf	1213	308
1532-SS19	uAuAusAfsgUfuauCfgagGfcUfcauUfcUfcAf	1214	308
1532-SS20	uAuAusAfsgUfuauCfgagGfcucAfuUfcUfcAf	1215	308
1532-SS21	uAuAusAfsgUfuauCfgagGfcUfcAfuUfcUfcAf	1216	308
1532-SS22	uAuAusAfsguuAfuCfgagGfcUfcAfuUfcUfcAf	1217	308
1532-SS23	uAuAusAfsguuauCfgAfgGfcUfcAfuUfcUfcAf	1218	308
1532-SS24	uAuAusAfsguuauCfgaGfGfcUfcAfuUfcUfcAf	1219	308
1533-CfinSS	uAuAuscsaGfaAfacaGfAfAfucaGfgUfgUfcAf	1220	309
1533-SS00	uAuAusCfsaGfaAfaCfaGfAfAfuCfaGfgUfgUfcAf	1221	309

1533-SS01	uAuAusCfsaGfaAfaCfaGfAfAfuCfaGfguguca	1222	309
1533-SS02	uAuAusCfsaGfaAfaCfaGfAfAfuCfaggugUfca	1223	309
1533-SS03	uAuAusCfsaGfaAfaCfaGfAfAfuCfaggugucAf	1224	309
1533-SS04	uAuAusCfsaGfaAfaCfaGfAfAfuCfaggUfguca	1225	309
1533-SS05	uAuAusCfsaGfaAfaCfaGfaAfuCfaGfgugucAf	1226	309
1533-SS06	uAuAusCfsaGfaAfaCfaGfaAfuCfaggugUfcAf	1227	309
1533-SS07	uAuAusCfsaGfaAfaCfaGfaAfuCfaggUfgucAf	1228	309
1533-SS08	uAuAusCfsaGfaAfaCfagAfAfuCfaggugUfcAf	1229	309
1533-SS09	uAuAusCfsaGfaAfaCfagaAfuCfaggUfgUfcAf	1230	309
1533-SS10	uAuAusCfsaGfaAfaCfagaAfuCfaGfgugUfcAf	1231	309
1533-SS11 1533-SS20	uAuAusCfsaGfaaaCfagAfAfuCfaGfgUfgUfcAf	1232	309
1533-SS12	uAuAusCfsaGfaaaCfaGfaAfuCfaGfgUfgUfcAf	1233	309
1533-SS13	uAuAusCfsaGfaAfaCfagaAfuCfaGfgUfgUfcAf	1234	309
1533-SS14	uAuAusCfsaGfaaaCfagaAfuCfaGfgUfgUfcAf	1235	309
1533-SS15	uAuAusCfsagaAfaCfagaAfuCfaGfgUfgUfcAf	1236	309
1533-SS16	uAuAusCfsagaaaCfagAfAfuCfaGfgUfgUfcAf	1237	309
1533-SS17	uAuAusCfsagaaaCfaGfaAfuCfaGfgUfgUfcAf	1238	309
1533-SS18	uAuAusCfsagaaaCfaGfAfAfuCfaGfgUfgUfcAf	1239	309
1533-SS19	uAuAusCfsagaAfaCfagAfAfuCfaGfgUfgUfcAf	1240	309
AM05341-SS	(NAG37)(invAb)GfcCfcCfuUfAfUfuGfuUfaUfaCfgausu(invAb)	1256	357
AM05342-SS	(NAG37)scsagccccuUfAfUfuguuauacgs(invdA)	1257	381
AM05489-SS	(NAG25)uauausasguuaucgAfGfGfcucauucucas(invAb)	1269	308
AM05491-SS	(NAG25)(invAb)uuaucgAfGfGfcucauucucas(invAb)	1270	1258
AM05494-SS	(NAG25)(invAb)GfcCfcCfuUfAfUfuGfuUfaUfaCfgas(invAb)	1271	1259
AM05499-SS	(NAG25)(invAb)gccccuUfAfUfuguuauacgausu(invAb)	1272	357
AM05500-SS	(NAG25)uauauscsagccccuUfAfUfuguuauacgas(invAb)	1273	310
AM05501-SS	(NAG25)(invAb)gccccuUfAfUfuguuauacgas(invAb)	1274	1259
AM05502-SS	(NAG25)sasagccccuUfAfUfuguuauacgs(invdA)	1275	1261
AM05503-SS	(NAG25)scsagccccuUfAfUfuguuauacgas(invAb)	1276	1260
AM05504-SS	(NAG25)sgsccccuUfAfUfuguuauacgas(invAb)	1277	371
AM05505-SS	(NAG25)sgsccccuUfAfUfuguuauacgs(invdA)	1278	371
AM05506-SS	(NAG25)sasagccccuUfAfUfuguuauacgas(invAb)	1279	1261

A sense strand containing a sequence listed in Table 2B can be hybridized to any antisense strand containing a sequence listed in Table 2A provided the two sequences have a region of at least 90% complementarity over a contiguous 16, 17, 18, 19, 20, or 21 nucleotide sequence. Representative LPA RNAi agents are represented by the Duplex ID Nos. shown in Tables 3A and 3B.

In some embodiments an LPA RNAi agent comprises of any of the Duplex ID Nos. presented herein. In some embodiments an LPA RNAi agent consists of any of the Duplex ID Nos. presented herein. In some embodiments, an LPA RNAi agent comprises the sense strand and

antisense strand nucleotide sequences of any of the Duplex ID Nos. presented herein. In some embodiments, an LPA RNAi agent comprises the sense strand and antisense strand nucleotide sequences of any of the Duplex ID Nos. presented herein and a targeting group and/or linking group wherein the targeting group and/or linking group is covalently linked (i.e. conjugated) to the sense strand or the antisense strand. In some embodiments, an LPA RNAi agent comprises the sense strand and antisense strand modified nucleotide sequences of any of the Duplex ID Nos. presented herein. In some embodiments, an LPA RNAi agent comprises the sense strand and antisense strand modified nucleotide sequences of any of the Duplex ID Nos. presented herein and a targeting group and/or linking group wherein the targeting group and/or linking group is covalently linked to the sense strand or the antisense strand.

Table 3A. LPA RNAi agent duplexes with Duplex ID numbers.

Duplex ID	Antisense Strand ID	Sense Strand ID	Duplex ID	Antisense Strand ID	Sense Strand ID	Duplex ID	Antisense Strand ID	Sense Strand ID
AD00571	AM01240-AS	AM01173-SS	AD02120	AM03257-AS	AM03229-SS	AD02500	AM03107-AS	AM03295-SS
AD00572	AM01241-AS	AM01174-SS	AD02121	AM03257-AS	AM03230-SS	AD02501	AM03279-AS	AM03295-SS
AD00573	AM01242-AS	AM01175-SS	AD02122	AM03257-AS	AM03231-SS	AD02502	AM03280-AS	AM03295-SS
AD00574	AM01243-AS	AM01176-SS	AD02123	AM03257-AS	AM03232-SS	AD02503	AM03281-AS	AM03295-SS
AD00575	AM01244-AS	AM01177-SS	AD02124	AM03257-AS	AM03233-SS	AD02504	AM03282-AS	AM03295-SS
AD00576	AM01245-AS	AM01178-SS	AD02125	AM03257-AS	AM03234-SS	AD02505	AM03283-AS	AM03295-SS
AD00577	AM01246-AS	AM01179-SS	AD02126	AM03257-AS	AM03235-SS	AD02506	AM03284-AS	AM03295-SS
AD00578	AM01247-AS	AM01180-SS	AD02127	AM03257-AS	AM03236-SS	AD02507	AM03300-AS	AM03295-SS
AD00579	AM01248-AS	AM01181-SS	AD02128	AM03257-AS	AM03237-SS	AD02508	AM03301-AS	AM03295-SS
AD00580	AM01249-AS	AM01182-SS	AD02129	AM03258-AS	AM03220-SS	AD02509	AM03107-AS	AM03296-SS
AD00581	AM01250-AS	AM01183-SS	AD02130	AM03258-AS	AM03221-SS	AD02510	AM03279-AS	AM03296-SS
AD00582	AM01251-AS	AM01184-SS	AD02131	AM03258-AS	AM03222-SS	AD02511	AM03280-AS	AM03296-SS
AD00583	AM01252-AS	AM01185-SS	AD02132	AM03258-AS	AM03223-SS	AD02512	AM03281-AS	AM03296-SS
AD00584	AM01253-AS	AM01186-SS	AD02133	AM03258-AS	AM03224-SS	AD02513	AM03282-AS	AM03296-SS
AD00585	AM01254-AS	AM01187-SS	AD02134	AM03258-AS	AM03225-SS	AD02514	AM03283-AS	AM03296-SS
AD00586	AM01255-AS	AM01188-SS	AD02135	AM03258-AS	AM03226-SS	AD02515	AM03284-AS	AM03296-SS
AD00587	AM01256-AS	AM01189-SS	AD02136	AM03258-AS	AM03227-SS	AD02516	AM03300-AS	AM03296-SS
AD00588	AM01257-AS	AM01190-SS	AD02137	AM03258-AS	AM03228-SS	AD02517	AM03301-AS	AM03296-SS
AD00589	AM01258-AS	AM01191-SS	AD02138	AM03258-AS	AM03229-SS	AD02518	AM03107-AS	AM03297-SS
AD00590	AM01259-AS	AM01192-SS	AD02139	AM03258-AS	AM03230-SS	AD02519	AM03279-AS	AM03297-SS
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AD02109	AM03256-AS	AM03236-SS	AD02489	AM03300-AS	AM03293-SS	AD03922	AM04971-AS	AM04867-SS
AD02110	AM03256-AS	AM03237-SS	AD02490	AM03301-AS	AM03293-SS	AD03923	AM04971-AS	AM04869-SS
AD02111	AM03257-AS	AM03220-SS	AD02491	AM03107-AS	AM03294-SS	AD03924	AM04972-AS	AM04820-SS
AD02112	AM03257-AS	AM03221-SS	AD02492	AM03279-AS	AM03294-SS	AD03925	AM04972-AS	AM04819-SS
AD02113	AM03257-AS	AM03222-SS	AD02493	AM03280-AS	AM03294-SS	AD03931	AM04979-AS	AM04978-SS
AD02114	AM03257-AS	AM03223-SS	AD02494	AM03281-AS	AM03294-SS	AD03932	AM04979-AS	AM04811-SS
AD02115	AM03257-AS	AM03224-SS	AD02495	AM03282-AS	AM03294-SS	AD03933	AM04979-AS	AM04869-SS
AD02116	AM03257-AS	AM03225-SS	AD02496	AM03283-AS	AM03294-SS	AD04017	AM03300-AS	AM05070-SS
AD02117	AM03257-AS	AM03226-SS	AD02497	AM03284-AS	AM03294-SS	AD04018	AM03972-AS	AM05072-SS
AD02118	AM03257-AS	AM03227-SS	AD02498	AM03300-AS	AM03294-SS	AD04017	AM03300-AS	AM05070-SS
AD02119	AM03257-AS	AM03228-SS	AD02499	AM03301-AS	AM03294-SS	AD04018	AM03972-AS	AM05072-SS
AD04170	AM03972-AS	AM05341-SS	AD04171	AM04877-AS	AM05342-SS	AD04110	AM04875-AS	AM04866-SS
AD04263	AM04879-AS	AM05489-SS	AD04272	AM04979-AS	AM05499-SS	AD04281	AM05496-AS	AM04412-SS
AD04264	AM05490-AS	AM04416-SS	AD04273	AM03972-AS	AM05494-SS	AD04282	AM04874-AS	AM05503-SS
AD04265	AM05490-AS	AM05491-SS	AD04274	AM05498-AS	AM05494-SS	AD04283	AM04874-AS	AM05502-SS
AD04266	AM05492-AS	AM04496-SS	AD04275	AM04979-AS	AM05494-SS	AD04284	AM04874-AS	AM05506-SS
AD04267	AM05493-AS	AM04496-SS	AD04276	AM03972-AS	AM05501-SS	AD04285	AM04877-AS	AM05503-SS
AD04268	AM05498-AS	AM04496-SS	AD04277	AM05498-AS	AM05501-SS	AD04286	AM05497-AS	AM05502-SS
AD04269	AM04979-AS	AM04496-SS	AD04278	AM04979-AS	AM05501-SS	AD04287	AM05497-AS	AM05506-SS
AD04270	AM03972-AS	AM05499-SS	AD04279	AM03300-AS	AM05500-SS	AD04288	AM04874-AS	AM05504-SS
AD04271	AM05498-AS	AM05499-SS	AD04280	AM05495-AS	AM04412-SS	AD04289	AM04874-AS	AM05505-SS

Table 3B. LPA RNAi agent duplexes with Duplex ID numbers.

Duplex ID	Antisense Strand ID	Sense Strand ID
SD0001	1533-AS00	1533-SS00
SD0002	1533-AS01	1533-SS00
SD0003	1533-AS02	1533-SS00
SD0004	1533-AS03	1533-SS00
SD0005	1533-AS04	1533-SS00
SD0006	1533-AS05	1533-SS00
SD0007	1533-AS06	1533-SS00
SD0008	1533-AS07	1533-SS00
SD0009	1533-AS08	1533-SS00
SD0010	1533-AS09	1533-SS00
SD0011	1533-AS10	1533-SS00
SD0012	1533-AS11	1533-SS00
SD0013	1533-AS12	1533-SS00
SD0014	1533-AS13	1533-SS00
SD0015	1533-AS14	1533-SS00
SD0016	1533-AS00	1533-SS01
SD0017	1533-AS01	1533-SS01
SD0018	1533-AS02	1533-SS01
SD0019	1533-AS03	1533-SS01
SD0020	1533-AS04	1533-SS01
SD0021	1533-AS05	1533-SS01
SD0022	1533-AS06	1533-SS01
SD0023	1533-AS07	1533-SS01
SD0024	1533-AS08	1533-SS01
SD0240	1533-AS08	1533-SS12
SD0241	1533-AS09	1533-SS12
SD0242	1533-AS10	1533-SS12
SD0243	1533-AS11	1533-SS12
SD0244	1533-AS12	1533-SS12
SD0245	1533-AS13	1533-SS12
SD0246	1533-AS14	1533-SS12
SD0247	1533-AS00	1533-SS13
SD0248	1533-AS01	1533-SS13
SD0249	1533-AS02	1533-SS13
SD0250	1533-AS03	1533-SS13
SD0251	1533-AS04	1533-SS13
SD0252	1533-AS05	1533-SS13
SD0253	1533-AS06	1533-SS13
SD0254	1533-AS07	1533-SS13
SD0255	1533-AS08	1533-SS13
SD0256	1533-AS09	1533-SS13
SD0257	1533-AS10	1533-SS13
SD0258	1533-AS11	1533-SS13
SD0259	1533-AS12	1533-SS13
SD0260	1533-AS13	1533-SS13
SD0261	1533-AS14	1533-SS13
SD0262	1533-AS00	1533-SS14
SD0263	1533-AS01	1533-SS14
SD0479	1532-AS01	1532-SS09
SD0480	1532-AS02	1532-SS09
SD0481	1532-AS03	1532-SS09
SD0482	1532-AS04	1532-SS09
SD0483	1532-AS05	1532-SS09
SD0484	1532-AS06	1532-SS09
SD0485	1532-AS07	1532-SS09
SD0486	1532-AS08	1532-SS09
SD0487	1532-AS09	1532-SS09
SD0488	1532-AS10	1532-SS09
SD0489	1532-AS11	1532-SS09
SD0490	1532-AS12	1532-SS09
SD0491	1532-AS13	1532-SS09
SD0492	1532-AS00	1532-SS10
SD0493	1532-AS01	1532-SS10
SD0494	1532-AS02	1532-SS10
SD0495	1532-AS03	1532-SS10
SD0496	1532-AS04	1532-SS10
SD0497	1532-AS05	1532-SS10
SD0498	1532-AS06	1532-SS10
SD0499	1532-AS07	1532-SS10
SD0500	1532-AS08	1532-SS10
SD0501	1532-AS09	1532-SS10
SD0502	1532-AS10	1532-SS10

SD0025	1533-AS09	1533-SS01	SD0264	1533-AS02	1533-SS14	SD0503	1532-AS11	1532-SS10
SD0026	1533-AS10	1533-SS01	SD0265	1533-AS03	1533-SS14	SD0504	1532-AS12	1532-SS10
SD0027	1533-AS11	1533-SS01	SD0266	1533-AS04	1533-SS14	SD0505	1532-AS13	1532-SS10
SD0028	1533-AS12	1533-SS01	SD0267	1533-AS05	1533-SS14	SD0506	1532-AS00	1532-SS11
SD0029	1533-AS13	1533-SS01	SD0268	1533-AS06	1533-SS14	SD0507	1532-AS01	1532-SS11
SD0030	1533-AS14	1533-SS01	SD0269	1533-AS07	1533-SS14	SD0508	1532-AS02	1532-SS11
SD0031	1533-AS00	1533-SS02	SD0270	1533-AS08	1533-SS14	SD0509	1532-AS03	1532-SS11
SD0032	1533-AS01	1533-SS02	SD0271	1533-AS09	1533-SS14	SD0510	1532-AS04	1532-SS11
SD0033	1533-AS02	1533-SS02	SD0272	1533-AS10	1533-SS14	SD0511	1532-AS05	1532-SS11
SD0034	1533-AS03	1533-SS02	SD0273	1533-AS11	1533-SS14	SD0512	1532-AS06	1532-SS11
SD0035	1533-AS04	1533-SS02	SD0274	1533-AS12	1533-SS14	SD0513	1532-AS07	1532-SS11
SD0036	1533-AS05	1533-SS02	SD0275	1533-AS13	1533-SS14	SD0514	1532-AS08	1532-SS11
SD0037	1533-AS06	1533-SS02	SD0276	1533-AS14	1533-SS14	SD0515	1532-AS09	1532-SS11
SD0038	1533-AS07	1533-SS02	SD0277	1533-AS00	1533-SS15	SD0516	1532-AS10	1532-SS11
SD0039	1533-AS08	1533-SS02	SD0278	1533-AS01	1533-SS15	SD0517	1532-AS11	1532-SS11
SD0040	1533-AS09	1533-SS02	SD0279	1533-AS02	1533-SS15	SD0518	1532-AS12	1532-SS11
SD0041	1533-AS10	1533-SS02	SD0280	1533-AS03	1533-SS15	SD0519	1532-AS13	1532-SS11
SD0042	1533-AS11	1533-SS02	SD0281	1533-AS04	1533-SS15	SD0520	1532-AS00	1532-SS12
SD0043	1533-AS12	1533-SS02	SD0282	1533-AS05	1533-SS15	SD0521	1532-AS01	1532-SS12
SD0044	1533-AS13	1533-SS02	SD0283	1533-AS06	1533-SS15	SD0522	1532-AS02	1532-SS12
SD0045	1533-AS14	1533-SS02	SD0284	1533-AS07	1533-SS15	SD0523	1532-AS03	1532-SS12
SD0046	1533-AS00	1533-SS03	SD0285	1533-AS08	1533-SS15	SD0524	1532-AS04	1532-SS12
SD0047	1533-AS01	1533-SS03	SD0286	1533-AS09	1533-SS15	SD0525	1532-AS05	1532-SS12
SD0048	1533-AS02	1533-SS03	SD0287	1533-AS10	1533-SS15	SD0526	1532-AS06	1532-SS12
SD0049	1533-AS03	1533-SS03	SD0288	1533-AS11	1533-SS15	SD0527	1532-AS07	1532-SS12
SD0050	1533-AS04	1533-SS03	SD0289	1533-AS12	1533-SS15	SD0528	1532-AS08	1532-SS12
SD0051	1533-AS05	1533-SS03	SD0290	1533-AS13	1533-SS15	SD0529	1532-AS09	1532-SS12
SD0052	1533-AS06	1533-SS03	SD0291	1533-AS14	1533-SS15	SD0530	1532-AS10	1532-SS12
SD0053	1533-AS07	1533-SS03	SD0292	1533-AS00	1533-SS16	SD0531	1532-AS11	1532-SS12

SD0054	1533-AS08	1533-SS03	SD0293	1533-AS01	1533-SS16	SD0532	1532-AS12	1532-SS12
SD0055	1533-AS09	1533-SS03	SD0294	1533-AS02	1533-SS16	SD0533	1532-AS13	1532-SS12
SD0056	1533-AS10	1533-SS03	SD0295	1533-AS03	1533-SS16	SD0534	1532-AS00	1532-SS13
SD0057	1533-AS11	1533-SS03	SD0296	1533-AS04	1533-SS16	SD0535	1532-AS01	1532-SS13
SD0058	1533-AS12	1533-SS03	SD0297	1533-AS05	1533-SS16	SD0536	1532-AS02	1532-SS13
SD0059	1533-AS13	1533-SS03	SD0298	1533-AS06	1533-SS16	SD0537	1532-AS03	1532-SS13
SD0060	1533-AS14	1533-SS03	SD0299	1533-AS07	1533-SS16	SD0538	1532-AS04	1532-SS13
SD0061	1533-AS00	1533-SS04	SD0300	1533-AS08	1533-SS16	SD0539	1532-AS05	1532-SS13
SD0062	1533-AS01	1533-SS04	SD0301	1533-AS09	1533-SS16	SD0540	1532-AS06	1532-SS13
SD0063	1533-AS02	1533-SS04	SD0302	1533-AS10	1533-SS16	SD0541	1532-AS07	1532-SS13
SD0064	1533-AS03	1533-SS04	SD0303	1533-AS11	1533-SS16	SD0542	1532-AS08	1532-SS13
SD0065	1533-AS04	1533-SS04	SD0304	1533-AS12	1533-SS16	SD0543	1532-AS09	1532-SS13
SD0066	1533-AS05	1533-SS04	SD0305	1533-AS13	1533-SS16	SD0544	1532-AS10	1532-SS13
SD0067	1533-AS06	1533-SS04	SD0306	1533-AS14	1533-SS16	SD0545	1532-AS11	1532-SS13
SD0068	1533-AS07	1533-SS04	SD0307	1533-AS00	1533-SS17	SD0546	1532-AS12	1532-SS13
SD0069	1533-AS08	1533-SS04	SD0308	1533-AS01	1533-SS17	SD0547	1532-AS13	1532-SS13
SD0070	1533-AS09	1533-SS04	SD0309	1533-AS02	1533-SS17	SD0548	1532-AS00	1532-SS14
SD0071	1533-AS10	1533-SS04	SD0310	1533-AS03	1533-SS17	SD0549	1532-AS01	1532-SS14
SD0072	1533-AS11	1533-SS04	SD0311	1533-AS04	1533-SS17	SD0550	1532-AS02	1532-SS14
SD0073	1533-AS12	1533-SS04	SD0312	1533-AS05	1533-SS17	SD0551	1532-AS03	1532-SS14
SD0074	1533-AS13	1533-SS04	SD0313	1533-AS06	1533-SS17	SD0552	1532-AS04	1532-SS14
SD0075	1533-AS14	1533-SS04	SD0314	1533-AS07	1533-SS17	SD0553	1532-AS05	1532-SS14
SD0076	1533-AS00	1533-SS05	SD0315	1533-AS08	1533-SS17	SD0554	1532-AS06	1532-SS14
SD0077	1533-AS01	1533-SS05	SD0316	1533-AS09	1533-SS17	SD0555	1532-AS07	1532-SS14
SD0078	1533-AS02	1533-SS05	SD0317	1533-AS10	1533-SS17	SD0556	1532-AS08	1532-SS14
SD0079	1533-AS03	1533-SS05	SD0318	1533-AS11	1533-SS17	SD0557	1532-AS09	1532-SS14
SD0080	1533-AS04	1533-SS05	SD0319	1533-AS12	1533-SS17	SD0558	1532-AS10	1532-SS14
SD0081	1533-AS05	1533-SS05	SD0320	1533-AS13	1533-SS17	SD0559	1532-AS11	1532-SS14
SD0082	1533-AS06	1533-SS05	SD0321	1533-AS14	1533-SS17	SD0560	1532-AS12	1532-SS14

SD0083	1533-AS07	1533-SS05	SD0322	1533-AS00	1533-SS18	SD0561	1532-AS13	1532-SS14
SD0084	1533-AS08	1533-SS05	SD0323	1533-AS01	1533-SS18	SD0562	1532-AS00	1532-SS15
SD0085	1533-AS09	1533-SS05	SD0324	1533-AS02	1533-SS18	SD0563	1532-AS01	1532-SS15
SD0086	1533-AS10	1533-SS05	SD0325	1533-AS03	1533-SS18	SD0564	1532-AS02	1532-SS15
SD0087	1533-AS11	1533-SS05	SD0326	1533-AS04	1533-SS18	SD0565	1532-AS03	1532-SS15
SD0088	1533-AS12	1533-SS05	SD0327	1533-AS05	1533-SS18	SD0566	1532-AS04	1532-SS15
SD0089	1533-AS13	1533-SS05	SD0328	1533-AS06	1533-SS18	SD0567	1532-AS05	1532-SS15
SD0090	1533-AS14	1533-SS05	SD0329	1533-AS07	1533-SS18	SD0568	1532-AS06	1532-SS15
SD0091	1533-AS00	1533-SS06	SD0330	1533-AS08	1533-SS18	SD0569	1532-AS07	1532-SS15
SD0092	1533-AS01	1533-SS06	SD0331	1533-AS09	1533-SS18	SD0570	1532-AS08	1532-SS15
SD0093	1533-AS02	1533-SS06	SD0332	1533-AS10	1533-SS18	SD0571	1532-AS09	1532-SS15
SD0094	1533-AS03	1533-SS06	SD0333	1533-AS11	1533-SS18	SD0572	1532-AS10	1532-SS15
SD0095	1533-AS04	1533-SS06	SD0334	1533-AS12	1533-SS18	SD0573	1532-AS11	1532-SS15
SD0096	1533-AS05	1533-SS06	SD0335	1533-AS13	1533-SS18	SD0574	1532-AS12	1532-SS15
SD0097	1533-AS06	1533-SS06	SD0336	1533-AS14	1533-SS18	SD0575	1532-AS13	1532-SS15
SD0098	1533-AS07	1533-SS06	SD0337	1533-AS00	1533-SS19	SD0576	1532-AS00	1532-SS16
SD0099	1533-AS08	1533-SS06	SD0338	1533-AS01	1533-SS19	SD0577	1532-AS01	1532-SS16
SD0100	1533-AS09	1533-SS06	SD0339	1533-AS02	1533-SS19	SD0578	1532-AS02	1532-SS16
SD0101	1533-AS10	1533-SS06	SD0340	1533-AS03	1533-SS19	SD0579	1532-AS03	1532-SS16
SD0102	1533-AS11	1533-SS06	SD0341	1533-AS04	1533-SS19	SD0580	1532-AS04	1532-SS16
SD0103	1533-AS12	1533-SS06	SD0342	1533-AS05	1533-SS19	SD0581	1532-AS05	1532-SS16
SD0104	1533-AS13	1533-SS06	SD0343	1533-AS06	1533-SS19	SD0582	1532-AS06	1532-SS16
SD0105	1533-AS14	1533-SS06	SD0344	1533-AS07	1533-SS19	SD0583	1532-AS07	1532-SS16
SD0106	1533-AS00	1533-SS07	SD0345	1533-AS08	1533-SS19	SD0584	1532-AS08	1532-SS16
SD0107	1533-AS01	1533-SS07	SD0346	1533-AS09	1533-SS19	SD0585	1532-AS09	1532-SS16
SD0108	1533-AS02	1533-SS07	SD0347	1533-AS10	1533-SS19	SD0586	1532-AS10	1532-SS16
SD0109	1533-AS03	1533-SS07	SD0348	1533-AS11	1533-SS19	SD0587	1532-AS11	1532-SS16
SD0110	1533-AS04	1533-SS07	SD0349	1533-AS12	1533-SS19	SD0588	1532-AS12	1532-SS16
SD0111	1533-AS05	1533-SS07	SD0350	1533-AS13	1533-SS19	SD0589	1532-AS13	1532-SS16

SD0112	1533-AS06	1533-SS07	SD0351	1533-AS14	1533-SS19	SD0590	1532-AS00	1532-SS17
SD0113	1533-AS07	1533-SS07	SD0352	1532-AS00	1532-SS00	SD0591	1532-AS01	1532-SS17
SD0114	1533-AS08	1533-SS07	SD0353	1532-AS01	1532-SS00	SD0592	1532-AS02	1532-SS17
SD0115	1533-AS09	1533-SS07	SD0354	1532-AS02	1532-SS00	SD0593	1532-AS03	1532-SS17
SD0116	1533-AS10	1533-SS07	SD0355	1532-AS03	1532-SS00	SD0594	1532-AS04	1532-SS17
SD0117	1533-AS11	1533-SS07	SD0356	1532-AS04	1532-SS00	SD0595	1532-AS05	1532-SS17
SD0118	1533-AS12	1533-SS07	SD0357	1532-AS05	1532-SS00	SD0596	1532-AS06	1532-SS17
SD0119	1533-AS13	1533-SS07	SD0358	1532-AS06	1532-SS00	SD0597	1532-AS07	1532-SS17
SD0120	1533-AS14	1533-SS07	SD0359	1532-AS07	1532-SS00	SD0598	1532-AS08	1532-SS17
SD0121	1533-AS00	1533-SS08	SD0360	1532-AS08	1532-SS00	SD0599	1532-AS09	1532-SS17
SD0122	1533-AS01	1533-SS08	SD0361	1532-AS09	1532-SS00	SD0600	1532-AS10	1532-SS17
SD0123	1533-AS02	1533-SS08	SD0362	1532-AS10	1532-SS00	SD0601	1532-AS11	1532-SS17
SD0124	1533-AS03	1533-SS08	SD0363	1532-AS11	1532-SS00	SD0602	1532-AS12	1532-SS17
SD0125	1533-AS04	1533-SS08	SD0364	1532-AS12	1532-SS00	SD0603	1532-AS13	1532-SS17
SD0126	1533-AS05	1533-SS08	SD0365	1532-AS13	1532-SS00	SD0604	1532-AS00	1532-SS18
SD0127	1533-AS06	1533-SS08	SD0366	1532-AS00	1532-SS01	SD0605	1532-AS01	1532-SS18
SD0128	1533-AS07	1533-SS08	SD0367	1532-AS01	1532-SS01	SD0606	1532-AS02	1532-SS18
SD0129	1533-AS08	1533-SS08	SD0368	1532-AS02	1532-SS01	SD0607	1532-AS03	1532-SS18
SD0130	1533-AS09	1533-SS08	SD0369	1532-AS03	1532-SS01	SD0608	1532-AS04	1532-SS18
SD0131	1533-AS10	1533-SS08	SD0370	1532-AS04	1532-SS01	SD0609	1532-AS05	1532-SS18
SD0132	1533-AS11	1533-SS08	SD0371	1532-AS05	1532-SS01	SD0610	1532-AS06	1532-SS18
SD0133	1533-AS12	1533-SS08	SD0372	1532-AS06	1532-SS01	SD0611	1532-AS07	1532-SS18
SD0134	1533-AS13	1533-SS08	SD0373	1532-AS07	1532-SS01	SD0612	1532-AS08	1532-SS18
SD0135	1533-AS14	1533-SS08	SD0374	1532-AS08	1532-SS01	SD0613	1532-AS09	1532-SS18
SD0136	1533-AS00	1533-SS09	SD0375	1532-AS09	1532-SS01	SD0614	1532-AS10	1532-SS18
SD0137	1533-AS01	1533-SS09	SD0376	1532-AS10	1532-SS01	SD0615	1532-AS11	1532-SS18
SD0138	1533-AS02	1533-SS09	SD0377	1532-AS11	1532-SS01	SD0616	1532-AS12	1532-SS18
SD0139	1533-AS03	1533-SS09	SD0378	1532-AS12	1532-SS01	SD0617	1532-AS13	1532-SS18
SD0140	1533-AS04	1533-SS09	SD0379	1532-AS13	1532-SS01	SD0618	1532-AS00	1532-SS19

SD0141	1533-AS05	1533-SS09	SD0380	1532-AS00	1532-SS02	SD0619	1532-AS01	1532-SS19
SD0142	1533-AS06	1533-SS09	SD0381	1532-AS01	1532-SS02	SD0620	1532-AS02	1532-SS19
SD0143	1533-AS07	1533-SS09	SD0382	1532-AS02	1532-SS02	SD0621	1532-AS03	1532-SS19
SD0144	1533-AS08	1533-SS09	SD0383	1532-AS03	1532-SS02	SD0622	1532-AS04	1532-SS19
SD0145	1533-AS09	1533-SS09	SD0384	1532-AS04	1532-SS02	SD0623	1532-AS05	1532-SS19
SD0146	1533-AS10	1533-SS09	SD0385	1532-AS05	1532-SS02	SD0624	1532-AS06	1532-SS19
SD0147	1533-AS11	1533-SS09	SD0386	1532-AS06	1532-SS02	SD0625	1532-AS07	1532-SS19
SD0148	1533-AS12	1533-SS09	SD0387	1532-AS07	1532-SS02	SD0626	1532-AS08	1532-SS19
SD0149	1533-AS13	1533-SS09	SD0388	1532-AS08	1532-SS02	SD0627	1532-AS09	1532-SS19
SD0150	1533-AS14	1533-SS09	SD0389	1532-AS09	1532-SS02	SD0628	1532-AS10	1532-SS19
SD0151	1533-AS00	1533-SS01	SD0390	1532-AS10	1532-SS02	SD0629	1532-AS11	1532-SS19
SD0152	1533-AS01	1533-SS01	SD0391	1532-AS11	1532-SS02	SD0630	1532-AS12	1532-SS19
SD0153	1533-AS02	1533-SS01	SD0392	1532-AS12	1532-SS02	SD0631	1532-AS13	1532-SS19
SD0154	1533-AS03	1533-SS01	SD0393	1532-AS13	1532-SS02	SD0632	1532-AS00	1532-SS20
SD0155	1533-AS04	1533-SS01	SD0394	1532-AS00	1532-SS03	SD0633	1532-AS01	1532-SS20
SD0156	1533-AS05	1533-SS01	SD0395	1532-AS01	1532-SS03	SD0634	1532-AS02	1532-SS20
SD0157	1533-AS06	1533-SS01	SD0396	1532-AS02	1532-SS03	SD0635	1532-AS03	1532-SS20
SD0158	1533-AS07	1533-SS01	SD0397	1532-AS03	1532-SS03	SD0636	1532-AS04	1532-SS20
SD0159	1533-AS08	1533-SS01	SD0398	1532-AS04	1532-SS03	SD0637	1532-AS05	1532-SS20
SD0160	1533-AS09	1533-SS01	SD0399	1532-AS05	1532-SS03	SD0638	1532-AS06	1532-SS20
SD0161	1533-AS10	1533-SS01	SD0400	1532-AS06	1532-SS03	SD0639	1532-AS07	1532-SS20
SD0162	1533-AS11	1533-SS01	SD0401	1532-AS07	1532-SS03	SD0640	1532-AS08	1532-SS20
SD0163	1533-AS12	1533-SS01	SD0402	1532-AS08	1532-SS03	SD0641	1532-AS09	1532-SS20
SD0164	1533-AS13	1533-SS01	SD0403	1532-AS09	1532-SS03	SD0642	1532-AS10	1532-SS20
SD0165	1533-AS14	1533-SS01	SD0404	1532-AS10	1532-SS03	SD0643	1532-AS11	1532-SS20
SD0166	1533-AS00	1533-SS01	SD0405	1532-AS11	1532-SS03	SD0644	1532-AS12	1532-SS20
SD0167	1533-AS01	1533-SS01	SD0406	1532-AS12	1532-SS03	SD0645	1532-AS13	1532-SS20
SD0168	1533-AS02	1533-SS01	SD0407	1532-AS13	1532-SS03	SD0646	1532-AS00	1532-SS21
SD0169	1533-AS03	1533-SS01	SD0408	1532-AS00	1532-SS04	SD0647	1532-AS01	1532-SS21

SD0170	1533-AS04	1533-SS01	SD0409	1532-AS01	1532-SS04	SD0648	1532-AS02	1532-SS21
SD0171	1533-AS05	1533-SS01	SD0410	1532-AS02	1532-SS04	SD0649	1532-AS03	1532-SS21
SD0172	1533-AS06	1533-SS01	SD0411	1532-AS03	1532-SS04	SD0650	1532-AS04	1532-SS21
SD0173	1533-AS07	1533-SS01	SD0412	1532-AS04	1532-SS04	SD0651	1532-AS05	1532-SS21
SD0174	1533-AS08	1533-SS01	SD0413	1532-AS05	1532-SS04	SD0652	1532-AS06	1532-SS21
SD0175	1533-AS09	1533-SS01	SD0414	1532-AS06	1532-SS04	SD0653	1532-AS07	1532-SS21
SD0176	1533-AS10	1533-SS01	SD0415	1532-AS07	1532-SS04	SD0654	1532-AS08	1532-SS21
SD0177	1533-AS11	1533-SS01	SD0416	1532-AS08	1532-SS04	SD0655	1532-AS09	1532-SS21
SD0178	1533-AS12	1533-SS01	SD0417	1532-AS09	1532-SS04	SD0656	1532-AS10	1532-SS21
SD0179	1533-AS13	1533-SS01	SD0418	1532-AS10	1532-SS04	SD0657	1532-AS11	1532-SS21
SD0180	1533-AS14	1533-SS01	SD0419	1532-AS11	1532-SS04	SD0658	1532-AS12	1532-SS21
SD0181	1533-AS00	1533-SS02	SD0420	1532-AS12	1532-SS04	SD0659	1532-AS13	1532-SS21
SD0182	1533-AS01	1533-SS02	SD0421	1532-AS13	1532-SS04	SD0660	1532-AS00	1532-SS22
SD0183	1533-AS02	1533-SS02	SD0422	1532-AS00	1532-SS05	SD0661	1532-AS01	1532-SS22
SD0184	1533-AS03	1533-SS02	SD0423	1532-AS01	1532-SS05	SD0662	1532-AS02	1532-SS22
SD0185	1533-AS04	1533-SS02	SD0424	1532-AS02	1532-SS05	SD0663	1532-AS03	1532-SS22
SD0186	1533-AS05	1533-SS02	SD0425	1532-AS03	1532-SS05	SD0664	1532-AS04	1532-SS22
SD0187	1533-AS06	1533-SS02	SD0426	1532-AS04	1532-SS05	SD0665	1532-AS05	1532-SS22
SD0188	1533-AS07	1533-SS02	SD0427	1532-AS05	1532-SS05	SD0666	1532-AS06	1532-SS22
SD0189	1533-AS08	1533-SS02	SD0428	1532-AS06	1532-SS05	SD0667	1532-AS07	1532-SS22
SD0190	1533-AS09	1533-SS02	SD0429	1532-AS07	1532-SS05	SD0668	1532-AS08	1532-SS22
SD0191	1533-AS10	1533-SS02	SD0430	1532-AS08	1532-SS05	SD0669	1532-AS09	1532-SS22
SD0192	1533-AS11	1533-SS02	SD0431	1532-AS09	1532-SS05	SD0670	1532-AS10	1532-SS22
SD0193	1533-AS12	1533-SS02	SD0432	1532-AS10	1532-SS05	SD0671	1532-AS11	1532-SS22
SD0194	1533-AS13	1533-SS02	SD0433	1532-AS11	1532-SS05	SD0672	1532-AS12	1532-SS22
SD0195	1533-AS14	1533-SS02	SD0434	1532-AS12	1532-SS05	SD0673	1532-AS13	1532-SS22
SD0196	1533-AS00	1533-CfinSS	SD0435	1532-AS13	1532-SS05	SD0674	1532-AS00	1532-SS23
SD0197	1533-AS01	1533-CfinSS	SD0436	1532-AS00	1532-SS06	SD0675	1532-AS01	1532-SS23
SD0198	1533-AS02	1533-CfinSS	SD0437	1532-AS01	1532-SS06	SD0676	1532-AS02	1532-SS23

SD0199	1533-AS03	1533-CfinSS	SD0438	1532-AS02	1532-SS06	SD0677	1532-AS03	1532-SS23
SD0200	1533-AS04	1533-CfinSS	SD0439	1532-AS03	1532-SS06	SD0678	1532-AS04	1532-SS23
SD0201	1533-AS05	1533-CfinSS	SD0440	1532-AS04	1532-SS06	SD0679	1532-AS05	1532-SS23
SD0202	1533-AS06	1533-CfinSS	SD0441	1532-AS05	1532-SS06	SD0680	1532-AS06	1532-SS23
SD0203	1533-AS07	1533-CfinSS	SD0442	1532-AS06	1532-SS06	SD0681	1532-AS07	1532-SS23
SD0204	1533-AS08	1533-CfinSS	SD0443	1532-AS07	1532-SS06	SD0682	1532-AS08	1532-SS23
SD0205	1533-AS09	1533-CfinSS	SD0444	1532-AS08	1532-SS06	SD0683	1532-AS09	1532-SS23
SD0206	1533-AS10	1533-CfinSS	SD0445	1532-AS09	1532-SS06	SD0684	1532-AS10	1532-SS23
SD0207	1533-AS11	1533-CfinSS	SD0446	1532-AS10	1532-SS06	SD0685	1532-AS11	1532-SS23
SD0208	1533-AS12	1533-CfinSS	SD0447	1532-AS11	1532-SS06	SD0686	1532-AS12	1532-SS23
SD0209	1533-AS13	1533-CfinSS	SD0448	1532-AS12	1532-SS06	SD0687	1532-AS13	1532-SS23
SD0210	1533-AS14	1533-CfinSS	SD0449	1532-AS13	1532-SS06	SD0688	1532-AS00	1532-SS24
SD0211	1533-CfinAS	1533-SS00	SD0450	1532-AS00	1532-SS07	SD0689	1532-AS01	1532-SS24
SD0212	1533-CfinAS	1533-SS01	SD0451	1532-AS01	1532-SS07	SD0690	1532-AS02	1532-SS24
SD0213	1533-CfinAS	1533-SS02	SD0452	1532-AS02	1532-SS07	SD0691	1532-AS03	1532-SS24
SD0214	1533-CfinAS	1533-SS03	SD0453	1532-AS03	1532-SS07	SD0692	1532-AS04	1532-SS24
SD0215	1533-CfinAS	1533-SS04	SD0454	1532-AS04	1532-SS07	SD0693	1532-AS05	1532-SS24
SD0216	1533-CfinAS	1533-SS05	SD0455	1532-AS05	1532-SS07	SD0694	1532-AS06	1532-SS24
SD0217	1533-CfinAS	1533-SS06	SD0456	1532-AS06	1532-SS07	SD0695	1532-AS07	1532-SS24
SD0218	1533-CfinAS	1533-SS07	SD0457	1532-AS07	1532-SS07	SD0696	1532-AS08	1532-SS24
SD0219	1533-CfinAS	1533-SS08	SD0458	1532-AS08	1532-SS07	SD0697	1532-AS09	1532-SS24
SD0220	1533-CfinAS	1533-SS09	SD0459	1532-AS09	1532-SS07	SD0698	1532-AS10	1532-SS24
SD0221	1533-CfinAS	1533-SS10	SD0460	1532-AS10	1532-SS07	SD0699	1532-AS11	1532-SS24
SD0222	1533-CfinAS	1533-SS11	SD0461	1532-AS11	1532-SS07	SD0700	1532-AS12	1532-SS24
SD0223	1533-CfinAS	1533-SS12	SD0462	1532-AS12	1532-SS07	SD0701	1532-AS13	1532-SS24
SD0224	1533-CfinAS	1533-SS13	SD0463	1532-AS13	1532-SS07	SD0702	1532-AS14	1532-SS00
SD0225	1533-CfinAS	1533-SS14	SD0464	1532-AS00	1532-SS08	SD0703	1532-AS15	1532-SS00
SD0226	1533-CfinAS	1533-SS15	SD0465	1532-AS01	1532-SS08	SD0704	1532-AS16	1532-SS00
SD0227	1533-CfinAS	1533-SS16	SD0466	1532-AS02	1532-SS08	SD0705	1532-AS17	1532-SS00

SD0228	1533-CfinAS	1533-SS17	SD0467	1532-AS03	1532-SS08	SD0706	1532-AS18	1532-SS00
SD0229	1533-CfinAS	1533-SS18	SD0468	1532-AS04	1532-SS08	SD0707	1532-AS19	1532-SS00
SD0230	1533-CfinAS	1533-SS19	SD0469	1532-AS05	1532-SS08	SD0708	1532-AS20	1532-SS00
SD0231	1533-CfinAS	1533-SS20	SD0470	1532-AS06	1532-SS08	SD0709	1532-AS21	1532-SS00
SD0232	1533-AS00	1533-SS12	SD0471	1532-AS07	1532-SS08	SD0710	1532-AS22	1532-SS00
SD0233	1533-AS01	1533-SS12	SD0472	1532-AS08	1532-SS08	SD0711	1532-AS23	1532-SS00
SD0234	1533-AS02	1533-SS12	SD0473	1532-AS09	1532-SS08	SD0712	1532-AS24	1532-SS00
SD0235	1533-AS03	1533-SS12	SD0474	1532-AS10	1532-SS08	SD0713	1532-AS25	1532-SS00
SD0236	1533-AS04	1533-SS12	SD0475	1532-AS11	1532-SS08	SD0714	1532-AS26	1532-SS00
SD0237	1533-AS05	1533-SS12	SD0476	1532-AS12	1532-SS08	SD0715	1532-AS27	1532-SS00
SD0238	1533-AS06	1533-SS12	SD0477	1532-AS13	1532-SS08			
SD0239	1533-AS07	1533-SS12	SD0478	1532-AS00	1532-SS09			

In some embodiments, an LPA RNAi agent comprises an antisense strand comprising the nucleotide sequence of SEQ ID NO:1242 (TCGUAUAACAAUAAGGGGC). In some embodiments, an LPA RNAi agent comprises an antisense strand comprising the nucleotide sequence of SEQ ID NO:1244 (UCGUAUAACAAUAAGGGG). In some embodiments, an LPA RNAi agent comprises an antisense strand comprising the nucleotide sequence of SEQ ID NO:1246 (UCGUAUAACAAUAAGGG). In some embodiments, an LPA RNAi agent comprises an antisense strand comprising the nucleotide sequence of SEQ ID NO:1248 (TGAGAAUGAGCCUCGAUAA). In some embodiments, an LPA RNAi agent comprises an antisense strand comprising the nucleotide sequence of SEQ ID NO:1250 (UGAGAAUGAGCCUCGAUA). In some embodiments, an LPA RNAi agent comprises an antisense strand comprising the nucleotide sequence of SEQ ID NO:1252 (UGAGAAUGAGCCUCGAU). In some embodiments, an LPA RNAi agent comprises an antisense strand comprising the nucleotide sequence of SEQ ID NO:1254 (UGUAUAACAAUAAGGGG). In some embodiments, an LPA RNAi agent comprises an antisense strand comprising the nucleotide sequence of SEQ ID NO:1280 (CGUAUAACAAUAAGGGGC). In some embodiments, an LPA RNAi agent comprises an antisense strand comprising the nucleotide sequence of SEQ ID NO:1281 (GAGAAUGAGCCUCGAUAA). In some embodiments, an LPA RNAi agent comprises an antisense strand comprising the nucleotide sequence of SEQ ID NO:1282 (UCGUAUAACAAUAAGGGGC). In some embodiments, an LPA RNAi agent comprises an antisense strand comprising the nucleotide sequence of SEQ ID NO:1283 (UGAGAAUGAGCCUCGAUAA). In some embodiments, one or more of the nucleotides is modified.

In some embodiments, an LPA RNAi agent comprises a sense strand comprising the nucleotide sequence of SEQ ID NO:1243 (GCCCCUUAUUGUUAUACGA). In some embodiments, an LPA RNAi agent comprises a sense strand comprising the nucleotide sequence of SEQ ID NO:1245 (CCCCUUAUUGUUAUACGA). In some embodiments, an LPA RNAi agent comprises a sense strand comprising the nucleotide sequence of SEQ ID NO:1247 (CCCUUAUUGUUAUACGA). In some embodiments, an LPA RNAi agent comprises a sense strand comprising the nucleotide sequence of SEQ ID NO:1249 (UUAUCGAGGCUCAUUCUCA). In some embodiments, an LPA RNAi agent comprises a sense strand comprising the nucleotide sequence of SEQ ID NO:1251 (UAUCGAGGCUCAUUCUCA). In some embodiments, an LPA RNAi agent comprises a

sense strand comprising the nucleotide sequence of SEQ ID NO:1253 (AUCGAGGCUCAUUCUCA). In some embodiments, an LPA RNAi agent comprises a sense strand comprising the nucleotide sequence of SEQ ID NO:1255 (CCCCUUAUUGUUAUACA). In some embodiments, an LPA RNAi agent comprises a sense strand comprising the nucleotide sequence of SEQ ID NO:1284 (GCCCCUUAUUGUUAUACG). In some embodiments, an LPA RNAi agent comprises a sense strand comprising the nucleotide sequence of SEQ ID NO:1285 (UUAUCGAGGCUCAUUCUC). In some embodiments, one or more of the nucleotides is modified.

In some embodiments, an LPA RNAi agent comprises an antisense strand comprising the nucleotide sequence of SEQ ID NO:1242 and a sense strand comprising the nucleotide sequence of SEQ ID NO:1243. In some embodiments, an LPA RNAi agent comprises an antisense strand comprising the nucleotide sequence of SEQ ID NO:1244 and a sense strand comprising the nucleotide sequence of SEQ ID NO:1245. In some embodiments, an LPA RNAi agent comprises an antisense strand comprising the nucleotide sequence of SEQ ID NO:1246 and a sense strand comprising the nucleotide sequence of SEQ ID NO:1247. In some embodiments, an LPA RNAi agent comprises an antisense strand comprising the nucleotide sequence of SEQ ID NO:1248 and a sense strand comprising the nucleotide sequence of SEQ ID NO:1249. In some embodiments, an LPA RNAi agent comprises an antisense strand comprising the nucleotide sequence of SEQ ID NO:1250 and a sense strand comprising the nucleotide sequence of SEQ ID NO:1251. In some embodiments, an LPA RNAi agent comprises an antisense strand comprising the nucleotide sequence of SEQ ID NO:1252 and a sense strand comprising the nucleotide sequence of SEQ ID NO:1253. In some embodiments, an LPA RNAi agent comprises an antisense strand comprising the nucleotide sequence of SEQ ID NO:1254 and sense strand comprising the nucleotide sequence of SEQ ID NO:1255. In some embodiments, an LPA RNAi agent comprises an antisense strand comprising the nucleotide sequence of SEQ ID NO:1280 and a sense strand comprising the nucleotide sequence of SEQ ID NO:1284. In some embodiments, an LPA RNAi agent comprises an antisense strand comprising the nucleotide sequence of SEQ ID NO:1281 and a sense strand comprising the nucleotide sequence of SEQ ID NO: 1285. In some embodiments, an LPA RNAi agent comprises an antisense strand comprising the nucleotide sequence of SEQ ID NO:1282 and a sense strand comprising the nucleotide sequence of SEQ ID NO:1259. In some embodiments, an LPA RNAi agent comprises an antisense strand comprising the nucleotide

sequence of SEQ ID NO:1283 and a sense strand comprising the nucleotide sequence of SEQ ID NO: 1249. In some embodiments, one or more of the nucleotides is modified.

In some embodiments, an LPA RNAi agent comprises an antisense strand comprising the nucleotide sequence of SEQ ID NO. 156, 164, or 188. In some embodiments, an LPA RNAi agent comprises a sense strand comprising the nucleotide sequence of SEQ ID NO. 310, 357, 384, or 376. In some embodiments, an LPA RNAi agent comprises an antisense strand and a sense strand comprising the nucleotide sequences of SEQ ID NOs:156/310, SEQ ID NOs:164/357, SEQ ID NOs:188/384, SEQ ID NOs:164/376, or SEQ ID NOs:164/384. In some embodiments, one or more of the nucleotides is modified.

In some embodiments, an LPA RNAi agent comprises an antisense strand comprising the nucleotide sequence of SEQ ID NO. 637, 709, 790, 787, or 788. In some embodiments, an LPA RNAi agent comprises a sense strand comprising the nucleotide sequence of SEQ ID NO:1132, 1135, 1189, 1191, or 1186. In some embodiments, an LPA RNAi agent comprises an antisense strand and a sense strand comprising the nucleotide sequences of SEQ ID NOs:637/1132, SEQ ID NOs:709/1135, SEQ ID NOs:790/1189, SEQ ID NOs:787/1191, or SEQ ID NOs:788/1186.

In some embodiments, an LPA RNAi agent comprises SEQ ID NO. 637, 709, 790, 787, or 788. In some embodiments, an LPA RNAi agent comprises SEQ ID NO:1132, 1135, 1189, 1191, or 1186. In some embodiments, an LPA RNAi agent comprises SEQ ID NOs:637/1132, SEQ ID NOs:709/1135, SEQ ID NOs:790/1189, SEQ ID NOs:787/1191, or SEQ ID NOs:788/1186.

In some embodiments, an LPA RNAi agent consists of SEQ ID NO. 637, 709, 790, 787, or 788. In some embodiments, an LPA RNAi agent consists of SEQ ID NO:1132, 1135, 1189, 1191, or 1186. In some embodiments, an LPA RNAi agent consists of SEQ ID NOs:637/1132, SEQ ID NOs:709/1135, SEQ ID NOs:790/1189, SEQ ID NOs:787/1191, or SEQ ID NOs:788/1186.

In some embodiments, an LPA RNAi agent comprises an antisense strand and a sense strand having the nucleotide sequences of any of the antisense strand/sense strand duplexes of Table 3A or 3B.

In some embodiments, an LPA RNAi agent comprises an antisense strand and a sense strand

having the nucleotide sequences of any of the antisense strand/sense strand duplexes of Table 3A or 3B, and further comprises an asialoglycoprotein receptor ligand targeting group.

In some embodiments, an LPA RNAi agent comprises an antisense strand and a sense strand having the nucleotide sequences of any of the antisense strand/sense strand duplexes of Table 3A or 3B, and further comprises a targeting group selected from the group consisting of (C11¬PEG3¬NAG3), (C11-PEG3-NAG3), (C6-PEG4-NAG3), (NAG 3), (NAG4), (NAG3¬AA2), (NAG3-Palm), (NAG13), (NAG18), (NAG24), (NAG25), (NAG25)s, (NAG26), (NAG27), (NAG28), (NAG29), (NAG30), (NAG30)s, (NAG31), (NAG13), (NAG31s), (NAG32), (NAG33), (NAG34), (NAG35), (NAG36), and (NAG37).

In some embodiments, an LPA RNAi agent comprises an antisense strand and a sense strand having the modified nucleotide sequences of any of the antisense strand/sense strand duplexes of Table 3A or 3B.

In some embodiments, an LPA RNAi agent comprises an antisense strand and a sense strand having the modified nucleotide sequences of any of the antisense strand/sense strand duplexes of Table 3A or 3B, and further comprises an asialoglycoprotein receptor ligand targeting group.

In some embodiments, an LPA RNAi agent comprises an antisense strand and a sense strand having the modified nucleotide sequences of any of the antisense strand/sense strand duplexes of Table 3A or 3B, and further comprises a targeting group selected from the group consisting of (C11-PEG3-NAG3), (C11-PEG3-NAG3), (C6-PEG4-NAG3), (NAG 3), (NAG4), (NAG3-AA2), (NAG3-Palm), (NAG13), (NAG18), (NAG24), (NAG25), (NAG25)s, (NAG26), (NAG27), (NAG28), (NAG29), (NAG30), (NAG30)s, (NAG31), (NAG13), (NAG31s), (NAG32), (NAG33), (NAG34), (NAG35), (NAG36), and (NAG37).

In some embodiments, an LPA RNAi agent comprises any of the duplexes of Table 3A or 3B.

In some embodiments, an LPA RNAi agent consists of any of the duplexes of Table 3A or 3B.

In some embodiments, an LPA RNAi agent comprises an antisense strand and a sense strand having the nucleotide sequences AD03460, AD03536, AD03851, AD03853, AD3847, or AD04110.

In some embodiments, an LPA RNAi agent comprises an antisense strand and a sense strand having the nucleotide sequences AD03460, AD03536, AD03851, AD03853, AD3847, or AD04110, and further comprises an asialoglycoprotein receptor ligand targeting group.

In some embodiments, an LPA RNAi agent comprises an antisense strand and a sense strand having the nucleotide sequences AD03460, AD03536, AD03851, AD03853, AD3847, or AD04110, and further comprises a targeting group selected from the group consisting of (C11-PEG3-NAG3), (C11-PEG3-NAG3), (C6-PEG4-NAG3), (NAG 3), (NAG4), (NAG3-AA2), (NAG3-Palm), (NAG13), (NAG18), (NAG24), (NAG25), (NAG25)s, (NAG26), (NAG27), (NAG28), (NAG29), (NAG30), (NAG30)s, (NAG31), (NAG13), (NAG31s), (NAG32), (NAG33), (NAG34), (NAG35), (NAG36), and (NAG37).

In some embodiments, an LPA RNAi agent comprises an antisense strand and a sense strand having the modified nucleotide sequences AD03460, AD03536, AD03851, AD03853, AD3847, or AD04110.

In some embodiments, an LPA RNAi agent comprises an antisense strand and a sense strand having the modified nucleotide sequences AD03460, AD03536, AD03851, AD03853, AD3847, or AD04110, and further comprises an asialoglycoprotein receptor ligand targeting group.

In some embodiments, an LPA RNAi agent comprises an antisense strand and a sense strand having the modified nucleotide sequences AD03460, AD03536, AD03851, AD03853, AD3847, or AD04110, and further comprises a targeting group selected from the group consisting of (C11-PEG3-NAG3), (C11-PEG3-NAG3), (C6-PEG4-NAG3), (NAG3), (NAG4), (NAG3-AA2), (NAG3-Palm), (NAG13), (NAG18), (NAG24), (NAG25), (NAG25)s, (NAG26), (NAG27), (NAG28), (NAG29), (NAG30), (NAG30)s, (NAG31), (NAG13), (NAG31s), (NAG32), (NAG33), (NAG34), (NAG35), (NAG36), and (NAG37).

In some embodiments, an LPA RNAi agent comprises AD03460, AD03536, AD03851, AD03853, AD3847, or AD04110.

In some embodiments, an LPA RNAi agent consists of AD03460, AD03536, AD03851, AD03853, AD3847, or AD04110.

Non-nucleotide Group

In some embodiments, an LPA RNAi agent contains or is conjugated to one or more non-nucleotide groups including, but not limited to a targeting group, linking group, delivery polymer, or a delivery vehicle. The non-nucleotide group can enhance targeting, delivery or attachment of the RNAi agent. Examples of targeting groups and linking groups are provided in Table 4. The non-nucleotide group can be covalently linked to the 3′ and/or 5′ end of either the sense strand and/or the antisense strand. In some embodiments, an LPA RNAi agent contains a non-nucleotide group linked to the 3′ and/or 5′ end of the sense strand. In some embodiments a non-nucleotide group is linked to the 5′ end of an LPA RNAi agent sense strand. A non-nucleotide group may linked directly or indirectly to the RNAi agent via a linker/linking group. In some embodiments a non-nucleotide group is linked to the RNAi agent via a labile, cleavable, or reversible bond or linker.

In some embodiments, a non-nucleotide group enhances the pharmacokinetic or biodistribution properties of an RNAi agent or conjugate to which it is attached to improve cell- or tissue-specific distribution and cell-specific uptake of the conjugate. In some embodiments, a non-nucleotide group enhances endocytosis of the RNAi agent.

Targeting Group

A targeting group can be monovalent, divalent, trivalent, tetravalent, or have higher valency. Representative targeting groups include, without limitation, compounds with affinity to cell surface molecule, cell receptor ligands, hapten, antibodies, monoclonal antibodies, antibody fragments, and antibody mimics with affinity to cell surface molecules. In some embodiments, a targeting group is linked to an RNAi agent using a linker, such as a PEG linker or one, two, or three abasic and/or ribitol groups. In some embodiments, a targeting group comprises a galactose cluster.

The LPA RNAi agents described herein may be synthesized having a reactive group, such as an amine group, at the 5′-terminus. The reactive group may be used to subsequently attach a targeting moiety using methods typical in the art.

In some embodiments, a targeting group comprises an asialoglycoprotein receptor ligand. In some embodiments, an asialoglycoprotein receptor ligand includes or consists of one or more galactose derivatives or galactose clusters. As used herein, the term galactose derivative includes both galactose and derivatives of galactose having affinity for the asialoglycoprotein receptor that is equal to or greater than that of galactose. Galactose derivatives include, but are not limited to: galactose, galactosamine, N-formylgalactosamine, N-acetyl-galactosamine, N-propionyl-galactosamine, N-n-butanoyl-galactosamine, and N-iso-butanoylgalactos-amine (see for example: Iobst, S.T. and Drickamer, K. *J.B.C.* 1996, *271*, 6686). Galactose derivatives and galactose clusters that are useful for in vivo targeting of oligonucleotides and other molecules to the liver are known in the art (see, for example, Baenziger and Fiete, 1980, Cell, 22, 611-620; Connolly et al., 1982, J. Biol. Chem., 257, 939-945). Galactose derivatives have been used to target molecules to hepatocytes *in vivo* through their binding to the asialoglycoprotein receptor (ASGPr) expressed on the surface of hepatocytes. Binding of ASGPr ligands to the ASGPr(s) facilitates cell-specific targeting to hepatocytes and endocytosis of the molecule into hepatocytes. The galactose cluster may be attached to the 3′ or 5′ end of the RNAi polynucleotide using methods known in the art.

As used herein, a galactose cluster comprises a molecule having two to four terminal galactose derivatives. A terminal galactose derivative is attached to a molecule through its C-1 carbon. In some embodiments, the galactose cluster is a galactose derivative trimer, tri-antennary galactose derivative, or tri-valent galactose derivative. In some embodiments, the galactose cluster is comprises N-acetylgalactosamines (GalNAc). In some embodiments, the galactose cluster comprises a tri-valent N-acetyl-galactosamine. In some embodiments, the galactose cluster is a galactose derivative tetramer, tetra-antennary galactose derivative, or tetra-valent galactose derivative. In some embodiments, the galactose cluster comprises a tetra-valent N-acetyl-galactosamine.

As used herein, a galactose trimer contains three galactose derivatives, each linked to a central branch point. As used herein, a galactose derivative tetramer contains four galactose derivatives, each linked to a central branch point. The galactose derivatives can be attached to the central branch point through the C-1 carbons of the saccharides. In some embodiments, the galactose derivatives are linked to the branch point via linkers or spacers. In some embodiments, the linker or spacer is a flexible hydrophilic spacer, such as a PEG group (see, for example, U.S. Patent No. 5885968; Biessen et al. J. Med. Chem. 1995 Vol. 39 p. 1538-

1546). In some embodiments, the PEG spacer is a PEG_3 spacer. The branch point can be any small molecule which permits attachment of the three galactose derivatives and further permits attachment of the branch point to the RNAi agent. An example of branch point group is a di-lysine or di-glutamate. Attachment of the branch point to the RNAi agent can occur through a linker or spacer. In some embodiments, the linker or spacer comprises a flexible hydrophilic spacer, such as, but not limited to: a PEG spacer. In some embodiments, a PEG spacer is a PEG_3 spacer (three ethylene units). In other embodiments, the PEG spacer has 1 to 20 ethylene units (PEG_1 to PEG_{20}). In some embodiments, a galactose derivative comprises an N-acetylgalactosamine (GalNAc or NAG). In some embodiments, the galactose cluster is comprised of a galactose derivative tetramer, which can be, for example, an N-acetyl-galactosamine tetramer.

In some embodiments, pharmaceutical compositions for delivering an LPA RNAi agent to a liver cell *in vivo* are described. Such pharmaceutical compositions can include, for example, an LPA RNAi agent conjugated to a galactose cluster. In some embodiments, the galactose cluster is comprised of a galactose derivative trimer, which can be, for example, an N-acetyl-galactosamine trimer, or galactose derivative tetramer, which can be, for example, an N-acetyl-galactosamine tetramer.

Targeting groups include, but are not limited to, (Chol-TEG), (TEG-Chol), (C11-PEG3-NAG3), (C_m-PEG_n-NAG3), (C_x-PEG_z-NAG3), (NAG 3), (NAG4), (NAG3-AA2), (NAG3-Palm), (NAG13), (NAG18), (NAG24), (NAG25), (NAG25)s, (NAG26), (NAG27), (NAG28), (NAG29), (NAG30), (NAG30)s, (NAG31), (NAG13), (NAG31s), (NAG32), (NAG33), (NAG34), (NAG35), (NAG36), and (NAG37).

Linking Group

In some embodiments, a linking group is conjugated to the RNAi agent. The linking group facilitates covalent linkage of the agent to a targeting group or delivery polymer or delivery vehicle. The linking group can be linked to the 3′ or the 5′ end of the RNAi agent sense strand or antisense strand. In some embodiments, the linking group is linked to the RNAi agent sense strand. In some embodiments, the linking group is conjugated to the 5′ or 3′ end of an RNAi agent sense strand. In some embodiments a linking group is conjugated to the 5′ end of an RNAi agent sense strand. Examples of linking groups, include, but are not limited to: Alk-SMPT-C6, Alk-SS-C6, DBCO-TEG, Me-Alk-SS-C6, and C6-SS-Alk-Me, reactive groups

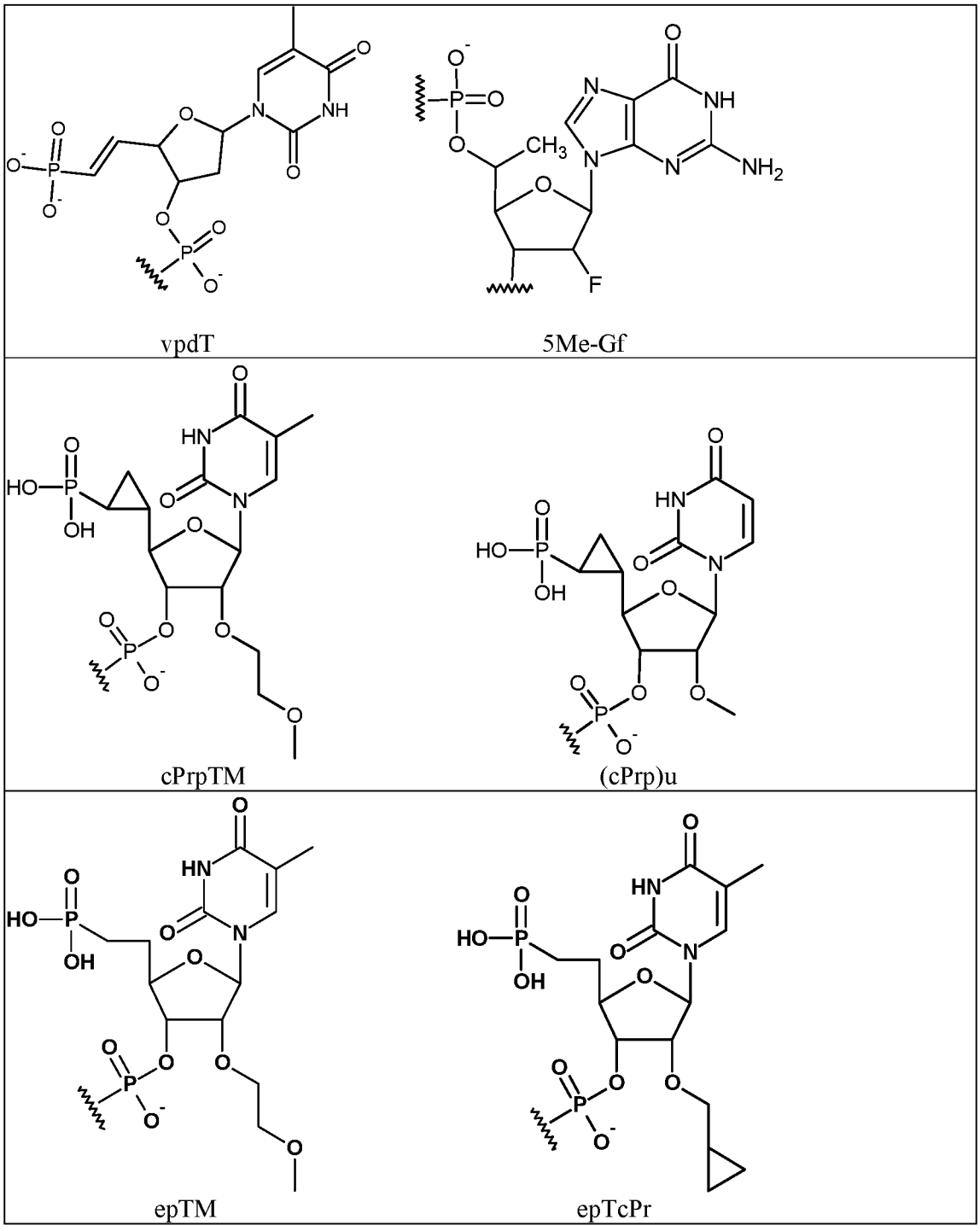
such a primary amines and alkynes, alkyl groups, abasic ribose, ribitol, and/or PEG groups.

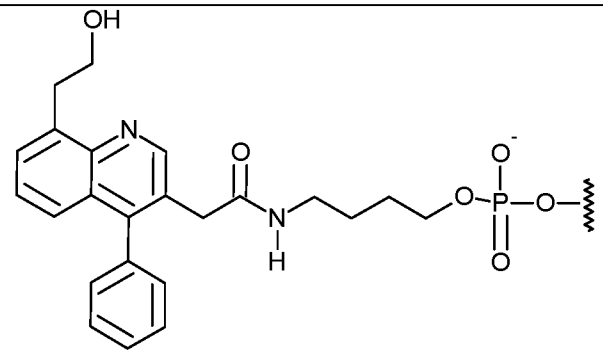
A linker or linking group is a connection between two atoms that links one chemical group (such as an RNAi agent) or segment of interest to another chemical group (such as a targeting group or delivery polymer) or segment of interest via one or more covalent bonds. A labile linkage contains a labile bond. A linkage may optionally include a spacer that increases the distance between the two joined atoms. A spacer may further add flexibility and/or length to the linkage. Spacers may include, but are not be limited to, alkyl groups, alkenyl groups, alkynyl groups, aryl groups, aralkyl groups, aralkenyl groups, and aralkynyl groups; each of which can contain one or more heteroatoms, heterocycles, amino acids, nucleotides, and saccharides. Spacer groups are well known in the art and the preceding list is not meant to limit the scope of the description.

Linking groups include, but are not limited to, Alkyl, PEG, (C6-PEG$_n$-Alk), (C$_n$-SMPT-Alk), and (C$_n$-SS-Alk-Me).

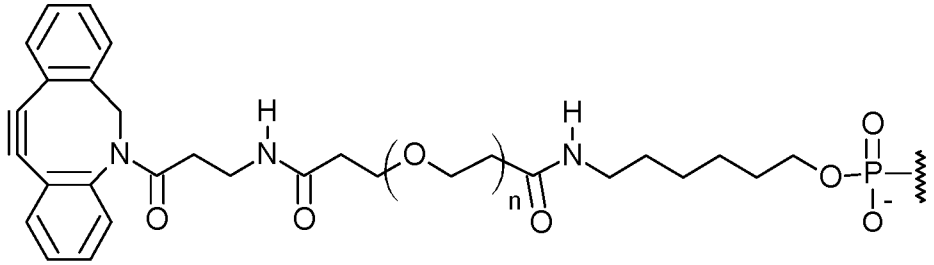
Any of the LPA RNAi agents listed in Tables 2A and 2B which contains a 3′ or 5′ targeting group or linking group, may alternatively contain no 3′ or 5′ targeting group or linking group, or may contain a different 3′ or 5′ targeting group or linking group including, but not limited to, those depicted in Table 4. Any of the LPA RNAi agent nucleotide sequences listed in Tables 1, 2A and 2B, whether modified or unmodified, may contain 3′ or 5′ targeting group or linking group, including, but not limited to, those depicted in Table 4. Any of the LPA RNAi agent duplexes listed in Tables 3A and 3B, whether modified or unmodified, may further comprise a targeting group or linking group, including, but not limited to, those depicted in Table 4, and the targeting group or linking group may be attached to the 3′ or 5′ terminus of either the sense strand or the antisense strand of the LPA RNAi agent duplex.

Table 4. Structures representing various modified nucleotides, targeting groups, and linking groups.

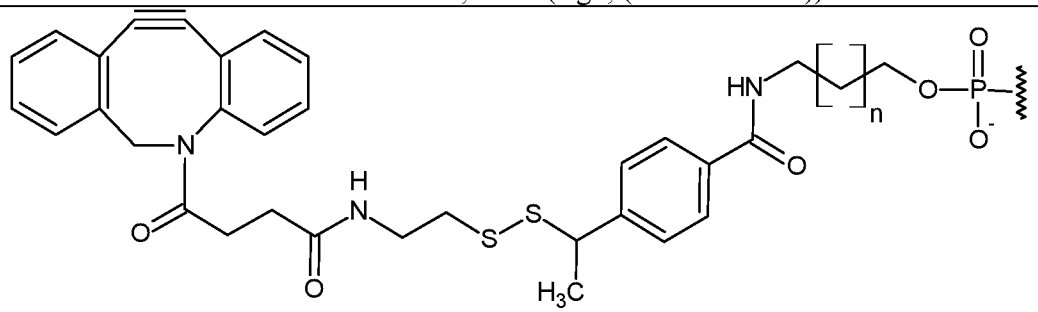




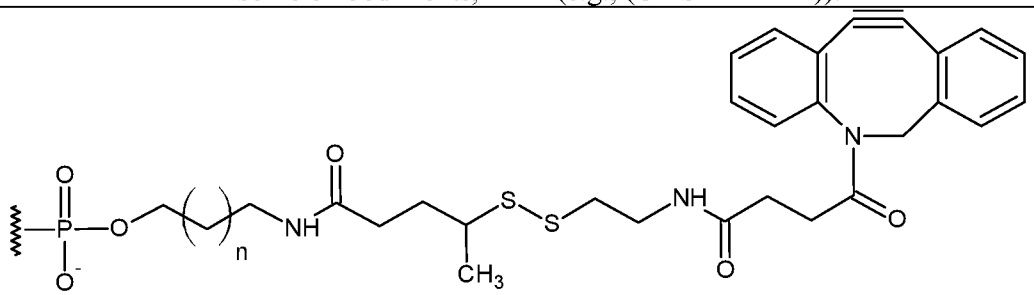
(PAZ)



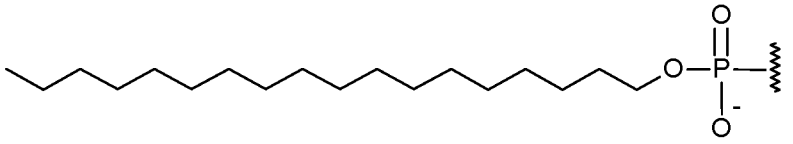
(Alk-PEG$_n$-C6) or (C6-PEG$_n$-Alk), wherein n = 1=12
In some embodiments, n = 5 (e.g.., (Alk-PEG5-C6)).



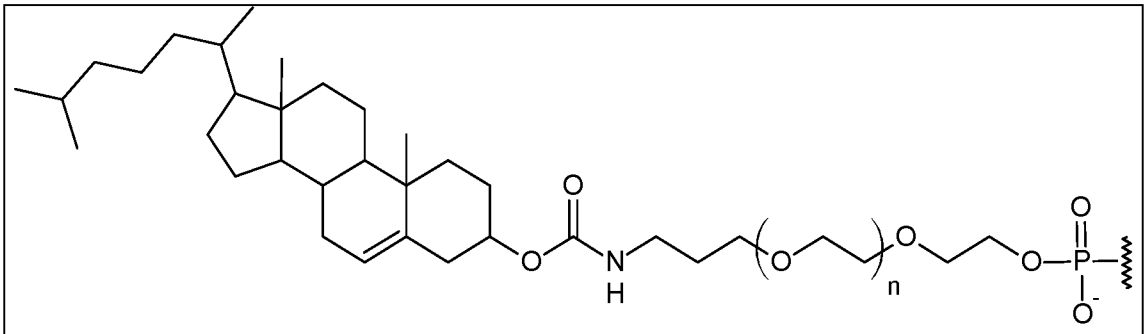
(C$_n$-SMPT-Alk) or (Alk-SMPT-C$_n$), wherein n = 1-10,
In some embodiments, n = 4 (e.g., (C6-SMPT-Alk)).



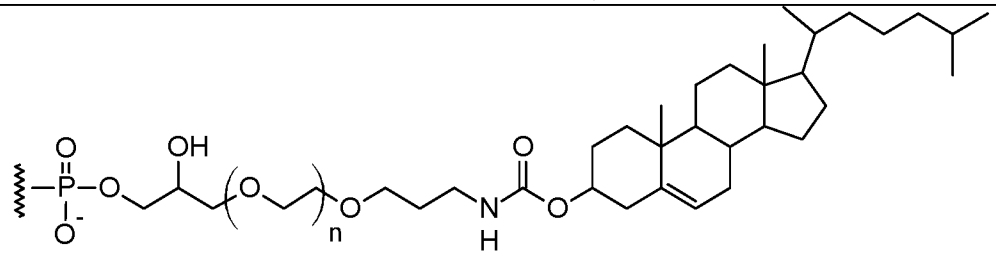
(C$_n$-SS-Alk-Me) or ((Me-Alk-SS-C$_n$); wherein n = 1-10
In some embodiments, n = 4 (e.g., (C6-SS-Alk-Me)).



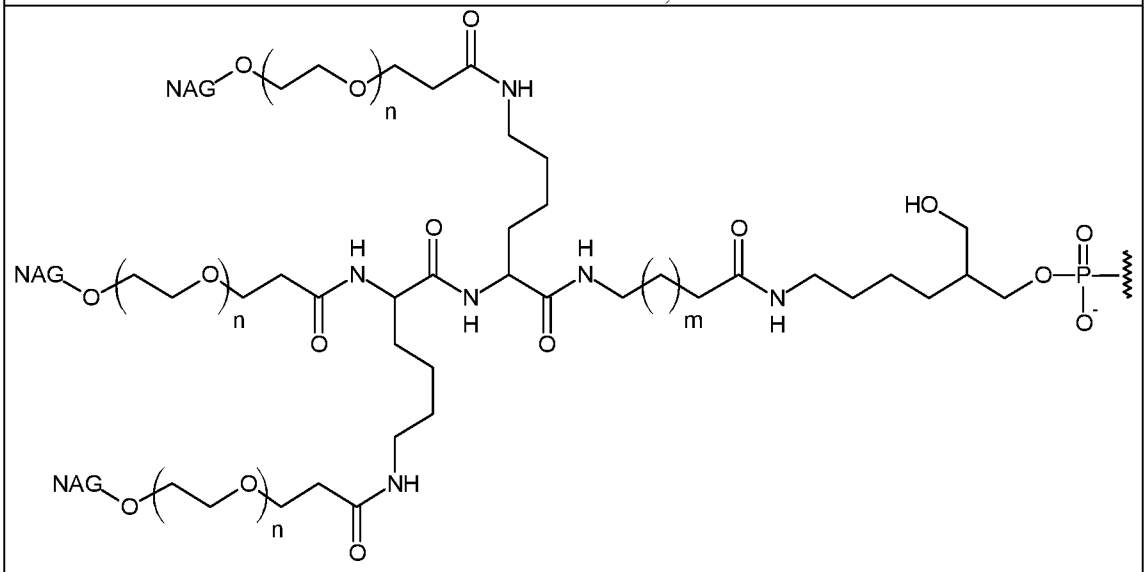
(Stearyl)



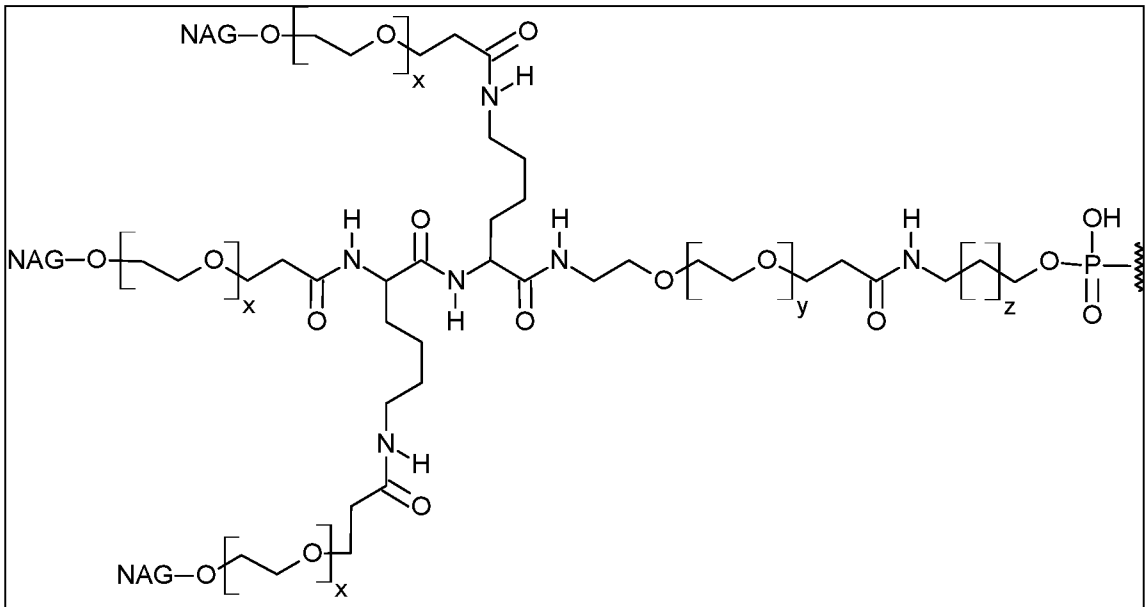
(Chol-TEG), wherein n = 1-10
In some embodiments, n = 2.



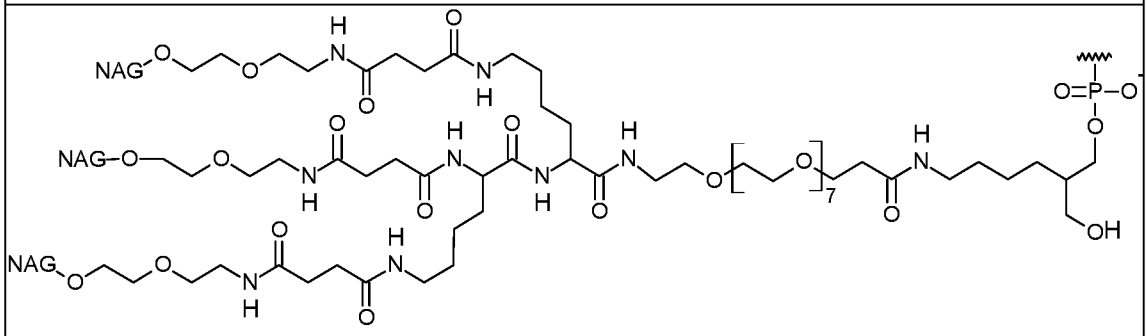
(TEG-Chol), wherein n = 1-10
In some embodiments, n = 3.



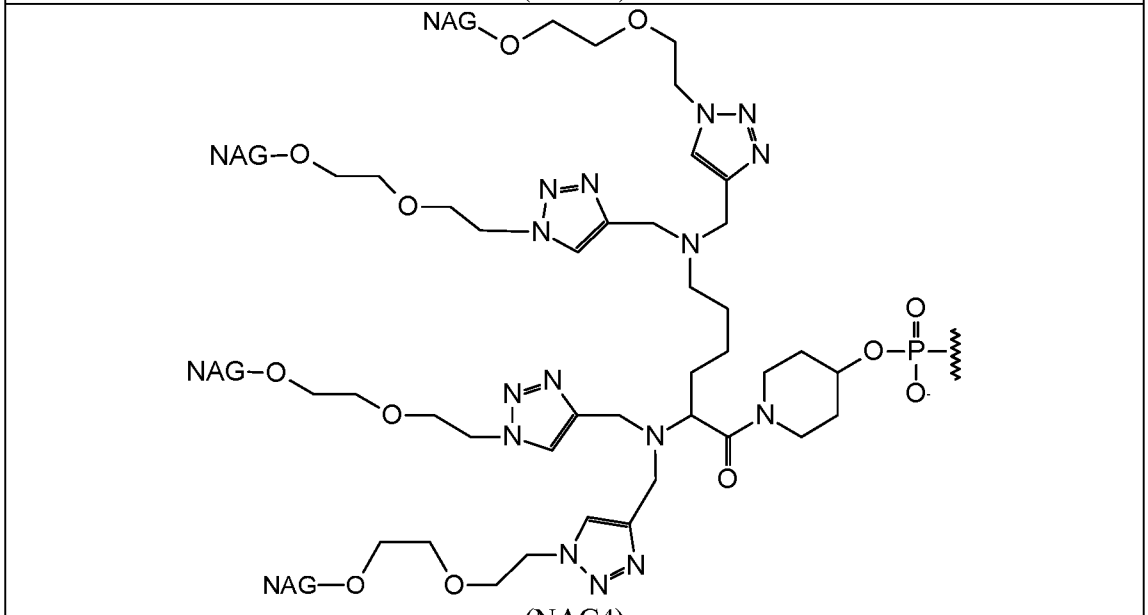
(NAG3-PEG$_n$-C$_m$) or (C$_m$-PEG$_n$-NAG3), wherein n =1-6 and m = 1-12
In some embodiments, n = 3 and m = 9 (e.g., (C11-PEG3-NAG3))



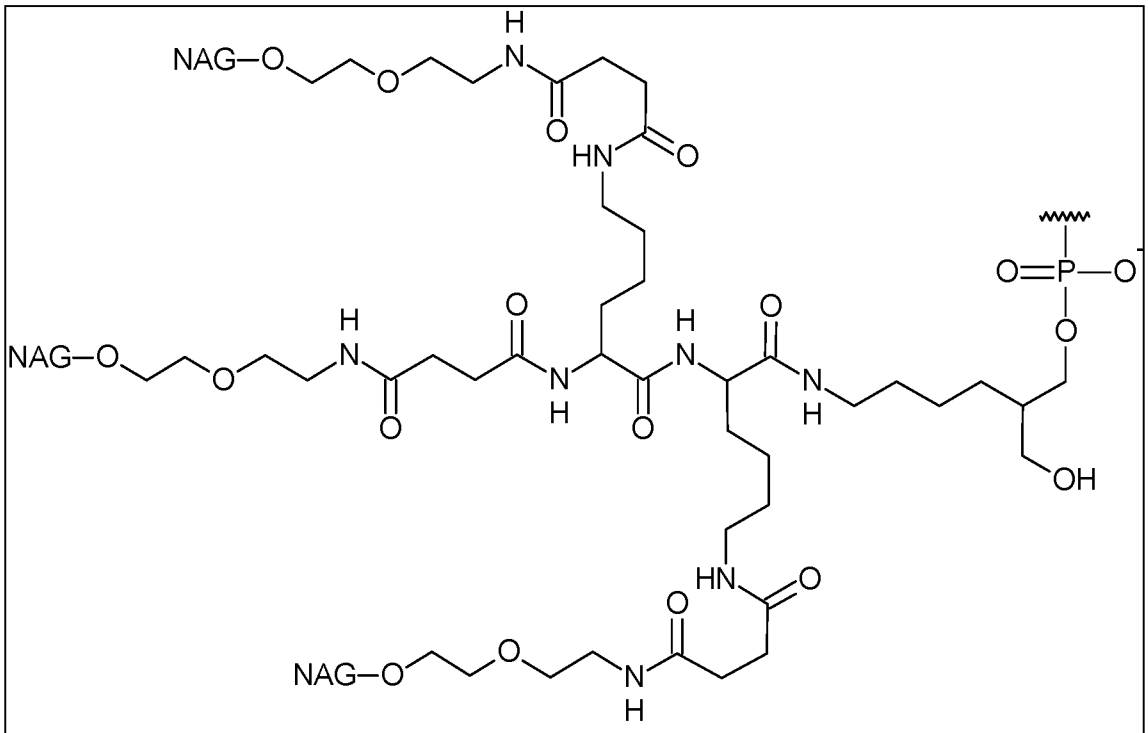
(C_x-PEG_z-NAG3), wherein x = 1-10, y - 1-10, and z = 1-10
In some embodiments, x = 3, y = 3, and z = 4 (C6-PEG4-NAG3)



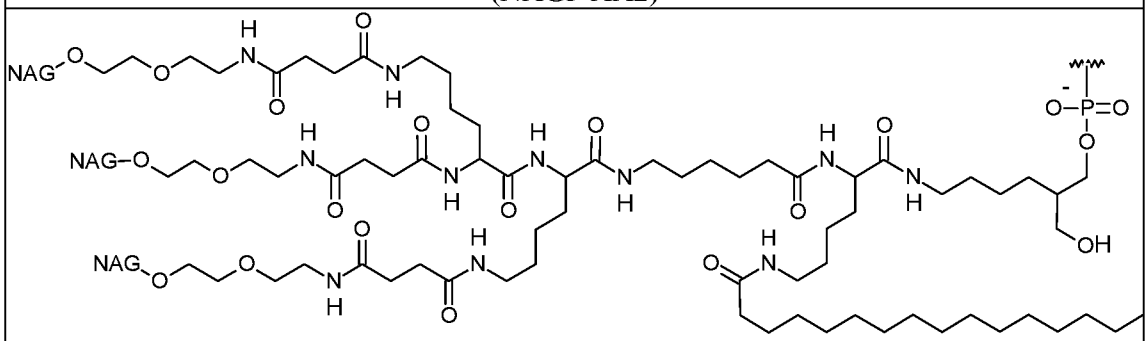
(NAG 3)



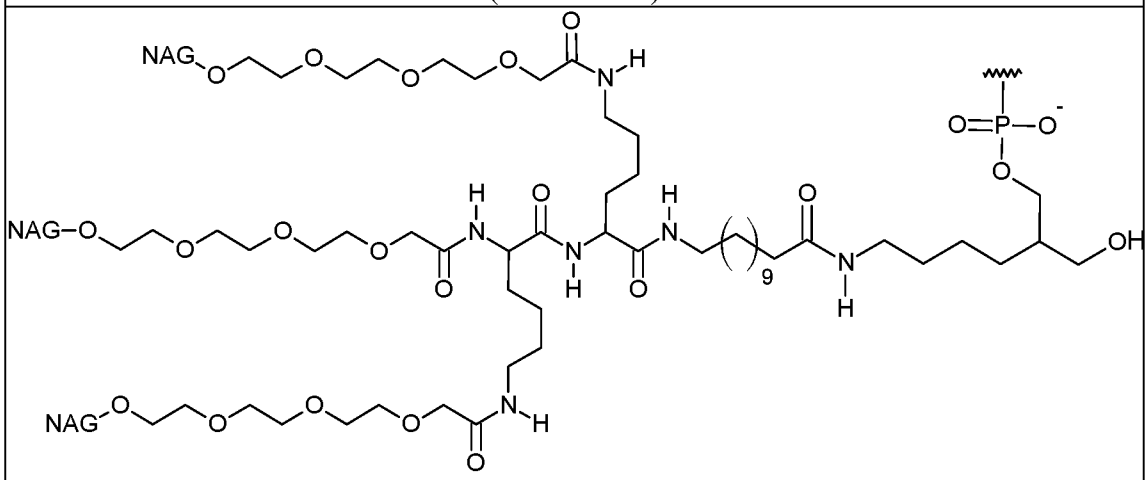
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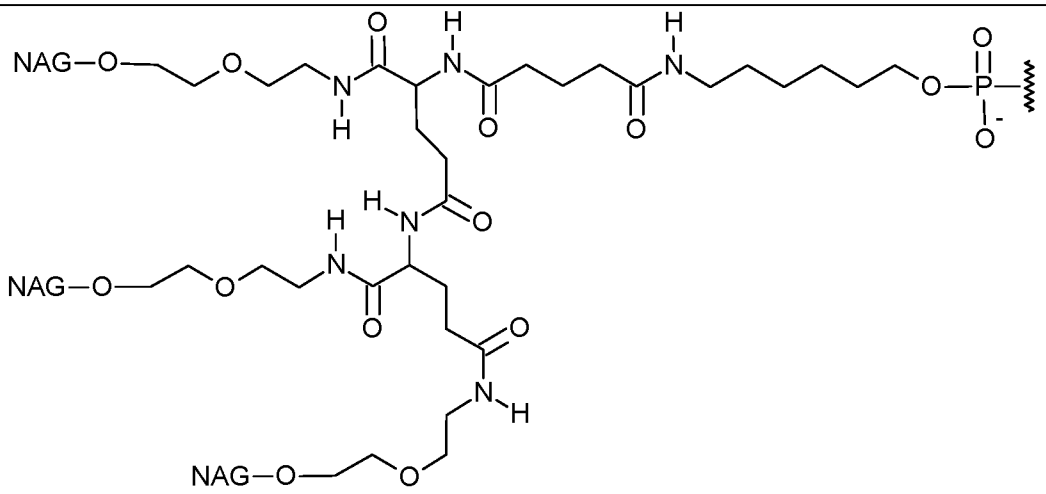
(NAG3-AA2)



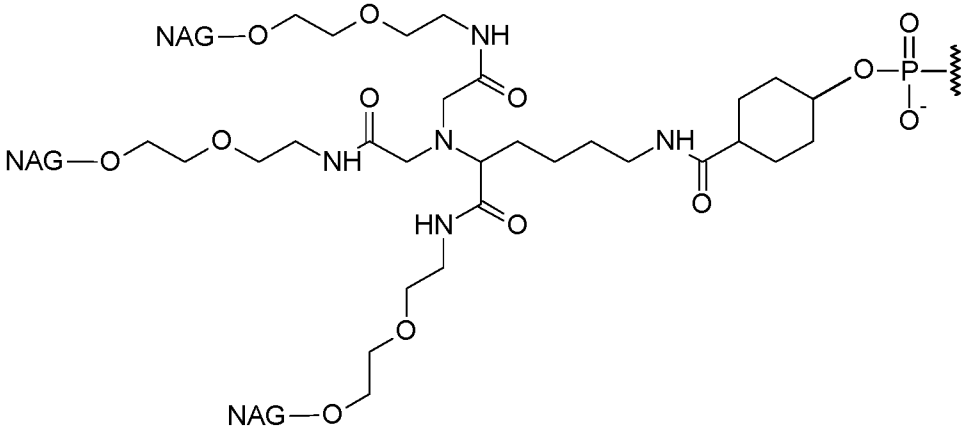
(NAG3-Palm)



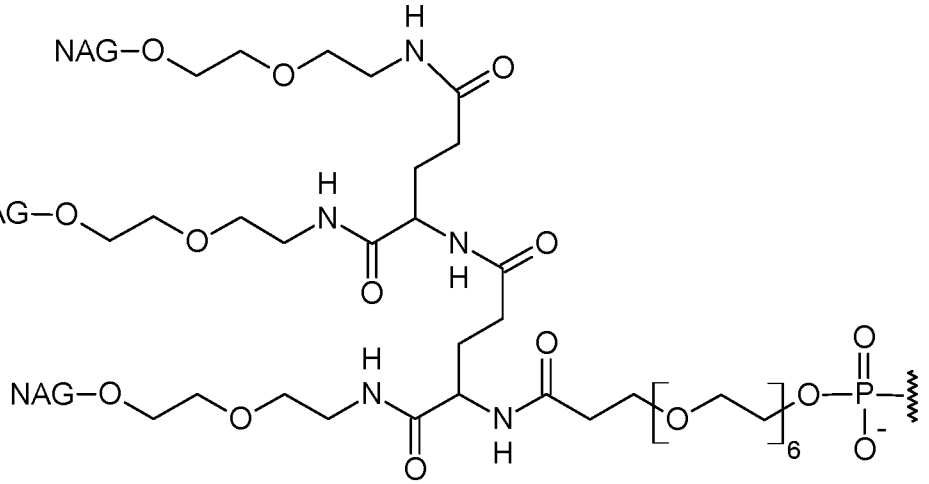
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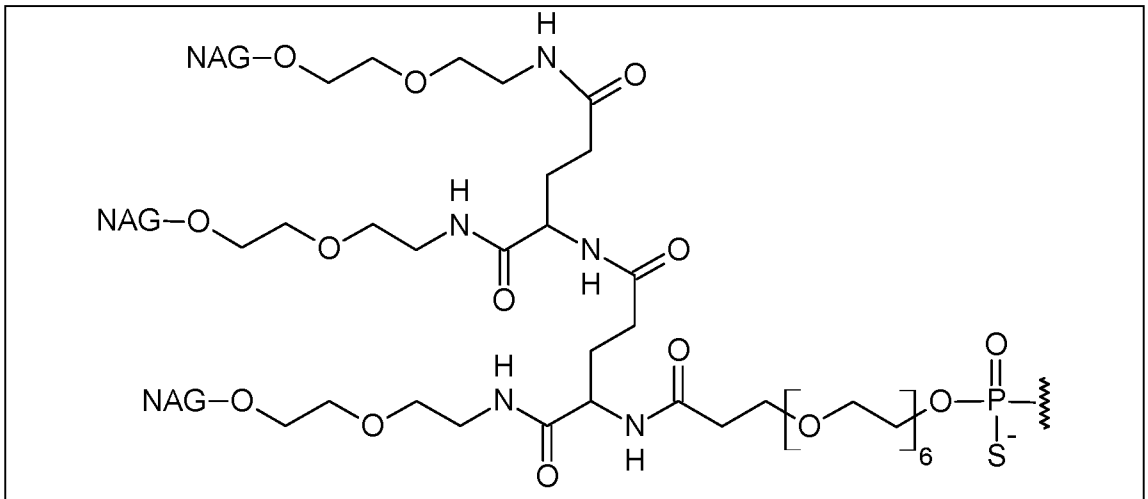
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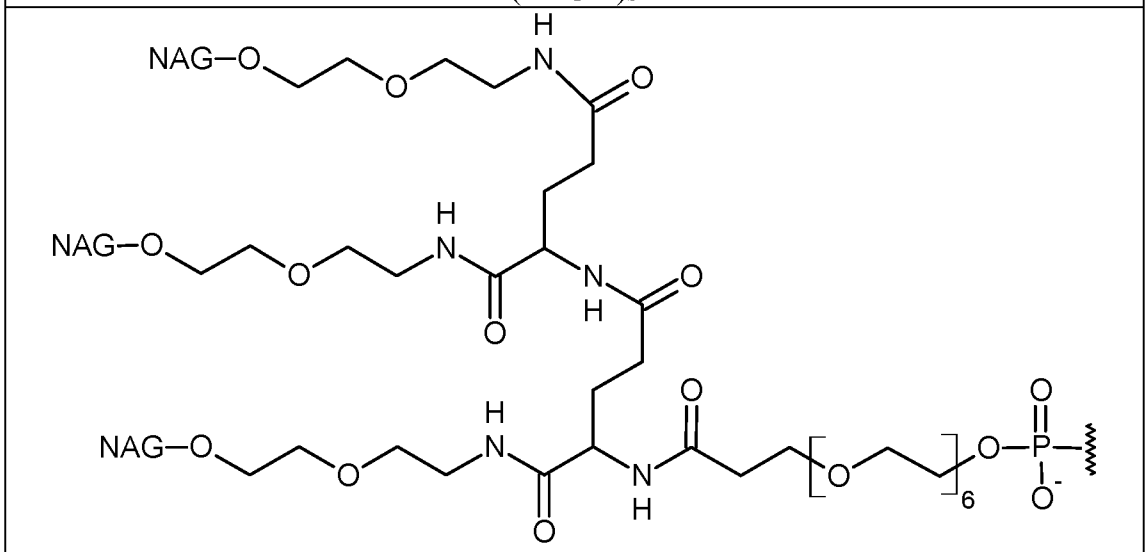
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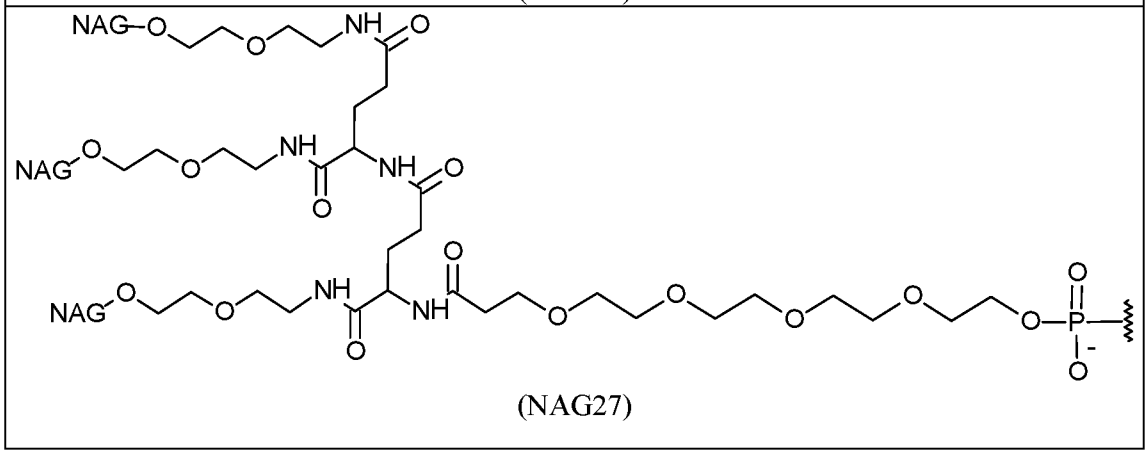
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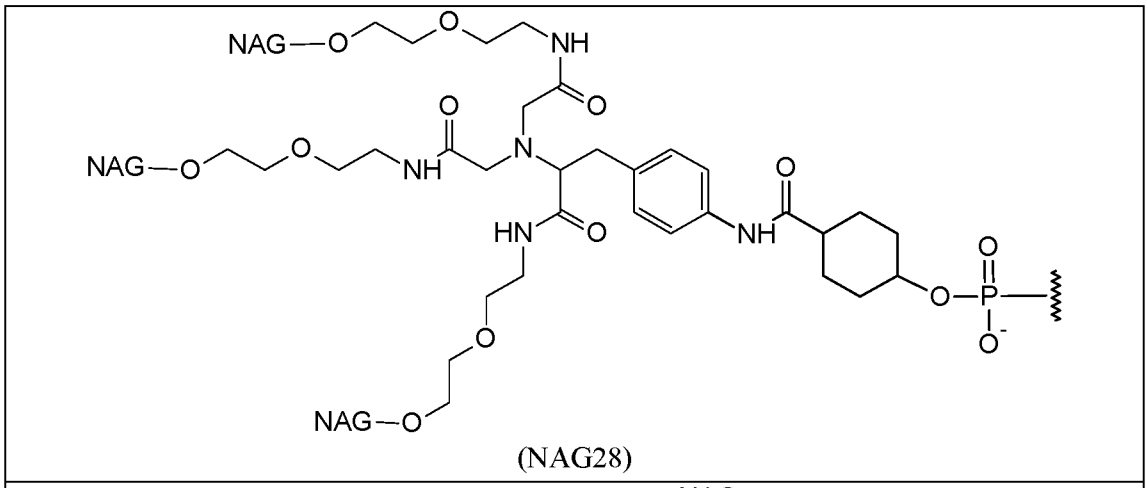
(NAG25)s



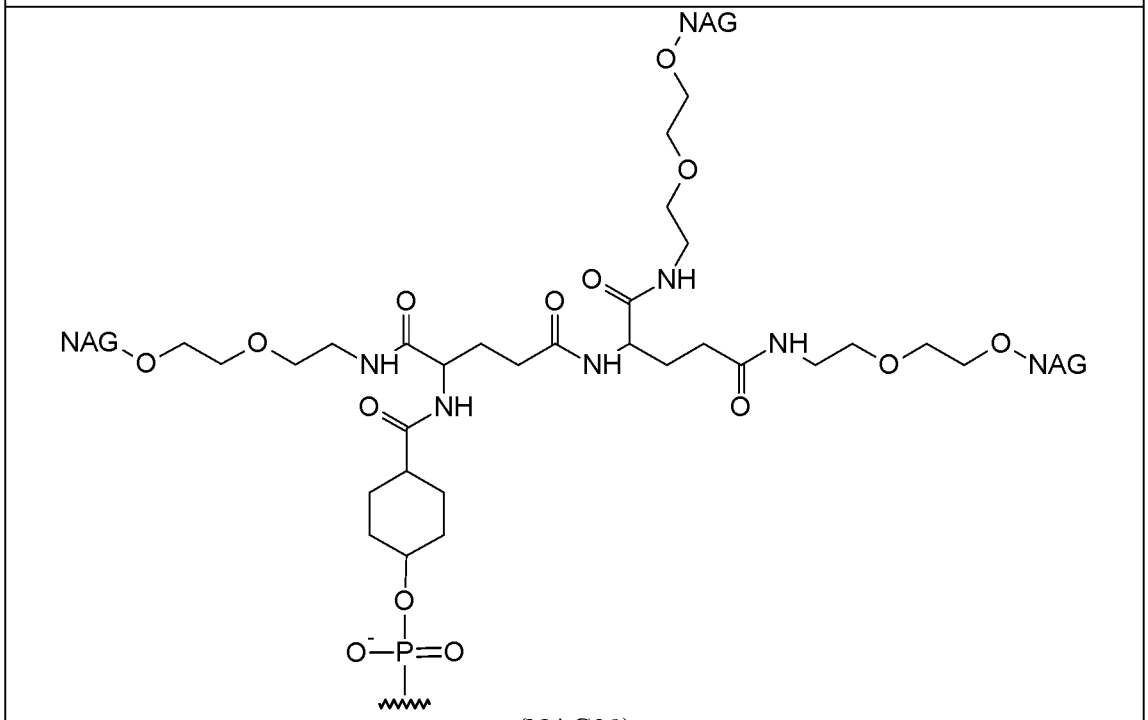
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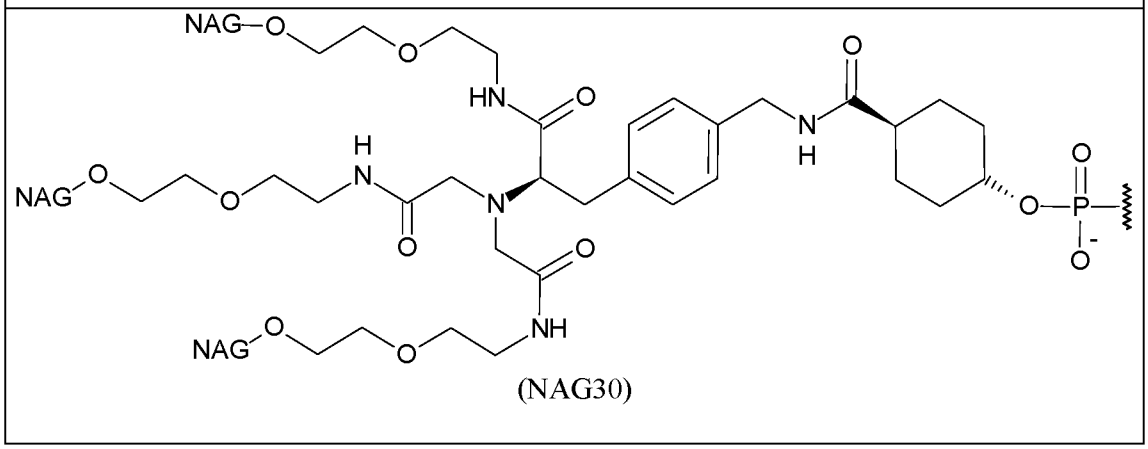
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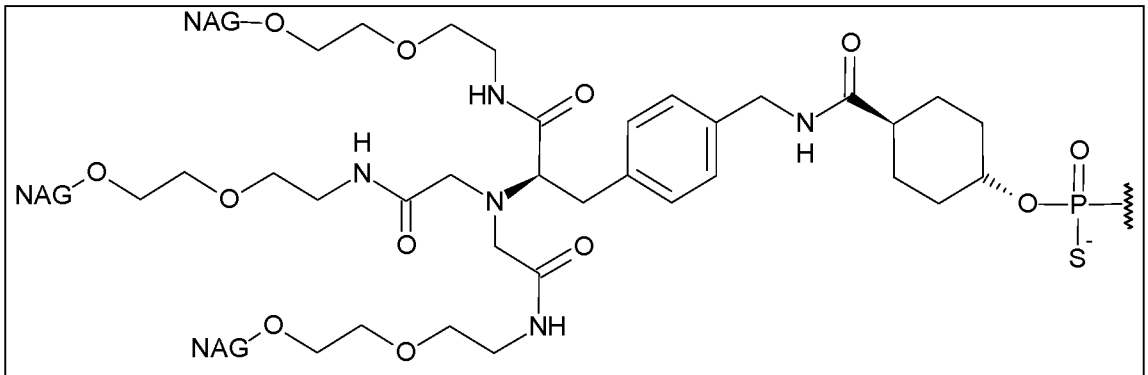
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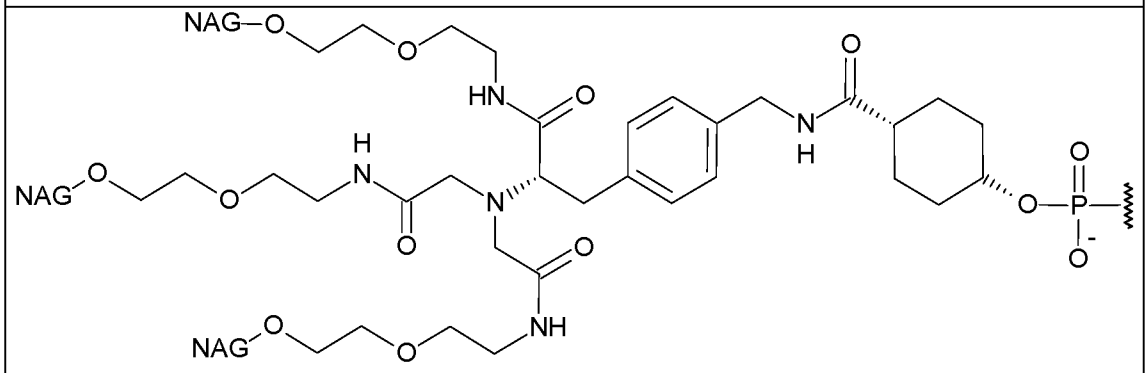
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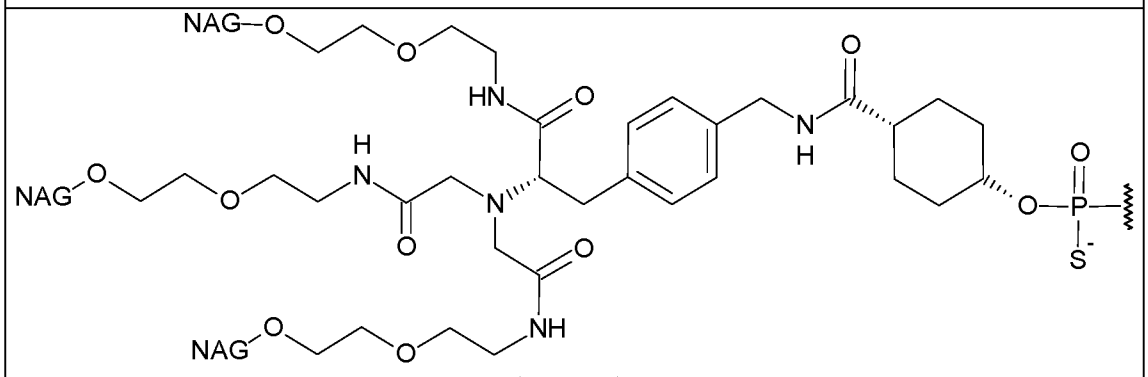
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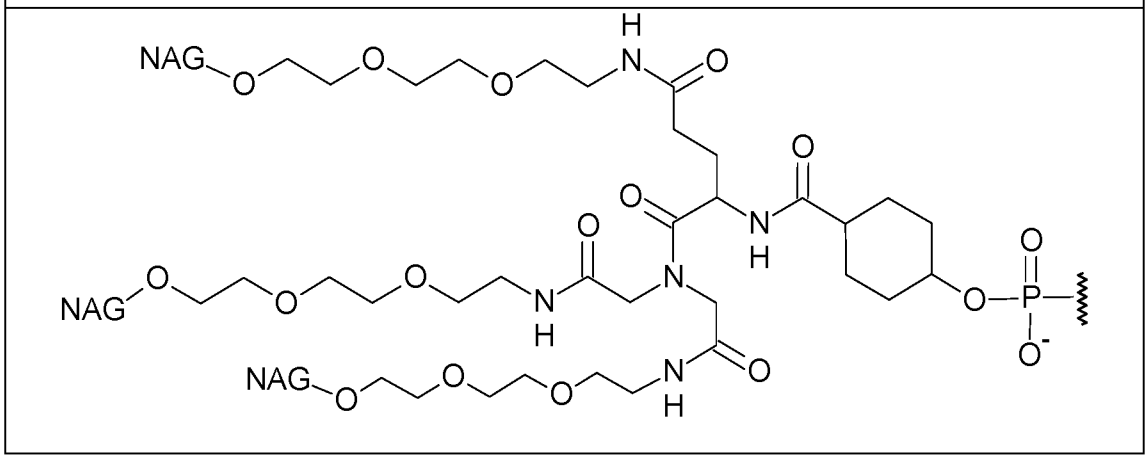
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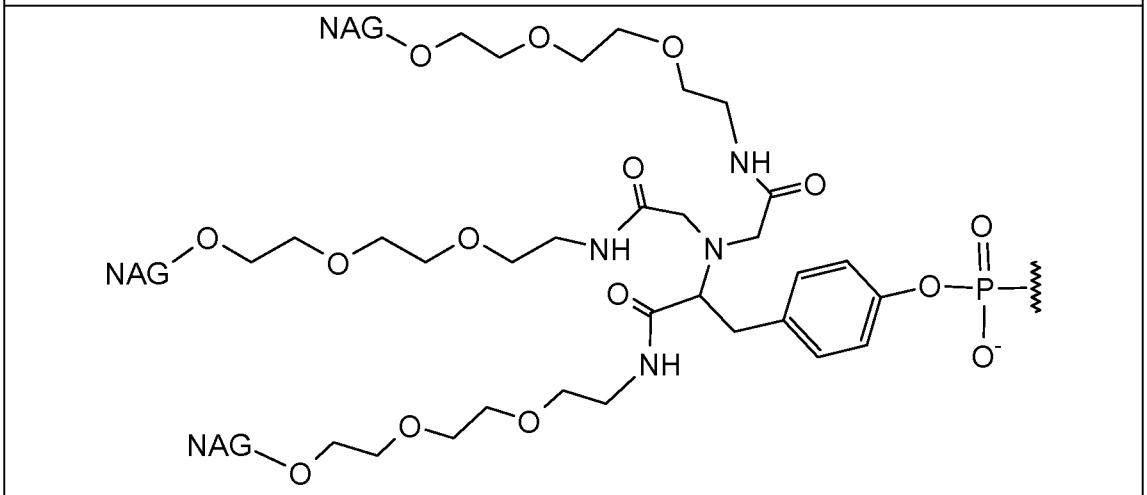
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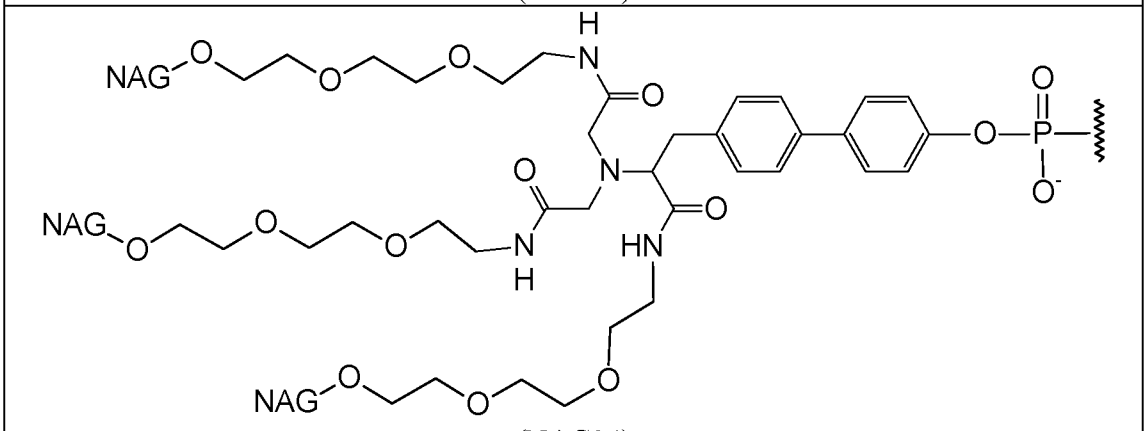
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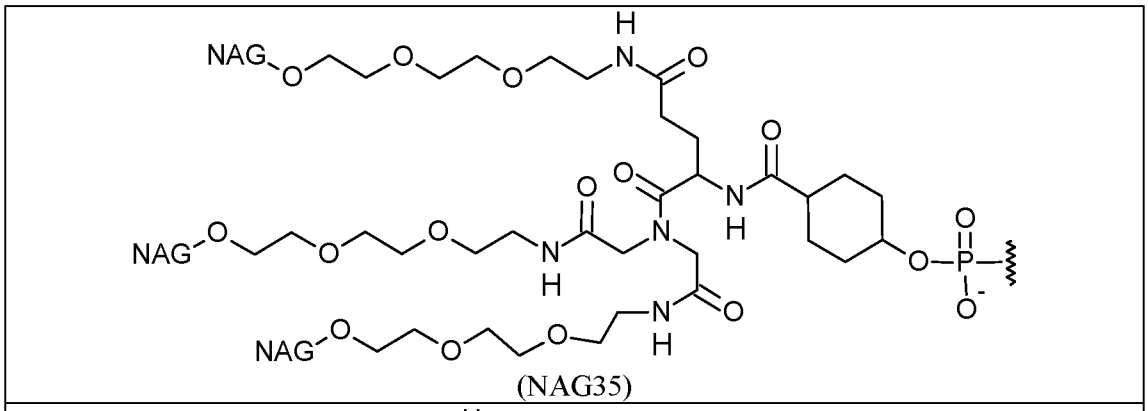
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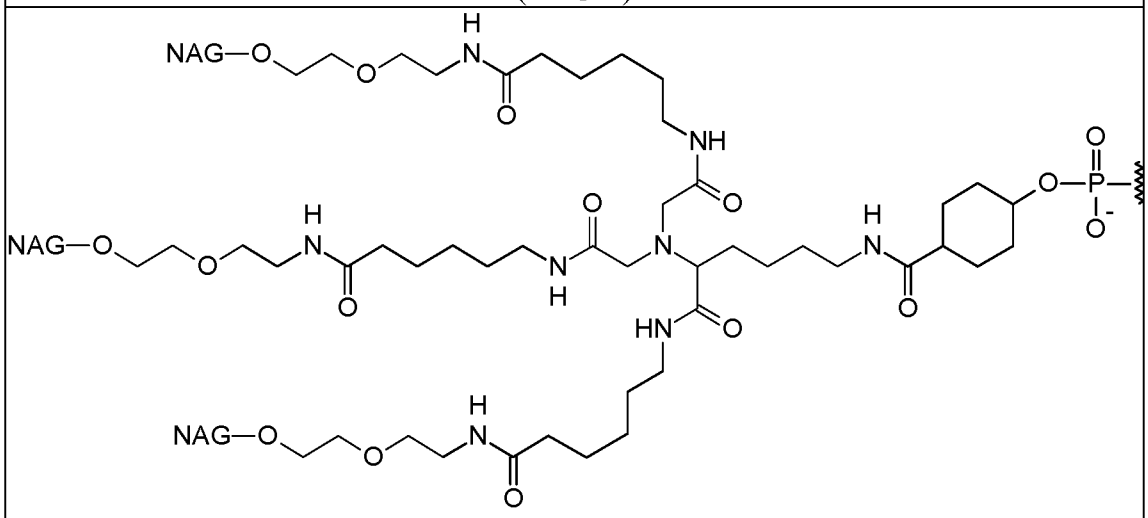
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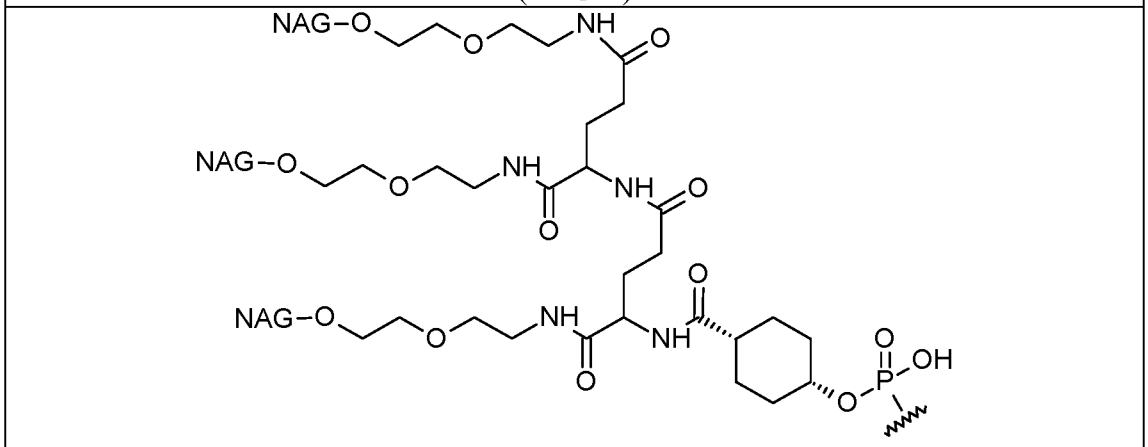
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(NAG35)

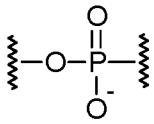


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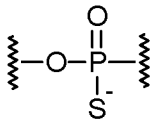


(NAG37)

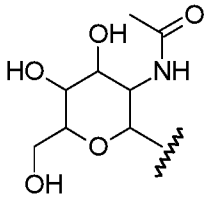
In each of the above structures, NAG comprises an N-Acetyl-Galactosamine or another ASGPR ligand. Each (NAGx) may be attached to an LPA RNAi agent via a phosphate group (as in (NAG25), (NAG30), and (NAG31)), or a phosphorothioate group, (as is (NAG25)s, (NAG30)s, and (NAG31)s), or another linking group. Alternatively, other linking groups known in the art may be used.



Phosphate group



phosphorothioate group



N-Acetyl galactosamine

Delivery Vehicles

In some embodiments, a delivery vehicle may be used to deliver an RNAi agent to a cell or tissue. A delivery vehicle is a compound that improves delivery of the RNAi agent to a cell or tissue. A delivery vehicle can include, or consist of, but is not limited to: a polymer, such as an amphipathic polymer, a membrane active polymer, a peptide, a melittin peptide, a melittin-like peptide (MLP), a lipid, a reversibly modified polymer or peptide, or a reversibly modified membrane active polyamine.

In some embodiments, the RNAi agents can be combined with lipids, nanoparticles, polymers, liposomes, micelles, DPCs or other delivery systems available in the art. The RNAi agents can also be chemically conjugated to targeting groups, lipids (including, but not limited to cholesterol and cholesteryl derivatives), nanoparticles, polymers, liposomes, micelles, DPCs (see, for example WO 2000/053722, WO 2008/0022309, WO 2011/104169, and WO 2012/083185, WO 2013/032829, WO 2013/158141, each of which is incorporated herein by reference), or other delivery systems available in the art.

Pharmaceutical Compositions

Described herein are methods for delivering LPA RNAi agents to liver cells in a mammal *in vivo*. In some embodiments, a delivery vehicle may be used. A delivery vehicle is a compound which improves delivery of the RNAi agent to the cell. A delivery vehicle can be, but is not limited to: a polymer, such as an amphipathic polymer, membrane active polymer, a peptide, such as a melittin or melittin-like peptide, a reversibly modified polymer or peptide, or a lipid. In some embodiments, an LPA RNAi agent is linked to a targeting ligand that comprises an asialoglycoprotein ligand. In some embodiments, an LPA RNAi agent is linked to a targeting ligand that comprises or consists of a galactose cluster.

An LPA RNAi agent can be used to inhibit expression of LPA in a cell, group of cells, or a

tissue, e.g., in a subject. In some embodiments, an LPA RNAi agent is used to formulate a composition, i.e. a pharmaceutical composition or medicament, for administering to a subject. As used herein, a pharmaceutical composition or medicament comprises a pharmacologically effective amount of at least one of the described LPA RNAi agents and one or more pharmaceutically acceptable excipients. Pharmaceutically acceptable excipients (excipients) are substances other than the Active Pharmaceutical ingredient (API, therapeutic product, e.g., LPA RNAi agent) that have been appropriately evaluated for safety and are intentionally included in the drug delivery system. Excipients do not exert or are not intended to exert a therapeutic effect at the intended dosage. Excipients may act to a) aid in processing of the drug delivery system during manufacture, b) protect, support or enhance stability, bioavailability or patient acceptability of the API, c) assist in product identification, and/or d) enhance any other attribute of the overall safety, effectiveness, of delivery of the API during storage or use. A pharmaceutically acceptable excipient may or may not be an inert substance.

Excipients include, but are not limited to: absorption enhancers, anti-adherents, anti-foaming agents, anti-oxidants, binders, buffering agents, carriers, coating agents, colors, delivery enhancers, delivery polymers, dextran, dextrose, diluents, disintegrants, emulsifiers, extenders, fillers, flavors, glidants, humectants, lubricants, oils, polymers, preservatives, saline, salts, solvents, sugars, suspending agents, sustained release matrices, sweeteners, thickening agents, tonicity agents, vehicles, water-repelling agents, and wetting agents.

A pharmaceutical composition can contain other additional components commonly found in pharmaceutical compositions. Such additional components include, but are not limited to: anti-pruritics, astringents, local anesthetics, or anti-inflammatory agents (e.g., antihistamine, diphenhydramine, etc.). It is also envisioned that cells, tissues or isolated organs that express or comprise the herein defined RNAi agents may be used as "pharmaceutical compositions". As used herein, "pharmacologically effective amount," "therapeutically effective amount," or simply "effective amount" refers to that amount of an RNAi agent to produce the intended pharmacological, therapeutic or preventive result.

In some embodiments, a described LPA RNAi agent is combined one or more additional therapeutics or treatments including, but not limited to: a second LPA RNAi agent or other RNAi agent, a small molecule drug, an antibody, an antibody fragment, and/or a vaccine. Examples of additional therapeutics include, but are not limited to, HMg Co-A reductase

inhibitors (statins), ezetimibe, PCSK-9 inhibitors, CTEP inhibitors, therapies targeting ANGPTL3, therapies targeting APOC3, and niacin.

The described RNAi agents and pharmaceutical compositions comprising LPA RNAi agents disclosed herein may be packaged or included in a kit, container, pack, or dispenser. The LPA RNAi agents and pharmaceutical compositions comprising said LPA RNAi agents may be packaged in pre-filled syringes or vials.

In some embodiments, pharmaceutical compositions comprising at least one of the described LPA RNAi agents are contemplated. These pharmaceutical compositions are useful in the inhibition of the expression of the LPA gene in a cell, a tissue, or an organism. In some embodiments, the described pharmaceutical compositions are used to treat a subject having a disease, condition, or disorder that would benefit from reduction or inhibition in LPA expression. In some embodiments, the described pharmaceutical compositions are used to treat a subject at risk of developing a disease, condition, or disorder that would benefit from reduction or inhibition in LPA expression. Diseases, conditions, or disorders that would benefit from reduction or inhibition in LPA expression include, but are not limited to: Berger's disease, peripheral artery disease, coronary artery disease, metabolic syndrome, acute coronary syndrome, aortic valve stenosis, aortic valve regurgitation, aortic dissection, retinal artery occlusion, cerebrovascular disease, mesenteric ischemia, superior mesenteric artery occlusion, renal artery stenosis, stable/unstable angina, acute coronary syndrome, heterozygous or homozygous familial hypercholesterolemia, hyperapobetalipoproteinemia, cerebrovascular atherosclerosis, cerebrovascular disease, and venous thrombosis. In some embodiments, the subject is a mammal, including, but not limited to, a human patient.

Cells, tissues, and non-human organisms that include at least one of the LPA RNAi agents described herein is contemplated. The cell, tissue, or non-human organism is made by delivering the RNAi agent to the cell, tissue, or non-human organism by any means available in the art. In some embodiments, the cell is a mammalian cell, including, but not limited to, a human cell. The cell, tissue, or non-human organisms are useful for research or as research tools (e.g., drug testing or diagnoses).

Method of Treatment

In some embodiments, the LPA RNAi agents described herein are used to treat a subject having a disease, condition, or disorder or at risk of having a disease, condition, or disorder that would benefit from reduction or inhibition in LPA expression. Treatment of a subject that would benefit from a reduction and/or inhibition of LPA gene expression includes therapeutic and/or prophylactic treatment. Examples of diseases, conditions, or disorders, include, but not limited to: Berger's disease, peripheral artery disease, coronary artery disease, metabolic syndrome, acute coronary syndrome, aortic valve stenosis, aortic valve regurgitation, aortic dissection, retinal artery occlusion, cerebrovascular disease, mesenteric ischemia, superior mesenteric artery occlusion, renal artery stenosis, stable/unstable angina, acute coronary syndrome, heterozygous or homozygous familial hypercholesterolemia, hyperapobetalipoproteinemia, cerebrovascular atherosclerosis, cerebrovascular disease, and venous thrombosis. In some embodiments, the method comprises administering a composition, such as a pharmaceutical composition, comprising an LPA RNAi agent described herein to a mammal to be treated.

In some embodiments, a therapeutically effective amount of one or more of the described LPA RNAi agents is administered to a subject, thereby inhibiting expression of LPA in the subject (e.g., an amount effective to inhibit expression of LPA in the subject). In some embodiments, one or more of the LPA RNAi agents described herein are used to treat a subject having a disease or disorder that would benefit from reduction or inhibition in LPA expression. In some embodiments, the described LPA RNAi agents are used to treat or prevent at least one symptom in a subject having a disease or disorder that would benefit from reduction or inhibition in LPA expression. The subject is administered a therapeutically effective amount of any one or more of the described RNAi agents thereby treating the symptom. In some embodiments, the subject is administered a prophylactically effective amount of any one or more of the described RNAi agents thereby preventing the at least one symptom.

In some embodiments, an LPA RNAi agent is used to treat or manage a clinical presentation wherein a subject in need of such treatment, prevention, or management is administered a therapeutically or prophylactically effective amount of one or more of the LPA RNAi agents or LPA RNAi agent-containing compositions described herein. In some embodiments, the method comprises administering a composition comprising an LPA RNAi agent described herein to a mammal to be treated.

In some embodiments, the methods further comprise the step of administering a second therapeutic or treatment. In some embodiments, the second therapeutic is another LPA RNAi agent (e.g., a *LPA* RNAi agent which targets a different sequence within the *LPA* target). In other embodiments, the second therapeutic can be selected from the group comprising: small molecule drug, antibody, antibody fragment, and vaccine.

The route of administration is the path by which an RNAi agent is brought into contact with the body. In general, methods of administering drugs and nucleic acids for treatment of a subject are well known in the art and can be applied to administration of the compositions described herein. The compounds described herein can be administered via any suitable route in a preparation appropriately tailored to the particular route. Thus, the compounds described herein can be administered by injection, for example, intravenously, intramuscularly, intracutaneously, subcutaneously, or intraperitoneally.

In some embodiments, the LPA RNAi agents or compositions described herein can be delivered to a cell, group of cells, tissue, or subject using oligonucleotide delivery technologies known in the art. In general, any suitable method recognized in the art for delivering a nucleic acid molecule (in vitro or in vivo) can be adapted for use with an LPA RNAi agent described herein. For example, delivery can be by local administration, (e.g., direct injection, implantation, or topical administering), systemic administration, or subcutaneous, intravenous, oral, intraperitoneal, or parenteral routes, including intracranial (e.g., intraventricular, intraparenchymal and intrathecal), intramuscular, transdermal, airway (aerosol), nasal, rectal, or topical (including buccal and sublingual) administration, In certain embodiments, the compositions are administered by subcutaneous or intravenous infusion or injection.

In some embodiments, the RNAi agents can be combined with lipids, nanoparticles, polymers, liposomes, micelles, DPCs or other delivery systems available in the art. The RNAi agents can also be chemically conjugated to targeting groups, lipids (including, but not limited to cholesterol and cholesteryl derivatives), nanoparticles, polymers, liposomes, micelles, DPCs (se e.g., WO 2000/053722, WO 2008/0022309, WO 2011/104169, and WO 2012/083185, each of which is incorporated herein by reference), or other delivery systems available in the art.
An LPA RNAi agent can be conjugated to a delivery polymer. In some embodiments, the delivery polymer is a reversibly masked/modified amphipathic membrane active polyamine.

Inhibition of expression

As used herein, the terms "silence," "reduce," "inhibit," "down-regulate," or "knockdown gene expression," when referring to an LPA gene, mean that the expression of the gene, as measured by the level of RNA transcribed from the gene or the level of polypeptide, protein, or protein subunit translated from the mRNA in a cell, group of cells, or tissue, in which the LPA gene is transcribed, is reduced when the cell, group of cells, or tissue, is treated with the described LPA RNAi agents as compared to a second cell, group of cells, or tissue that has or has not been so treated or compared to the same cell, group of cells, or tissue, prior to administration of the LPA RNAi agent.

In some embodiments, the gene expression level and/or mRNA level of LPA in a subject to whom a described LPA RNAi agent is administered is reduced by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 98% relative to the subject prior to being administered the LPA RNAi agent or to a subject not receiving the LPA RNAi agent. The gene expression level and/or mRNA level in the subject may be reduced in a cell, group of cells, and/or tissue of the subject. In some embodiments, the protein level of LPA in a subject to whom a described LPA RNAi agent has been administered is reduced by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 98% relative to the subject prior to being administered the LPA RNAi agent or to a subject not receiving the LPA RNAi agent. The protein level in the subject may be reduced in a cell, group of cells, tissue, blood, and/or other fluid of the subject. A reduction in gene expression, mRNA, or protein levels can be assessed by any methods known in the art. Reduction or decrease in LPA mRNA level and/or protein level are collectively referred to herein as a reduction or decrease in LPA or inhibiting or reducing the expression of LPA.

Introducing into a cell, when referring to an RNAi agent, means functionally delivering the RNAi agent into the cell. By functional delivery, it is meant that the RNAi agent is delivered to the cell and has the expected biological activity, (e.g., sequence-specific inhibition of gene expression).

Cells and Tissues and non-Human organisms

Cells, tissues, and non-human organisms that include at least one of the LPA RNAi agents described herein is contemplated. The cell, tissue, or non-human organism is made by

delivering the RNAi agent to the cell, tissue, or non-human organism.

The above provided embodiments and items are now illustrated with the following, non-limiting examples.

EXAMPLES

Example 1. *RNAi agent synthesis.*

A) Synthesis. LPA RNAi agents were synthesized according to phosphoramidite technology on solid phase used in oligonucleotide synthesis. Depending on the scale either a MerMade96E (Bioautomation) or a MerMade12 (Bioautomation) was used. Syntheses were performed on a solid support made of controlled pore glass (CPG, 500 Å or 600Å, obtained from Prime Synthesis, Aston, PA, USA). All DNA, 2′-modified RNA, and UNA phosphoramidites were purchased from Thermo Fisher Scientific (Milwaukee, WI, USA). Specifically, the following 2′-O-Methyl phosphoramidites were used: (5′-O-dimethoxytrityl-N^6-(benzoyl)-2′-O-methyl-adenosine-3′-O-(2-cyanoethyl-N,N-diisopropy-lamino) phosphoramidite, 5′-O-dimethoxy-trityl-N^4-(acetyl)-2′-O-methyl-cytidine-3′-O-(2-cyanoethyl-N,N-diisopropyl-amino) phosphoramidite, (5′-O-dimethoxytrityl-N^2-(isobutyryl)-2′-O-methyl-guanosine-3′-O-(2-cyano-ethyl-N,N-diisopropylamino)phosphoramidite, and 5′-O-dimethoxy-trityl-2′-O-methyl-uridine-3′-O-(2-cyanoethyl-N,N-diisopropylamino)phosphoramidite. The 2′-Deoxy-2′-fluoro-phosphor-amidites carried the same protecting groups as the 2′-O-methyl RNA amidites. The following UNA phosphoramidites were used: 5′-(4,4'-Dimethoxytrityl)-N-benzoyl-2′,3′-seco-adenosine, 2′-benzoyl-3′-[(2-cyanoethyl)-(N,N-diisopropyl)]-phosphor-amidite, 5′-(4,4'-Dimethoxytrityl)-N-acetyl-2′,3′-seco-cytosine, 2′-benzoyl-3′-[(2-cyanoethyl)-(N,N-diiso-propyl)]-phosphoramidite, 5′-(4,4'-Dimethoxytrityl)-N-isobutyryl-2′,3′-seco-guanosine, 2′-benzoyl-3′-[(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite, and 5′-(4,4'-Dimethoxy-trityl)-2′,3′-seco-uridine, 2′-benzoyl-3′-[(2-cyanoethyl)-(N,N- diiso-propyl)]-phosphoramidite. All amidites were dissolved in anhydrous acetonitrile (50 mM) and molecular sieves (3Å) were added. In order to introduce the TEG-Cholesterol at the 5′-end of the oligomers, the 1-Dimethoxytrityloxy-3-O-(N-cholesteryl-3-aminopropyl)-triethyleneglycol-glyceryl-2-O-(2-cyanoethyl)-(N,N,-diisopropyl)-phosphoramidite from Glen Research (Sterling, VA, USA) was employed. The 5′-modifications were introduced without any modification of the synthesis cycle. 5-Benzylthio-1H-tetrazole (BTT, 250 mM in acetonitrile) was used as activator solution. Coupling times were 10 min (RNA), 180 sec (Cholesterol), 90 sec (2′OMe and UNA), and 60 sec (2′F and DNA). In order to introduce phosphorothioate linkages, a 100 mM solution of

3-phenyl 1,2,4-dithiazoline-5-one (POS, obtained from PolyOrg, Inc., Leominster, MA, USA) in anhydrous Acetonitrile was employed. See Tables 1, 2A, and 2B for specific sequences.

B. Cleavage and deprotection of support bound oligomer. After finalization of the solid phase synthesis, the dried solid support was treated with a 1:1 volume solution of 40 wt. % methylamine in water and 28% ammonium hydroxide solution (Aldrich) for two hours at 30°C. The solution was evaporated and the solid residue was reconstituted in water (see below).

C. Purification. Crude Cholesterol containing oligomers were purified by reverse phase HPLC using a Waters XBridge BEH300 C4 5u Prep column and a Shimadzu LC-8 system. Buffer A was 100 mM TEAA, pH 7.5 and contained 5% Acetonitrile and buffer B was 100 mM TEAA and contained 95% Acetonitrile. UV traces at 260 nm were recorded. Appropriate fractions were then run on size exclusion HPLC using a GE Healthcare XK 16/40 column packed with Sephadex G-25 medium with a running buffer of 100mM ammonium bicarbonate, pH 6.7 and 20% Acetonitrile. Other crude oligomers were purified by anionic exchange HPLC using a TKSgel SuperQ-5PW 13u column and Shimadzu LC-8 system. Buffer A was 20 mM Tris, 5 mM EDTA, pH 9.0 and contained 20% Acetonitrile and buffer B was the same as buffer A with the addition of 1.5 M sodium chloride. UV traces at 260 nm were recorded. Appropriate fractions were pooled then run on size exclusion HPLC as described for cholesterol containing oligomers.

D. Annealing. Complementary strands were mixed by combining equimolar solutions (sense and antisense) in 0.2× PBS (Phosphate-Buffered Saline, 1×, Corning, Cellgro) to form the RNAi agents. This solution was placed into a thermomixer at 70°C, heated to 95°C, held at 95°C for 5 min, and cooled to room temperature slowly. Some RNAi agents were lyophilized and stored at −15 to −25°C. Duplex concentration was determined by measuring the solution absorbance on a UV-Vis spectrometer in 0.2× PBS. The solution absorbance at 260 nm was then multiplied by a conversion factor and the dilution factor to determine the duplex concentration. Unless otherwise stated, all conversion factor was 0.037 mg/(mL·cm). For some experiments, a conversion factor was calculated from an experimentally determined extinction coefficient.

Example 2. *Primary in vitro analysis of LPA RNAi agents.* Candidate sequences identified as human and non-human primate cross-reactive by in silico analysis were screened. 108 in silico-

identified potential LPA RNAi agents were synthesized and screened for efficacy in vitro in three groups. For screening purposes, the human LPA cDNA sequence (accession # NM_005577.1) was sub-cloned from a commercially available mammalian expression vector (Origene, Rockville, MD) into a commercially-available, reporter-based screening plasmid, psiCHECK2 (Promega, Madison, WI) which generated a Renilla luciferase/LPA fusion mRNA. For LPA RNAi agent efficacy in the human background, Hep3B cells, a human hepatocellular carcinoma line, were plated at ~10,000 cells per well in 96-well format. Each of the 108 LPA RNAi agents was co-transfected at two or three concentrations (1 nM and 0.1 nM, or 0.02, 0.2 and 2 nM) with 50-100 ng LPA-psiCHECK2 plasmid DNA per well and 0.2 µL LipoFectamine 2000 per well. Gene knockdown was determined by measuring Renilla luciferase levels normalized to the levels of constitutively-expressed firefly luciferase, also present on the psiCHECK2 plasmid, using the Dual Luciferase Reporter Assay (Promega, Madison, WI) (Tables 5A and 5B).

Table 5A. *In vitro* analyses of LPA RNAi agents, inhibition of LPA expression.

Duplex ID#	Relative R_{luc}-LPA expression				Duplex ID#	Relative R_{luc}-LPA expression			
	1nM		0.1nM			1nM		0.1nM	
	Average	SD	Average	SD		Average	SD	Average	SD
AD00571	1.012	0.146	1.107	0.174	AD00605	1.006	0.193	1.006	0.146
AD00572	0.776	0.062	1.075	0.089	AD00606	0.509	0.039	0.570	0.054
AD00573	0.708	0.054	0.708	0.134	AD00607	0.816	0.091	0.906	0.068
AD00574	0.441	0.028	0.525	0.056	AD00608	0.883	0.111	1.158	0.054
AD00575	0.242	0.038	0.365	0.035	AD00609	0.515	0.079	0.691	0.137
AD00576	0.166	0.047	0.341	0.073	AD00610	0.628	0.057	0.748	0.090
AD00577	0.702	0.115	0.934	0.036	AD00611	1.320	0.066	1.116	0.046
AD00578	0.272	0.008	0.599	0.200	AD00612	1.103	0.193	1.100	0.052
AD00579	0.290	0.031	0.447	0.066	AD00613	0.910	0.094	0.878	0.040
AD00580	0.825	0.145	0.991	0.123	AD00614	1.101	0.111	1.097	0.043
AD00581	0.654	0.095	0.986	0.127	AD00615	1.051	0.140	0.898	0.161
AD00582	0.610	0.178	0.791	0.244	AD00616	0.898	0.101	1.029	0.042
AD00583	0.824	0.208	0.845	0.240	AD00617	0.715	0.023	0.802	0.150
AD00584	0.800	0.150	0.683	0.077	AD00618	0.434	0.073	0.441	0.199
AD00585	0.387	0.059	0.488	0.151	AD00619	0.758	0.003	0.820	0.165
AD00586	0.754	0.116	0.927	0.103	AD00620	0.984	0.124	0.926	0.080
AD00587	0.921	0.074	0.923	0.052	AD00621	0.308	0.033	0.267	0.044
AD00588	0.763	0.203	0.954	0.169	AD00622	0.493	0.072	0.790	0.009
AD00589	0.838	0.115	1.026	0.216	AD00623	0.641	0.081	0.599	0.014
AD00590	0.959	0.091	0.991	0.285	AD00624	0.795	0.019	0.985	0.123
AD00591	0.970	0.172	0.984	0.244	AD00625	0.768	0.121	0.944	0.117
AD00592	0.600	0.060	0.886	0.069	AD00626	0.981	0.081	1.036	0.036
AD00593	0.555	0.097	0.883	0.130	AD00627	0.943	0.163	0.936	0.038

AD00594	0.645	0.056	0.567	0.008	AD00628	0.765	0.069	0.995	0.090
AD00595	0.812	0.132	1.076	0.285	AD00629	1.001	0.184	1.199	0.064
AD00596	0.658	0.116	0.787	0.153	AD00630	0.963	0.149	1.154	0.141
AD00597	0.999	0.120	1.083	0.143	AD00631	0.979	0.084	1.038	0.088
AD00598	0.501	0.067	0.631	0.036	AD00632	0.781	0.048	0.858	0.101
AD00599	0.890	0.098	0.871	0.143	AD00633	0.817	0.072	1.027	0.143
AD00600	0.393	0.018	0.729	0.172	AD00634	0.807	0.087	0.978	0.256
AD00601	0.896	0.180	1.142	0.140	AD00635	0.496	0.073	0.377	0.023
AD00602	0.653	0.134	0.955	0.062	AD00636	0.615	0.102	0.748	0.072
AD00603	0.730	0.118	0.799	0.187	AD00637	0.792	0.056	1.070	0.048
AD00604	0.892	0.058	0.956	0.107					

Table 5B. *In vitro* analyses of LPA RNAi agents, inhibition of LPA expression.

Duplex ID#	Relative R_{luc}-LPA expression					
	2nM		0.2nM		0.02nM	
	Average	SD	Average	SD	Average	SD
AD01068	0.780	0.110	0.792	0.326	0.861	0.138
AD01069	0.483	0.345	1.062	0.181	0.869	0.112
AD01070	0.747	0.441	1.010	0.015	1.015	0.319
AD01071	1.014	0.254	0.850	0.251	0.857	0.284
AD01072	0.919	0.107	1.137	0.345	0.727	0.124
AD01073	0.539	0.224	1.066	0.195	1.180	0.356
AD01074	0.713	0.545	0.953	0.419	0.841	0.077
AD01075	0.703	0.379	0.913	0.204	0.965	0.216
AD01076	1.145	0.485	1.027	0.287	0.647	0.154
AD01077	0.672	0.074	1.166	0.384	0.703	0.106
AD01078	0.575	0.192	0.847	0.237	0.908	0.071
AD01079	0.863	0.673	1.093	0.187	1.004	0.086
AD01328	0.623	0.089	1.205	0.367	1.238	0.089
AD01329	0.467	0.068	1.161	0.159	1.115	0.102
AD01330	1.158	0.124	0.920	0.143	1.156	0.107
AD01331	1.476	0.225	1.092	0.269	1.304	0.320
AD01332	1.145	0.109	1.100	0.454	0.941	0.510
AD01333	0.829	0.011	1.382	0.252	1.338	0.303
AD01334	0.653	0.122	1.323	0.183	1.095	0.109
AD01335	0.858	0.089	1.632	0.318	1.201	0.159
AD01336	1.019	0.081	1.724	0.353	1.008	0.072
AD01337	0.834	0.143	1.494	0.657	1.130	0.309
AD01338	1.276	0.340	0.719	0.118	0.896	0.118
AD01339	1.240	0.298	1.114	0.287	0.960	0.104
AD01340	1.055	0.423	1.272	0.136	1.338	0.299
AD01341	1.206	0.438	1.510	0.315	1.046	0.143
AD01342	1.243	0.324	1.137	0.298	1.159	0.047
AD01343	1.113	0.140	1.045	0.151	1.108	0.094
AD01344	0.931	0.182	1.317	0.244	1.328	0.037
AD01345	0.795	0.233	0.799	0.032	1.418	0.184
AD01346	1.095	0.224	1.045	0.073	1.465	0.109
AD01347	1.122	0.021	1.209	0.161	1.153	0.159

AD01348	1.022	0.068	1.228	0.244	1.097	0.049
AD01349	0.934	0.151	1.217	0.080	1.068	0.149
AD01350	0.871	0.295	1.318	0.225	0.942	0.395
AD01351	1.414	0.065	1.121	0.180	1.029	0.049
AD01352	0.868	0.088	1.024	0.385	1.049	0.176
AD01353	1.150	0.478	1.164	0.276	0.898	0.175
AD01354	0.999	0.119	1.378	0.292	1.507	0.289
AD01355	0.943	0.092	1.066	0.268	1.411	0.113
AD01356	1.116	0.351	1.072	0.196	1.000	0.145

Table 5C. *In vitro* analyses of 10 mM LPA RNAi agents, inhibition of LPA expression.

Duplex No.	LPA levels	Duplex No.	LPA levels	Duplex No.	LPA levels
AD01803	0.77 ± 0.06	AD01827	1.23 ± 0.07	AD01921	0.59 ± 0.06
AD01805	0.77 ± 0.02	AD01828	1.02 ± 0.09	AD01922	0.50 ± 0.04
AD01806	1.01 ± 0.02	AD01829	1.05 ± 0.07	AD01923	0.59 ± 0.04
AD01807	0.97 ± 0.09	AD01830	1.00 ± 0.35	AD01924	0.50 ± 0.02
AD01808	0.78 ± 0.12	AD01831	1.02 ± 0.07	AD01925	0.54 ± 0.05
AD01809	1.06 ± 0.13	AD01832	1.04 ± 0.06	AD01926	0.52 ± 0.05
AD01810	1.06 ± 0.05	AD01896	0.71 ± 0.14	AD01927	0.57 ± 0.04
AD01811	0.86 ± 0.05	AD01897	0.87 ± 0.10	AD01928	0.50 ± 0.06
AD01812	1.08 ± 0.04	AD01898	1.16 ± 0.03	AD01929	0.55 ± 0.04
AD01813	0.99 ± 0.13	AD01899	0.79 ± 0.11	AD01930	0.54 ± 0.06
AD01814	0.57 ± 0.05	AD01900	0.82 ± 0.06	AD01931	0.54 ± 0.07
AD01815	0.65 ± 0.00	AD01901	0.54 ± 0.04	AD01932	0.51 ± 0.01
AD01816	0.84 ± 0.08	AD01902	0.62 ± 0.00	AD01933	0.56 ± 0.06
AD01817	0.75 ± 0.10	AD01903	0.66 ± 0.08	AD01934	0.52 ± 0.08
AD01818	0.94 ± 0.07	AD01912	0.59 ± 0.01	AD01935	0.58 ± 0.03
AD01819	1.21 ± 0.08	AD01913	0.60 ± 0.04	AD01936	0.53 ± 0.02
AD01820	1.22 ± 0.12	AD01914	0.50 ± 0.03	AD01937	0.57 ± 0.04
AD01821	1.16 ± 0.01	AD01915	0.58 ± 0.08	AD01938	0.58 ± 0.03
AD01822	1.22 ± 0.04	AD01916	0.49 ± 0.04	AD01939	0.65 ± 0.05
AD01823	0.91 ± 0.05	AD01917	0.53 ± 0.04	AD01940	0.49 ± 0.03
AD01824	1.22 ± 0.13	AD01918	0.47 ± 0.04	AD01941	0.57 ± 0.02
AD01825	1.25 ± 0.05	AD01919	0.60 ± 0.02		
AD01826	1.18 ± 0.15	AD01920	0.60 ± 0.03		

Table 5D. *In vitro* analyses of 1 mM LPA RNAi agents, inhibition of LPA expression.

Duplex No.	LPA levels	Duplex No.	LPA levels	Duplex No.	LPA levels
AD01760	0.10 ± 0.01	AD02330	0.37 ± 0.01	AD02090	0.68 ± 0.04
AD01722	0.14 ± 0.01	AD02243	0.37 ± 0.02	AD02161	0.68 ± 0.04
AD01757	0.15 ± 0.00	AD02255	0.38 ± 0.02	AD02324	0.68 ± 0.02
AD01719	0.15 ± 0.00	AD02257	0.38 ± 0.00	AD02177	0.69 ± 0.07
AD01738	0.18 ± 0.01	AD02169	0.38 ± 0.02	AD02179	0.69 ± 0.07
AD01755	0.19 ± 0.01	AD02081	0.38 ± 0.00	AD02527	0.69 ± 0.03
AD01741	0.20 ± 0.00	AD02186	0.38 ± 0.02	AD02305	0.69 ± 0.06
AD01759	0.23 ± 0.02	AD01744	0.38 ± 0.03	AD02092	0.70 ± 0.02

AD01747	0.23 ± 0.03	AD02075	0.38 ± 0.01	AD02535	0.70 ± 0.10
AD01752	0.24 ± 0.03	AD02135	0.38 ± 0.03	AD02376	0.71 ± 0.04
AD01736	0.24 ± 0.02	AD02114	0.38 ± 0.04	AD01743	0.71 ± 0.02
AD02311	0.25 ± 0.05	AD02188	0.38 ± 0.04	AD02289	0.71 ± 0.04
AD02201	0.25 ± 0.03	AD02318	0.38 ± 0.02	AD02530	0.71 ± 0.06
AD01750	0.25 ± 0.00	AD02388	0.38 ± 0.02	AD01709	0.71 ± 0.12
AD01756	0.25 ± 0.01	AD02115	0.38 ± 0.04	AD02249	0.71 ± 0.06
AD02291	0.25 ± 0.03	AD02133	0.38 ± 0.00	AD02534	0.71 ± 0.03
AD02292	0.26 ± 0.01	AD02183	0.38 ± 0.04	AD02213	0.71 ± 0.02
AD02266	0.26 ± 0.02	AD02116	0.38 ± 0.02	AD02529	0.71 ± 0.03
AD01763	0.26 ± 0.01	AD02132	0.39 ± 0.03	AD01711	0.71 ± 0.06
AD02259	0.26 ± 0.03	AD02400	0.39 ± 0.02	AD02341	0.72 ± 0.06
AD02327	0.26 ± 0.02	AD02338	0.39 ± 0.04	AD02233	0.72 ± 0.06
AD02274	0.27 ± 0.03	AD02112	0.39 ± 0.01	AD02342	0.73 ± 0.04
AD02297	0.27 ± 0.02	AD02354	0.39 ± 0.05	AD02395	0.73 ± 0.06
AD02147	0.27 ± 0.03	AD01749	0.40 ± 0.06	AD02306	0.73 ± 0.09
AD02365	0.27 ± 0.04	AD02312	0.40 ± 0.02	AD02344	0.73 ± 0.04
AD02260	0.27 ± 0.03	AD02240	0.40 ± 0.00	AD02145	0.74 ± 0.09
AD02368	0.27 ± 0.01	AD02313	0.40 ± 0.03	AD02326	0.74 ± 0.06
AD02265	0.28 ± 0.03	AD01710	0.40 ± 0.05	AD02414	0.74 ± 0.04
AD02293	0.28 ± 0.04	AD02301	0.40 ± 0.05	AD02379	0.74 ± 0.06
AD02350	0.28 ± 0.02	AD02425	0.40 ± 0.04	AD02532	0.75 ± 0.04
AD02202	0.28 ± 0.03	AD02099	0.41 ± 0.04	AD02178	0.75 ± 0.11
AD02203	0.28 ± 0.03	AD01723	0.41 ± 0.04	AD02195	0.75 ± 0.05
AD02258	0.28 ± 0.05	AD02391	0.41 ± 0.03	AD02123	0.76 ± 0.07
AD02295	0.28 ± 0.03	AD02392	0.41 ± 0.05	AD02164	0.77 ± 0.09
AD02363	0.28 ± 0.04	AD02083	0.41 ± 0.01	AD01726	0.77 ± 0.01
AD02273	0.28 ± 0.02	AD02155	0.41 ± 0.02	AD02231	0.77 ± 0.05
AD02386	0.28 ± 0.02	AD02082	0.41 ± 0.01	AD02180	0.77 ± 0.04
AD02309	0.28 ± 0.03	AD02336	0.41 ± 0.01	AD02412	0.77 ± 0.05
AD02382	0.29 ± 0.01	AD02101	0.41 ± 0.02	AD02251	0.77 ± 0.02
AD02256	0.29 ± 0.02	AD01728	0.42 ± 0.01	AD02396	0.78 ± 0.13
AD02367	0.29 ± 0.03	AD02424	0.42 ± 0.04	AD02160	0.78 ± 0.04
AD02275	0.29 ± 0.04	AD02175	0.42 ± 0.02	AD02533	0.78 ± 0.05
AD02206	0.29 ± 0.01	AD02225	0.42 ± 0.05	AD02290	0.78 ± 0.03
AD02332	0.29 ± 0.02	AD02086	0.43 ± 0.02	AD02378	0.78 ± 0.07
AD01717	0.29 ± 0.03	AD01725	0.43 ± 0.06	AD02394	0.79 ± 0.04
AD02296	0.29 ± 0.01	AD02374	0.43 ± 0.03	AD02415	0.79 ± 0.05
AD02264	0.29 ± 0.03	AD02390	0.43 ± 0.04	AD02181	0.79 ± 0.08
AD02278	0.29 ± 0.03	AD02227	0.43 ± 0.02	AD02492	0.79 ± 0.06
AD02385	0.29 ± 0.00	AD02137	0.43 ± 0.06	AD02397	0.79 ± 0.05
AD02205	0.29 ± 0.04	AD02085	0.43 ± 0.01	AD02398	0.79 ± 0.09
AD02149	0.29 ± 0.02	AD02407	0.43 ± 0.03	AD02416	0.79 ± 0.04
AD02239	0.30 ± 0.05	AD02100	0.44 ± 0.04	AD02144	0.79 ± 0.09
AD01748	0.30 ± 0.02	AD02406	0.44 ± 0.04	AD02531	0.79 ± 0.06
AD02404	0.30 ± 0.01	AD02136	0.44 ± 0.02	AD02489	0.80 ± 0.04
AD01721	0.30 ± 0.03	AD02209	0.44 ± 0.03	AD02307	0.80 ± 0.10
AD02277	0.30 ± 0.05	AD02154	0.44 ± 0.02	AD02308	0.80 ± 0.11
AD02152	0.30 ± 0.01	AD02171	0.44 ± 0.01	AD02182	0.80 ± 0.08
AD02237	0.30 ± 0.02	AD02261	0.45 ± 0.02	AD02198	0.80 ± 0.11

AD02098	0.30 ± 0.03	AD02271	0.45 ± 0.00	AD02199	0.80 ± 0.10
AD02381	0.30 ± 0.02	AD02371	0.45 ± 0.03	AD02200	0.80 ± 0.06
AD02315	0.30 ± 0.02	AD02173	0.45 ± 0.07	AD02125	0.81 ± 0.06
AD02366	0.30 ± 0.01	AD02319	0.45 ± 0.01	AD02141	0.81 ± 0.01
AD02242	0.31 ± 0.03	AD02176	0.46 ± 0.01	AD02516	0.81 ± 0.06
AD02294	0.31 ± 0.02	AD02428	0.46 ± 0.02	AD02127	0.81 ± 0.06
AD02346	0.31 ± 0.04	AD02410	0.46 ± 0.01	AD02380	0.81 ± 0.03
AD02329	0.31 ± 0.02	AD01746	0.46 ± 0.05	AD02124	0.81 ± 0.05
AD02348	0.31 ± 0.01	AD01732	0.46 ± 0.02	AD02197	0.81 ± 0.02
AD01714	0.31 ± 0.05	AD02157	0.47 ± 0.02	AD02159	0.81 ± 0.09
AD01724	0.31 ± 0.01	AD02372	0.47 ± 0.03	AD02485	0.82 ± 0.04
AD02170	0.31 ± 0.02	AD02427	0.47 ± 0.02	AD02142	0.82 ± 0.08
AD02352	0.31 ± 0.02	AD02370	0.47 ± 0.01	AD02126	0.82 ± 0.08
AD02093	0.31 ± 0.01	AD02172	0.47 ± 0.04	AD02254	0.82 ± 0.10
AD02383	0.31 ± 0.02	AD02158	0.47 ± 0.02	AD02232	0.82 ± 0.04
AD02284	0.31 ± 0.04	AD02270	0.48 ± 0.04	AD02146	0.82 ± 0.04
AD02219	0.31 ± 0.04	AD02426	0.48 ± 0.04	AD02490	0.82 ± 0.03
AD02279	0.31 ± 0.03	AD02361	0.48 ± 0.04	AD01745	0.82 ± 0.09
AD02299	0.31 ± 0.05	AD02245	0.48 ± 0.02	AD02162	0.83 ± 0.04
AD01740	0.31 ± 0.02	AD02373	0.48 ± 0.01	AD02471	0.83 ± 0.11
AD02417	0.32 ± 0.01	AD02084	0.48 ± 0.05	AD02487	0.83 ± 0.09
AD02364	0.32 ± 0.02	AD02194	0.48 ± 0.03	AD02523	0.83 ± 0.10
AD02262	0.32 ± 0.03	AD01753	0.48 ± 0.06	AD02483	0.83 ± 0.03
AD02369	0.32 ± 0.01	AD02320	0.48 ± 0.03	AD02128	0.84 ± 0.09
AD01731	0.32 ± 0.02	AD02268	0.48 ± 0.05	AD02143	0.84 ± 0.05
AD02349	0.32 ± 0.01	AD02226	0.49 ± 0.01	AD02214	0.84 ± 0.13
AD02095	0.32 ± 0.02	AD02156	0.49 ± 0.01	AD02217	0.84 ± 0.07
AD02281	0.32 ± 0.01	AD02409	0.49 ± 0.03	AD02250	0.84 ± 0.08
AD02224	0.32 ± 0.06	AD02244	0.49 ± 0.02	AD02163	0.85 ± 0.04
AD02148	0.32 ± 0.04	AD02189	0.49 ± 0.06	AD02525	0.85 ± 0.06
AD01718	0.33 ± 0.01	AD01764	0.50 ± 0.02	AD02481	0.85 ± 0.03
AD02333	0.33 ± 0.01	AD02174	0.50 ± 0.04	AD02235	0.85 ± 0.03
AD02403	0.33 ± 0.01	AD02117	0.50 ± 0.01	AD02539	0.86 ± 0.05
AD02317	0.33 ± 0.03	AD02208	0.50 ± 0.05	AD02470	0.86 ± 0.07
AD02399	0.33 ± 0.02	AD02104	0.51 ± 0.03	AD02469	0.86 ± 0.04
AD02222	0.33 ± 0.01	AD02408	0.51 ± 0.06	AD02480	0.86 ± 0.07
AD02310	0.33 ± 0.02	AD02272	0.51 ± 0.04	AD02488	0.87 ± 0.05
AD01733	0.33 ± 0.01	AD02122	0.51 ± 0.06	AD02511	0.87 ± 0.05
AD02131	0.33 ± 0.01	AD02140	0.51 ± 0.04	AD02482	0.87 ± 0.04
AD02353	0.33 ± 0.03	AD02362	0.51 ± 0.04	AD02519	0.87 ± 0.08
AD02263	0.33 ± 0.03	AD01739	0.52 ± 0.04	AD02491	0.88 ± 0.05
AD02204	0.33 ± 0.01	AD02121	0.52 ± 0.06	AD02216	0.88 ± 0.00
AD02080	0.33 ± 0.00	AD02138	0.52 ± 0.04	AD02215	0.88 ± 0.03
AD02298	0.33 ± 0.03	AD02358	0.52 ± 0.02	AD02468	0.88 ± 0.06
AD01737	0.33 ± 0.01	AD01734	0.53 ± 0.06	AD02526	0.88 ± 0.06
AD02220	0.33 ± 0.04	AD01713	0.53 ± 0.04	AD02234	0.88 ± 0.14
AD02302	0.33 ± 0.00	AD02285	0.53 ± 0.03	AD02518	0.89 ± 0.05
AD02097	0.33 ± 0.00	AD02102	0.53 ± 0.07	AD02218	0.89 ± 0.04
AD02328	0.33 ± 0.02	AD02303	0.53 ± 0.03	AD02515	0.89 ± 0.03
AD02221	0.33 ± 0.01	AD02212	0.53 ± 0.01	AD02536	0.89 ± 0.11

AD02421	0.33 ± 0.02	AD02139	0.53 ± 0.03	AD02537	0.89 ± 0.04
AD02420	0.33 ± 0.03	AD02230	0.54 ± 0.08	AD02465	0.89 ± 0.07
AD02347	0.33 ± 0.04	AD02103	0.54 ± 0.04	AD02196	0.90 ± 0.03
AD02134	0.34 ± 0.01	AD02191	0.54 ± 0.03	AD02253	0.90 ± 0.05
AD02078	0.34 ± 0.03	AD02429	0.54 ± 0.02	AD02484	0.90 ± 0.09
AD02151	0.34 ± 0.02	AD01716	0.54 ± 0.09	AD02467	0.91 ± 0.00
AD02238	0.34 ± 0.03	AD02360	0.54 ± 0.02	AD02538	0.91 ± 0.10
AD02168	0.34 ± 0.00	AD01762	0.54 ± 0.01	AD02478	0.91 ± 0.01
AD02096	0.34 ± 0.03	AD01735	0.55 ± 0.07	AD02479	0.92 ± 0.05
AD01758	0.34 ± 0.05	AD02248	0.55 ± 0.05	AD02540	0.92 ± 0.08
AD02077	0.34 ± 0.02	AD02193	0.55 ± 0.01	AD02524	0.92 ± 0.03
AD02345	0.34 ± 0.02	AD02119	0.55 ± 0.01	AD02466	0.92 ± 0.05
AD02384	0.34 ± 0.02	AD02287	0.55 ± 0.02	AD02520	0.92 ± 0.06
AD02094	0.34 ± 0.01	AD02357	0.56 ± 0.01	AD02498	0.92 ± 0.06
AD02419	0.34 ± 0.04	AD01708	0.57 ± 0.06	AD02472	0.92 ± 0.05
AD02401	0.34 ± 0.02	AD02247	0.57 ± 0.06	AD02106	0.93 ± 0.08
AD02402	0.34 ± 0.03	AD02430	0.58 ± 0.07	AD02486	0.93 ± 0.02
AD01712	0.34 ± 0.04	AD02339	0.58 ± 0.03	AD02236	0.93 ± 0.04
AD02276	0.34 ± 0.01	AD02321	0.59 ± 0.03	AD02543	0.93 ± 0.12
AD02150	0.34 ± 0.02	AD02269	0.59 ± 0.02	AD02517	0.94 ± 0.05
AD02166	0.34 ± 0.03	AD02210	0.59 ± 0.04	AD02505	0.94 ± 0.10
AD02351	0.34 ± 0.02	AD02211	0.60 ± 0.02	AD02464	0.94 ± 0.06
AD02241	0.35 ± 0.04	AD02091	0.60 ± 0.03	AD02499	0.94 ± 0.16
AD02282	0.35 ± 0.01	AD02120	0.60 ± 0.07	AD02500	0.94 ± 0.05
AD02130	0.35 ± 0.04	AD02229	0.60 ± 0.03	AD02544	0.95 ± 0.07
AD01751	0.35 ± 0.03	AD01727	0.60 ± 0.02	AD02541	0.95 ± 0.15
AD02356	0.35 ± 0.03	AD01730	0.60 ± 0.02	AD02509	0.95 ± 0.09
AD02405	0.35 ± 0.04	AD02190	0.60 ± 0.07	AD02508	0.95 ± 0.10
AD02129	0.35 ± 0.01	AD02411	0.60 ± 0.06	AD02510	0.95 ± 0.03
AD02355	0.35 ± 0.01	AD02322	0.61 ± 0.03	AD02521	0.96 ± 0.16
AD02423	0.35 ± 0.06	AD02433	0.61 ± 0.02	AD02507	0.96 ± 0.03
AD02316	0.35 ± 0.02	AD01761	0.62 ± 0.05	AD02105	0.96 ± 0.09
AD02331	0.35 ± 0.02	AD01720	0.62 ± 0.02	AD02495	0.96 ± 0.05
AD02335	0.35 ± 0.01	AD02228	0.62 ± 0.06	AD02504	0.97 ± 0.04
AD02187	0.35 ± 0.03	AD02393	0.62 ± 0.03	AD02493	0.97 ± 0.06
AD02314	0.36 ± 0.04	AD02359	0.62 ± 0.03	AD02542	0.97 ± 0.06
AD02300	0.36 ± 0.03	AD02323	0.62 ± 0.05	AD02503	0.98 ± 0.05
AD02387	0.36 ± 0.06	AD02118	0.63 ± 0.05	AD02107	0.98 ± 0.05
AD02337	0.36 ± 0.04	AD02286	0.63 ± 0.04	AD02477	0.98 ± 0.06
AD01729	0.36 ± 0.01	AD02087	0.63 ± 0.04	AD02501	0.98 ± 0.07
AD02283	0.36 ± 0.02	AD01715	0.63 ± 0.06	AD02497	0.98 ± 0.05
AD02185	0.36 ± 0.01	AD02192	0.63 ± 0.02	AD02494	0.98 ± 0.13
AD02167	0.36 ± 0.01	AD02431	0.64 ± 0.06	AD02475	1.00 ± 0.07
AD02076	0.36 ± 0.04	AD02340	0.64 ± 0.03	AD02514	1.00 ± 0.00
AD02418	0.36 ± 0.01	AD02432	0.64 ± 0.02	AD02474	1.00 ± 0.03
AD02422	0.36 ± 0.03	AD02089	0.65 ± 0.07	AD02502	1.01 ± 0.01
AD02111	0.36 ± 0.02	AD02267	0.65 ± 0.11	AD02522	1.01 ± 0.04
AD02079	0.37 ± 0.02	AD02246	0.65 ± 0.07	AD02476	1.01 ± 0.09
AD01754	0.37 ± 0.04	AD02325	0.65 ± 0.03	AD02513	1.02 ± 0.03
AD02334	0.37 ± 0.02	AD02343	0.66 ± 0.05	AD02109	1.02 ± 0.06

AD02280	0.37 ± 0.05	AD02375	0.66 ± 0.04	AD02252	1.02 ± 0.08
AD02113	0.37 ± 0.03	AD02288	0.66 ± 0.06	AD02496	1.04 ± 0.05
AD02389	0.37 ± 0.03	AD02088	0.66 ± 0.01	AD02473	1.05 ± 0.04
AD02223	0.37 ± 0.04	AD02413	0.66 ± 0.03	AD02506	1.05 ± 0.05
AD02184	0.37 ± 0.02	AD02377	0.67 ± 0.05	AD01742	1.07 ± 0.24
AD02153	0.37 ± 0.02	AD02528	0.67 ± 0.04	AD02110	1.08 ± 0.07
AD02165	0.37 ± 0.02	AD02434	0.67 ± 0.05	AD02512	1.09 ± 0.17
AD02207	0.37 ± 0.01	AD02304	0.67 ± 0.02	AD02108	1.11 ± 0.04

Example 3. *LPA RNAi agent EC_{50} determination.* Ten-point EC_{50} curves were generated using the same cells and transfection conditions, with LPA RNAi agent concentrations ranging from 150fM–3nM. EC_{50} were determined using GraphPad Prism software (Table 6).

Table 6. EC_{50} values (nM) determined *in vitro* for the indicated LPA RNAi agents.

Duplex ID#	EC_{50} (nM)	Duplex ID#	EC_{50} (nM)
AD00575	0.073	AD00635	0.577
AD00576	0.038	AD01070	0.6388
AD00578	0.112	AD01072	0.1068
AD00579	0.083	AD01073	0.1154
AD00621	0.100	AD01074	0.2903

Example 4. *In vitro analysis of Structure-Activity Relationship (SAR) designed LPA RNAi agents*. LPA RNAi agent SAR sets (364 sequences based on AD01532 and 351 sequences based on AD01533) were synthesized and screened for efficacy in vitro. For screening purposes, 2756 bp of the human LPA cDNA sequence from KIV-3 to KIV-9 (accession # NM_005577.1) was synthesized and cloned (GeneWiz, South Plainfield, NJ) into a commercially-available, reporter-based screening plasmid, psiCHECK2 (Promega, Madison, WI) which generated a Renilla luciferase/LPA fusion mRNA. For LPA RNAi agent efficacy in the human background, HuH7 cells, a human hepatocellular carcinoma line, were plated at ~7500 cells per well in 96-well format. Each of the LPA RNAi agents was co-transfected at two concentrations (1nM and 0.1nM, or 10nM and 1nM) with 25 ng LPA-psiCHECK2 plasmid DNA per well and 0.2µL LipoFectamine 2000 per well. Gene knockdown was determined by measuring Renilla luciferase levels normalized to the levels of constitutively-expressed firefly luciferase, also present on the psiCHECK2 plasmid, using the Dual Luciferase Reporter Assay (Promega, Madison, WI) (Tables 7A and 7B).

Table 7A. Efficacy screen results of LPA RNAi agents *in vitro*, as determined by dual-

luciferase reporter assay.

Duplex ID No.	Relative R_{luc}-LPA expression		Duplex ID No.	Relative R_{luc}-LPA expression	
	1 nM	0.1 nM		1 nM	0.1 nM
SD0001	0.570	0.907	SD0117	0.946	1.021
SD0002	0.873	1.061	SD0118	0.879	0.977
SD0003	0.955	1.020	SD0119	0.963	1.016
SD0004	0.845	1.007	SD0120	0.967	0.948
SD0005	0.603	0.891	SD0121	0.651	0.897
SD0006	0.551	0.780	SD0122	1.085	1.111
SD0007	0.510	0.797	SD0123	1.153	1.052
SD0008	0.544	0.892	SD0124	0.955	0.936
SD0009	0.564	0.878	SD0125	0.928	0.928
SD0010	0.542	1.051	SD0126	1.033	0.933
SD0011	0.513	0.873	SD0127	0.637	0.717
SD0012	0.533	0.963	SD0128	0.630	0.653
SD0013	0.541	0.979	SD0129	1.052	1.192
SD0014	0.551	0.987	SD0130	1.025	1.107
SD0015	0.488	0.951	SD0131	1.280	1.059
SD0016	0.588	0.868	SD0132	1.094	1.024
SD0017	1.023	1.005	SD0133	1.113	1.031
SD0018	0.866	0.965	SD0134	0.928	0.991
SD0019	0.792	1.005	SD0135	0.804	1.023
SD0020	0.633	0.860	SD0136	1.028	1.104
SD0021	0.572	0.797	SD0137	0.902	1.149
SD0022	0.610	0.874	SD0138	0.942	1.015
SD0023	0.550	0.836	SD0139	0.984	1.068
SD0024	0.597	0.859	SD0140	0.953	1.091
SD0025	0.587	0.899	SD0141	0.925	1.022
SD0026	0.570	0.898	SD0142	0.906	0.994
SD0027	0.580	0.825	SD0143	0.898	0.990
SD0028	0.612	0.885	SD0144	0.858	0.972
SD0029	0.528	0.866	SD0145	0.917	0.947
SD0030	0.657	0.825	SD0146	0.850	0.906
SD0031	0.560	0.914	SD0147	0.933	0.995
SD0032	0.664	0.976	SD0148	0.856	0.994
SD0033	0.787	1.035	SD0149	0.882	0.985
SD0034	0.739	1.002	SD0150	0.810	1.002
SD0035	0.658	0.949	SD0151	0.813	0.909
SD0036	0.554	0.896	SD0152	0.963	1.031
SD0037	0.557	0.873	SD0153	1.058	0.936
SD0038	0.528	0.854	SD0154	0.968	0.944
SD0039	0.511	0.847	SD0155	0.969	0.940
SD0040	0.554	0.976	SD0156	0.933	0.807
SD0041	0.559	0.823	SD0157	0.906	0.913

SD0042	0.496	0.825	SD0158	0.926	0.964
SD0043	0.563	0.851	SD0159	0.805	0.850
SD0044	0.476	0.861	SD0160	0.895	0.965
SD0045	0.542	0.841	SD0161	0.865	1.006
SD0046	0.651	0.980	SD0162	0.935	1.029
SD0047	0.967	0.995	SD0163	0.928	0.985
SD0048	0.694	0.936	SD0164	0.920	0.957
SD0049	0.960	0.946	SD0165	1.039	1.110
SD0050	0.692	0.971	SD0166	1.061	1.023
SD0051	0.611	0.905	SD0167	1.020	0.982
SD0052	0.657	0.849	SD0168	1.053	0.989
SD0053	0.642	0.848	SD0169	1.002	1.018
SD0054	0.598	0.852	SD0170	1.078	0.982
SD0055	0.494	0.828	SD0171	0.838	0.923
SD0056	0.524	0.885	SD0172	1.025	0.934
SD0057	0.582	0.816	SD0173	0.864	0.963
SD0058	0.597	0.866	SD0174	1.020	1.043
SD0059	0.560	0.905	SD0175	1.128	1.046
SD0060	0.594	0.849	SD0176	1.009	1.110
SD0061	0.571	1.058	SD0177	0.735	0.975
SD0062	0.871	1.157	SD0178	0.824	1.074
SD0063	0.969	1.138	SD0179	0.690	0.895
SD0064	0.555	1.019	SD0180	0.572	0.914
SD0065	0.671	0.953	SD0181	0.904	1.028
SD0066	0.561	0.951	SD0182	1.176	1.093
SD0067	0.612	0.904	SD0183	1.247	1.090
SD0068	0.573	0.938	SD0184	1.097	0.974
SD0069	0.574	0.975	SD0185	1.045	0.985
SD0070	0.606	1.030	SD0186	0.940	0.943
SD0071	0.494	0.959	SD0187	0.883	0.994
SD0072	0.557	0.892	SD0188	ND	ND
SD0073	0.593	0.984	SD0189	0.872	0.977
SD0074	0.544	0.894	SD0190	0.861	1.166
SD0075	0.552	0.937	SD0191	0.779	1.044
SD0076	0.513	1.058	SD0192	0.796	1.116
SD0077	0.930	1.071	SD0193	0.975	1.112
SD0078	0.984	1.006	SD0194	0.876	1.058
SD0079	0.853	1.031	SD0195	0.747	0.970
SD0080	0.577	0.942	SD0196	0.787	1.086
SD0081	0.595	1.044	SD0197	1.276	1.127
SD0082	0.652	0.962	SD0198	1.144	1.140
SD0083	0.583	0.928	SD0199	1.136	1.101
SD0084	0.540	1.049	SD0200	0.814	0.911
SD0085	0.523	0.961	SD0201	0.733	0.915
SD0086	0.536	0.956	SD0202	0.576	0.933
SD0087	0.586	0.987	SD0203	0.593	0.824

SD0088	0.563	0.892	SD0204	0.882	1.038
SD0089	0.555	0.947	SD0205	0.681	1.012
SD0090	0.599	0.928	SD0206	0.600	0.927
SD0091	0.665	0.854	SD0207	0.738	0.974
SD0092	1.002	0.917	SD0208	0.638	0.883
SD0093	1.047	0.880	SD0209	0.641	0.878
SD0094	0.867	0.911	SD0210	0.544	0.886
SD0095	0.919	0.868	SD0211	0.702	0.920
SD0096	0.666	0.887	SD0212	0.704	0.854
SD0097	0.673	0.737	SD0213	0.655	0.887
SD0098	0.567	0.809	SD0214	0.629	0.860
SD0099	0.604	0.909	SD0215	0.598	0.850
SD0100	0.557	0.880	SD0216	0.611	0.782
SD0101	0.545	0.806	SD0217	0.710	0.806
SD0102	0.728	0.900	SD0218	0.738	0.758
SD0103	0.719	0.928	SD0219	0.664	0.809
SD0104	0.766	0.955	SD0220	1.133	0.891
SD0105	0.965	0.927	SD0221	0.940	0.914
SD0106	1.161	1.006	SD0222	0.853	0.882
SD0107	1.048	0.966	SD0223	0.691	0.889
SD0108	1.066	0.985	SD0224	0.997	1.033
SD0109	1.111	0.917	SD0225	0.954	0.998
SD0110	1.152	0.954	SD0226	1.202	0.997
SD0111	1.045	0.944	SD0227	0.948	1.017
SD0112	1.089	1.019	SD0228	0.786	0.947
SD0113	0.949	0.935	SD0229	0.620	0.830
SD0114	0.875	1.033	SD0230	0.840	0.972
SD0115	1.022	1.077	SD0231	0.904	0.890
SD0116	0.947	1.028			

Table 7B. Efficacy screen results of LPA RNAi agents *in vitro*, as determined by dual-luciferase reporter assay.

Duplex ID #	Relative R_{luc}-LPA expression 10nM	1nM	Duplex ID #	Relative R_{luc}-LPA expression 10nM	1nM
SD0232	0.659	0.699	SD0474	0.621	0.598
SD0233	0.942	1.252	SD0475	0.564	0.472
SD0234	0.967	1.358	SD0476	0.769	0.631
SD0235	0.910	0.890	SD0477	0.734	0.613
SD0236	0.742	0.822	SD0478	0.460	0.411
SD0237	0.758	0.831	SD0479	0.713	0.802
SD0238	0.700	0.737	SD0480	0.883	0.892
SD0239	0.645	0.765	SD0481	0.926	0.899
SD0240	0.701	0.773	SD0482	1.180	0.937

SD0241	0.770	0.821	SD0483	0.805	0.986
SD0242	0.626	0.719	SD0484	0.920	1.104
SD0243	0.759	0.848	SD0485	0.510	0.524
SD0244	0.798	0.953	SD0486	0.626	0.598
SD0245	0.764	0.821	SD0487	0.628	0.640
SD0246	0.812	0.690	SD0488	0.597	0.637
SD0247	0.786	0.844	SD0489	0.482	0.486
SD0248	1.011	1.167	SD0490	0.685	0.664
SD0249	1.118	1.189	SD0491	0.650	0.662
SD0250	1.021	1.239	SD0492	0.454	0.490
SD0251	1.041	1.151	SD0493	1.006	1.040
SD0252	1.070	1.124	SD0494	0.933	1.024
SD0253	1.044	1.131	SD0495	0.927	1.016
SD0254	0.861	0.948	SD0496	0.921	1.004
SD0255	0.751	0.829	SD0497	0.690	0.846
SD0256	0.931	1.037	SD0498	0.970	0.913
SD0257	1.024	1.037	SD0499	0.448	0.399
SD0258	0.935	1.030	SD0500	0.614	0.485
SD0259	1.089	1.081	SD0501	0.609	0.521
SD0260	0.955	1.008	SD0502	0.626	0.526
SD0261	0.923	0.980	SD0503	0.493	0.410
SD0262	0.908	1.107	SD0504	0.727	0.551
SD0263	1.060	1.449	SD0505	0.688	0.541
SD0264	1.041	1.419	SD0506	0.319	0.338
SD0265	1.065	1.373	SD0507	0.927	0.897
SD0266	0.950	1.376	SD0508	0.929	0.972
SD0267	0.963	1.214	SD0509	0.853	0.925
SD0268	1.023	1.299	SD0510	0.755	0.935
SD0269	0.908	1.066	SD0511	0.480	0.559
SD0270	0.963	1.081	SD0512	0.834	0.854
SD0271	1.088	1.189	SD0513	0.440	0.323
SD0272	0.966	1.135	SD0514	0.415	0.414
SD0273	0.953	1.192	SD0515	0.442	0.343
SD0274	1.049	1.217	SD0516	0.422	0.341
SD0275	1.006	1.206	SD0517	0.346	0.320
SD0276	0.969	1.064	SD0518	0.488	0.420
SD0277	0.686	0.796	SD0519	0.435	0.390
SD0278	0.985	1.305	SD0520	0.819	0.737
SD0279	0.985	1.301	SD0521	1.058	0.903
SD0280	0.978	1.237	SD0522	1.088	0.933
SD0281	1.038	1.230	SD0523	1.075	0.948
SD0282	0.933	1.191	SD0524	1.067	0.900
SD0283	0.930	1.152	SD0525	0.917	0.858
SD0284	0.907	1.117	SD0526	1.126	1.055
SD0285	0.625	0.870	SD0527	0.832	0.776
SD0286	0.984	1.056	SD0528	0.980	0.886

SD0287	0.906	0.965	SD0529	1.059	0.821
SD0288	1.052	1.123	SD0530	0.934	0.844
SD0289	0.997	1.215	SD0531	0.832	0.883
SD0290	0.892	1.197	SD0532	0.936	0.868
SD0291	0.907	1.065	SD0533	0.900	0.946
SD0292	0.689	0.862	SD0534	1.012	0.984
SD0293	0.955	1.190	SD0535	1.041	1.095
SD0294	1.095	1.157	SD0536	1.113	1.097
SD0295	0.851	1.004	SD0537	1.125	0.957
SD0296	1.018	1.106	SD0538	1.059	1.162
SD0297	0.737	0.760	SD0539	0.901	0.963
SD0298	0.790	0.828	SD0540	0.900	0.924
SD0299	0.721	0.713	SD0541	1.033	0.911
SD0300	0.796	0.869	SD0542	0.958	0.906
SD0301	0.781	0.841	SD0543	0.870	0.816
SD0302	0.621	0.720	SD0544	1.100	0.853
SD0303	0.684	0.852	SD0545	0.881	0.794
SD0304	0.774	0.842	SD0546	0.897	0.813
SD0305	0.778	0.799	SD0547	1.005	0.785
SD0306	0.718	0.793	SD0548	0.972	0.866
SD0307	0.982	0.883	SD0549	1.019	1.121
SD0308	1.297	1.193	SD0550	0.986	1.015
SD0309	1.123	1.208	SD0551	0.966	1.033
SD0310	0.961	1.073	SD0552	0.893	1.028
SD0311	1.168	1.019	SD0553	0.976	0.998
SD0312	0.923	0.824	SD0554	0.938	0.935
SD0313	0.883	0.871	SD0555	0.886	0.875
SD0314	0.670	0.650	SD0556	1.181	1.142
SD0315	0.988	0.958	SD0557	1.016	0.999
SD0316	0.908	0.880	SD0558	1.026	0.968
SD0317	0.754	0.850	SD0559	0.928	0.844
SD0318	0.963	0.944	SD0560	0.990	0.805
SD0319	0.945	0.862	SD0561	0.836	0.791
SD0320	0.961	0.875	SD0562	1.021	0.772
SD0321	0.841	0.797	SD0563	0.886	0.946
SD0322	0.546	0.521	SD0564	1.194	1.254
SD0323	0.581	0.895	SD0565	1.010	1.033
SD0324	0.692	0.900	SD0566	1.110	0.993
SD0325	0.506	0.796	SD0567	0.995	0.895
SD0326	0.634	0.709	SD0568	0.964	0.901
SD0327	0.522	0.592	SD0569	0.853	0.876
SD0328	0.602	0.632	SD0570	0.832	0.860
SD0329	0.504	0.615	SD0571	1.036	0.959
SD0330	0.445	0.601	SD0572	1.013	0.902
SD0331	0.457	0.579	SD0573	0.948	0.793
SD0332	0.500	0.601	SD0574	0.868	0.812

SD0333	0.447	0.618	SD0575	0.946	0.712
SD0334	0.490	0.528	SD0576	0.922	0.774
SD0335	0.421	0.555	SD0577	0.824	0.800
SD0336	0.488	0.533	SD0578	0.997	0.950
SD0337	1.714	0.978	SD0579	1.048	1.143
SD0338	1.262	1.350	SD0580	1.071	0.935
SD0339	1.259	1.357	SD0581	0.987	0.869
SD0340	0.996	1.277	SD0582	0.946	0.816
SD0341	1.190	1.183	SD0583	0.932	0.789
SD0342	0.818	0.923	SD0584	1.062	0.866
SD0343	0.803	0.855	SD0585	1.155	0.891
SD0344	0.708	0.883	SD0586	0.960	0.819
SD0345	1.132	0.901	SD0587	0.934	0.832
SD0346	0.847	0.890	SD0588	1.033	0.781
SD0347	0.659	0.780	SD0589	0.972	0.798
SD0348	0.730	0.945	SD0590	0.925	0.704
SD0349	0.825	0.886	SD0591	1.061	0.915
SD0350	0.826	0.897	SD0592	1.129	0.996
SD0351	0.730	0.842	SD0593	0.856	0.895
SD0352	0.297	0.276	SD0594	0.840	0.956
SD0353	0.773	0.746	SD0595	0.882	0.857
SD0354	0.663	0.722	SD0596	0.856	0.896
SD0355	0.620	0.626	SD0597	0.869	0.697
SD0356	0.546	0.599	SD0598	0.878	0.700
SD0357	0.298	0.411	SD0599	0.808	0.857
SD0358	0.313	0.318	SD0600	0.856	0.823
SD0359	0.273	0.282	SD0601	0.742	0.713
SD0360	0.256	0.257	SD0602	0.740	0.846
SD0361	0.269	0.276	SD0603	0.808	0.816
SD0362	0.270	0.276	SD0604	0.561	0.527
SD0363	0.350	0.272	SD0605	0.711	0.880
SD0364	0.227	0.243	SD0606	0.852	0.922
SD0365	0.228	0.233	SD0607	0.695	0.887
SD0366	0.264	0.241	SD0608	0.635	0.917
SD0367	0.262	0.252	SD0609	0.655	0.874
SD0368	0.571	0.597	SD0610	0.596	0.765
SD0369	0.539	0.531	SD0611	0.482	0.508
SD0370	0.521	0.545	SD0612	0.629	0.578
SD0371	0.302	0.319	SD0613	0.616	0.503
SD0372	0.353	0.335	SD0614	0.716	0.682
SD0373	0.279	0.255	SD0615	0.570	0.491
SD0374	0.266	0.194	SD0616	0.671	0.668
SD0375	0.246	0.238	SD0617	0.713	0.721
SD0376	0.258	0.238	SD0618	0.819	0.862
SD0377	0.246	0.226	SD0619	0.925	0.968
SD0378	0.237	0.226	SD0620	0.859	0.978

SD0379	0.262	0.226	SD0621	0.923	1.075
SD0380	0.247	0.240	SD0622	0.900	0.988
SD0381	0.639	0.657	SD0623	0.908	0.969
SD0382	0.267	0.517	SD0624	0.775	0.889
SD0383	0.473	0.547	SD0625	0.827	0.850
SD0384	0.456	0.563	SD0626	0.832	0.796
SD0385	0.264	0.393	SD0627	0.916	0.796
SD0386	0.329	0.325	SD0628	0.863	0.898
SD0387	0.186	0.231	SD0629	0.915	0.869
SD0388	0.217	0.248	SD0630	0.893	0.856
SD0389	0.230	0.275	SD0631	0.940	0.848
SD0390	0.210	0.270	SD0632	0.878	0.911
SD0391	0.247	0.224	SD0633	0.934	1.074
SD0392	0.257	0.236	SD0634	0.915	1.019
SD0393	0.252	0.253	SD0635	0.911	0.912
SD0394	0.267	0.251	SD0636	0.852	0.911
SD0395	0.594	0.675	SD0637	0.997	0.965
SD0396	0.511	0.678	SD0638	0.983	0.935
SD0397	0.457	0.618	SD0639	0.806	0.823
SD0398	0.516	0.601	SD0640	0.838	0.846
SD0399	0.261	0.389	SD0641	0.906	0.861
SD0400	0.327	0.300	SD0642	0.740	0.836
SD0401	0.230	0.250	SD0643	0.739	0.725
SD0402	0.231	0.260	SD0644	0.780	0.762
SD0403	0.237	0.221	SD0645	0.739	0.819
SD0404	0.258	0.243	SD0646	0.734	0.798
SD0405	0.253	0.246	SD0647	0.789	0.913
SD0406	0.228	0.230	SD0648	0.707	0.946
SD0407	0.228	0.215	SD0649	0.943	1.077
SD0408	0.247	0.255	SD0650	0.729	0.872
SD0409	0.565	0.667	SD0651	0.666	0.879
SD0410	0.796	0.863	SD0652	0.704	0.882
SD0411	0.633	0.646	SD0653	0.661	0.726
SD0412	0.613	0.699	SD0654	0.751	0.881
SD0413	0.294	0.439	SD0655	0.727	0.822
SD0414	0.416	0.310	SD0656	0.746	0.839
SD0415	0.275	0.238	SD0657	0.849	0.842
SD0416	0.241	0.290	SD0658	0.835	0.796
SD0417	0.257	0.284	SD0659	0.972	0.830
SD0418	0.267	0.306	SD0660	0.772	0.672
SD0419	0.249	0.229	SD0661	0.883	0.918
SD0420	0.243	0.240	SD0662	0.934	0.952
SD0421	0.250	0.241	SD0663	0.974	0.891
SD0422	0.230	0.237	SD0664	0.939	0.936
SD0423	0.555	0.684	SD0665	1.116	0.919
SD0424	0.614	0.682	SD0666	0.924	0.954

SD0425	0.592	0.733	SD0667	0.780	0.744
SD0426	0.604	0.699	SD0668	0.795	0.726
SD0427	0.281	0.449	SD0669	0.819	0.754
SD0428	0.301	0.330	SD0670	0.856	0.830
SD0429	0.230	0.261	SD0671	0.844	0.758
SD0430	0.241	0.273	SD0672	0.978	0.952
SD0431	0.232	0.255	SD0673	0.860	0.845
SD0432	0.247	0.288	SD0674	0.526	0.566
SD0433	0.238	0.280	SD0675	0.661	0.961
SD0434	0.224	0.293	SD0676	0.690	0.916
SD0435	0.249	0.240	SD0677	0.672	0.939
SD0436	0.428	0.445	SD0678	0.821	0.973
SD0437	0.542	0.829	SD0679	0.943	0.952
SD0438	1.106	1.048	SD0680	1.018	0.991
SD0439	0.930	1.096	SD0681	0.561	0.580
SD0440	1.033	1.023	SD0682	0.777	0.688
SD0441	0.630	0.657	SD0683	0.654	0.639
SD0442	0.912	0.913	SD0684	0.691	0.622
SD0443	0.392	0.375	SD0685	0.518	0.555
SD0444	0.552	0.441	SD0686	0.661	0.738
SD0445	0.561	0.514	SD0687	0.722	0.644
SD0446	0.550	0.442	SD0688	0.416	0.385
SD0447	0.415	0.362	SD0689	0.571	0.870
SD0448	0.566	0.503	SD0690	0.697	0.946
SD0449	0.579	0.475	SD0691	0.616	0.840
SD0450	0.463	0.424	SD0692	0.644	0.850
SD0451	0.925	0.929	SD0693	0.781	0.733
SD0452	0.963	0.939	SD0694	1.022	0.902
SD0453	0.967	0.952	SD0695	0.458	0.448
SD0454	0.948	0.883	SD0696	0.500	0.455
SD0455	0.746	0.645	SD0697	0.454	0.444
SD0456	0.840	0.860	SD0698	0.497	0.467
SD0457	0.473	0.402	SD0699	0.369	0.416
SD0458	0.555	0.514	SD0700	0.622	0.552
SD0459	0.566	0.472	SD0701	0.542	0.528
SD0460	0.609	0.478	SD0702	0.301	0.423
SD0461	0.408	0.355	SD0703	0.376	0.367
SD0462	0.630	0.532	SD0704	0.373	0.334
SD0463	0.631	0.497	SD0705	0.315	0.347
SD0464	0.549	0.510	SD0706	0.339	0.351
SD0465	0.966	0.809	SD0707	0.245	0.263
SD0466	0.910	0.841	SD0708	0.572	0.703
SD0467	0.904	0.878	SD0709	0.313	0.484
SD0468	0.999	1.009	SD0710	0.297	0.431
SD0469	0.734	0.760	SD0711	0.284	0.397
SD0470	0.925	0.806	SD0712	0.300	0.471

SD0471	0.559	0.482	SD0713	0.297	0.417
SD0472	0.572	0.543	SD0714	0.300	0.438
SD0473	0.652	0.594	SD0715	0.280	0.430

Example 5. *In vivo analysis of RNAi agent efficacy in transiently transgenic and transgenic mice.*

A) Administration and sample collection. In order to evaluate the efficacy of LPA RNAi agents *in vivo*, transiently transgenic mice were used. At least 30 days prior to cholesterol-conjugated LPA RNAi agent administration, wild-type mice were injected by hydrodynamic tail vein injection with a plasmid containing the SEAP gene under the control of the mouse albumin promoter. *LPA* gene target sequences were cloned in the 3′ UTR of the plasmid. These mice are noted as SEAP-LPA HTV mice. Cholesterol-conjugated LPA RNAi agents were administered to mice using MLP delivery polymer on day 1 (WO 2012/083185, incorporated herein by reference; melittin was synthesized and modified with CDM-NAG to yield MLP delivery polymer as described therein). Each mouse received an intravenous (IV) injection into the tail vein of 200-250 μL solution containing a dose of LPA RNAi agent + MLP delivery polymer (1:1 w/w RNAi agent: MLP delivery polymer in most cases). In some experiments, LPA RNAi agents were directly conjugated to a delivery polymer. Polymer conjugated LPA RNAi agents were similarly injected into tail vein. The indicated LPA RNAi agent (Table 8B) was conjugated to a polyacrylate polymer, ARF1164-106A-5, having 54.4% ethoxy ethyl amino acrylate (EEAA) amine monomers and 45.6% propyl acrylate propyl monomers (MW 41962 g/mol, polymer synthesized as described in WO 2013/158141) and masked with 3× ACit-NAG, 6× ACit-PEG (polymer masked as described in WO 2012/092373 and PCT/US16/34512). Control serum (pre-treatment) samples were taken from the mice pre-injection on days −4, or −1. Post injection serum samples were taken from the mice days 4, 8, 15, 22, 29, 36, and 43. For some mice, samples were collected on day 3 or day 5, instead of day 4.

In additional experiments, LPA RNAi agents were evaluated *in vivo* using transiently transgenic mice expressing full length *LPA*. At least 30 days prior to cholesterol-targeted LPA RNAi agent administration, immune compromised (Nod.scid) mice were injected by hydrodynamic tail vein injection with a minicircle containing the *LPA* cDNA under the control of the mouse albumin promoter. These mice are noted as LPA mc HTV mice. Either cholesterol-targeted or NAG (also termed GalNAc)-conjugated LPA RNAi agents were

administered to mice on day 1. For Cholesterol-targeted RNAi agents, each mouse received an intravenous (IV) injection into the tail vein of 200-250 μL solution containing a dose of RNAi agent + MLP delivery polymer (1:1 w/w RNAi agent:MLP delivery polymer). For NAG conjugated LPA RNAi agents, mice received a subcutaneous (SC) injection into the loose skin on the back between the shoulders of 300 μl solution containing a dose of the RNAi agent in buffered saline. For some sample, the LPA RNAi agent was administered either with or without MLP delivery peptide. RNAi agents delivered with MLP delivery peptide were administered by intravenous (IV) injection into the tail vein of 200-250 μL solution containing a dose of RNAi agent + MLP delivery polymer (1:2 w/w RNAi agent: MLP delivery polymer in most cases). Control serum (pre-treatment) samples were taken from the mice pre-injection on days −4, or −1. Post injection serum samples were taken from the mice days 4, 8, 15, 22, 29, 36, and 43. For some mice, samples were collected on day 3 or day 5, instead of day 4.

In further experiments, LPA RNAi agents were administered to apo(a) and Lp(a) transgenic mice (Frazer KA et al 1995, Nature Genetics 9:424-431). This mouse expresses human apo(a) from a YAC containing the full *LPA* gene (encoding apo(a) protein) with additional sequences both 5′ and 3′. Lp(a) mice were bred by crossing apo(a) YAC-containing mice to human apoB-100 expressing mice (Callow MJ et al 1994, PNAS 91:2130-2134). Cholesterol-targeted RNAi agents and NAG conjugated RNAi agents were administered as described above. Control serum (pre-treatment) samples were taken from the mice pre-injection on day −1. Post injection serum samples were taken from the mice days 4, 8, 15, 22, 29, 36, 43, 50, 57 and 64.

B) LPA expression knockdown analyses. For SEAP-LPA HTV mice, SEAP protein levels in serum were monitored by assaying serum from the mice using Phospha-Light™, a chemiluminescent reporter gene assay system (Life Technologies). For normalization, SEAP level for each animal at a given time point was divided by the pre-treatment level of expression in that animal to determine the ratio of expression “normalized to pre-treatment”. Expression at a specific time point was then averaged amongst individuals within the group.

For LPA mc HTV mice and transgenic mice, human apo(a) protein levels in serum were monitored by assaying serum from mice using an ELISA for apo(a) (Abcam). For normalization, apo(a) level for each animal at a time point was divided by the pre-treatment level of expression in that animal (in this case at day 1) to determine the ratio of expression “normalized to day 1”. Expression at a specific time point was then normalized to the saline

control group by dividing the "normalized to day 1" ratio for an individual animal by the mean "normalized to day 1" ratio of all mice in the saline control group. This resulted in expression for each time point normalized to that in the control group.

Lp(a) levels were determined on a Cobas Integra 400 (Roche Diagnostics) according to the manufacturer's recommendations. For normalization, apo(a) level for each animal at a time point was divided by the pre-treatment level of expression in that animal (in this case at day 1) to determine the ratio of expression "normalized to day 1". Expression at a specific time point was then normalized to the saline control group by dividing the "normalized to day 1" ratio for an individual animal by the mean "normalized to day 1" ratio of all mice in the saline control group. This resulted in expression for each time point normalized to that in the control group.

Table 8A. Relative LPA levels in mouse following intravenous administration of cholesterol-conjugated LPA RNAi agents + MLP delivery polymer.

Duplex ID	LPA RNAi agent (mg/kg)	MLP (mg/kg)	Relative LPA
AD01184	2	2	0.20
AD01187	2	2	0.18
AD01190	2	2	0.17
AD01193	2	2	0.22
AD01196	2	2	0.02
AD01197	2	2	0.065
AD01198	2	2	0.051
AD01199	2	2	0.070
AD01200	2	2	0.094
AD01201	2	2	0.029
AD01202	8	8	0.14
AD01205	2	2	0.21
AD01206	2	2	0.37
AD01207	2	2	0.19
AD01208	2	2	0.35
AD01209	2	2	0.16
AD01210	2	2	0.18
AD01211	2	2	0.38
AD01212	2	2	0.26
AD01213	2	2	0.30
AD02662	2	2	0.0010
AD02663	2	2	0.010
AD02664	2	2	0.0010

Table 8B. Relative LPA levels in mouse following intravenous administration of delivery polymer-conjugated LPA RNAi agents.

Duplex ID	LPA RNAi agent (mg/kg)	Relative LPA
AD01462	0.5	0.38
AD01463	0.5	0.41
AD01466	0.5	0.33
AD01467	0.5	0.46

Table 8C. Relative LPA levels in mouse following subcutaneous administration of NAG-conjugated LPA RNAi agents.

Duplex ID	LPA RNAi agent (mg/kg)	Relative LPA	Duplex ID	LPA RNAi agent (mg/kg)	Relative LPA
AD01529	10	0.068	AD02920	10	0.050
AD01530	10	0.43	AD02921	10	0.040
AD01531	10	0.62	AD02922	10	0.080
AD01532	10	0.18	AD02923	10	0.040
AD01533	10	0.30	AD02924	10	0.050
AD01534	10	0.44	AD02925	10	0.030
AD01765	10	0.14	AD02926	10	0.17
AD01766	10	0.52	AD02927	10	0.31
AD01767	10	0.51	AD02928	10	0.081
AD01768	10	0.15	AD02929	10	0.065
AD01769	10	0.56	AD02930	10	0.15
AD01770	10	0.29	AD02931	10	0.13
AD01772	10	0.25	AD02932	10	0.11
AD01773	10	0.28	AD03049	3	0.20
AD01774	10	0.24	AD03050	3	0.087
AD01780	10	0.34	AD03051	3	0.070
AD01804	10	0.68	AD03052	3	0.080
AD01976	10	0.27	AD03053	3	0.23
AD01977	10	0.27	AD03054	3	0.050
AD01978	10	0.53	AD03058	3	0.27
AD01979	10	0.044	AD03059	3	0.22
AD01980	10	0.087	AD03060	3	0.31
AD01981	10	0.074	AD03061	3	0.16
AD01982	10	0.066	AD03062	3	0.20
AD01983	10	0.078	AD03063	3	0.13
AD01984	10	0.036	AD03064	3	0.21
AD01985	10	0.0070	AD03065	3	0.085
AD01986	10	0.019	AD03066	3	0.10
AD01987	10	0.019	AD03067	3	0.094
AD01988	10	0.042	AD03068	3	0.17
AD01989	10	0.053	AD03069	3	0.077
AD01990	10	0.017	AD03070	3	0.36

AD02001	10	0.021	AD03071	3	0.043
AD02003	10	0.050	AD03072	3	0.031
AD02004	10	0.050	AD03073	3	0.019
AD02005	10	0.040	AD03074	3	0.016
AD02006	10	0.11	AD03075	3	0.062
AD02007	10	0.21	AD03114	1	0.33
AD02008	10	0.080	AD03115	1	0.30
AD02009	10	0.090	AD03116	1	0.21
AD02010	10	0.16	AD03117	1	0.14
AD02011	10	0.070	AD03118	1	0.30
AD02435	10	0.038	AD03119	1	0.10
AD02436	10	0.027	AD03120	1	0.080
AD02437	10	0.052	AD03121	1	0.14
AD02438	10	0.063	AD03122	1	0.14
AD02439	10	0.073	AD03123	1	0.34
AD02440	10	0.13	AD03156	1	0.084
AD02545	10	0.079	AD03157	1	0.016
AD02546	10	0.045	AD03158	1	0.037
AD02547	10	0.055	AD03159	1	0.63
AD02548	10	0.13	AD03272	1	0.13
AD02549	10	0.071	AD03273	1	0.20
AD02550	10	0.039	AD03274	1	0.21
AD02551	10	0.057	AD03275	1	0.15
AD02552	10	0.033	AD03276	1	0.11
AD02553	10	0.14	AD03277	1	0.13
AD02554	10	0.14	AD03278	1	0.13
AD02555	10	0.18	AD03279	1	0.21
AD02556	10	0.10	AD03341	1	0.13
AD02557	10	0.10	AD03421	1	0.29
AD02558	10	0.071	AD03430	1	0.12
AD02559	10	0.039	AD03432	1	0.16
AD02560	10	0.058	AD03434	1	0.11
AD02561	10	0.12	AD03436	1	0.21
AD02609	3	0.59	AD03438	1	0.25
AD02610	3	0.36	AD03440	1	0.21
AD02611	3	0.35	AD03460	1	0.090
AD02612	3	0.37	AD03462	1	0.40
AD02613	3	0.24	AD03495	1	0.28
AD02614	3	0.24	AD03536	1	0.14
AD02615	3	0.14	AD03538	0.5	0.26
AD02616	3	0.25	AD03539	0.5	0.21
AD02617	3	0.090	AD03540	1	0.15
AD02618	3	0.11	AD03541	0.5	0.10
AD02619	3	0.020	AD03542	1	0.94
AD02620	3	0.11	AD03547	1	0.19
AD02682	10	0.11	AD03548	1	0.73
AD02683	10	0.14	AD03549	1	0.29

AD02684	10	0.79	AD03573	1	0.15
AD02685	10	0.78	AD03574	1	0.15
AD02686	10	0.19	AD03575	1	0.13
AD02687	10	0.27	AD03576	1	0.18
AD02696	3	0.050	AD03577	0.5	0.18
AD02710	3	0.040	AD03578	0.5	0.38
AD02711	3	0.040	AD03579	0.5	0.53
AD02712	3	0.49	AD03603	1	0.083
AD02713	3	0.040	AD03604	1	0.091
AD02714	3	0.040	AD03605	1	0.19
AD02715	3	0.070	AD03608	1	0.18
AD02716	3	0.080	AD03609	1	0.16
AD02717	3	0.12	AD03610	1	0.23
AD02745	3	0.25	AD03611	1	0.40
AD02746	3	0.22	AD03612	1	0.21
AD02747	3	0.081	AD03629	1	0.11
AD02748	3	0.17	AD03668	1	0.070
AD02749	3	0.17	AD03705	0.5	0.11
AD02750	3	0.066	AD03707	0.5	0.11
AD02751	3	0.070	AD03720	0.5	0.14
AD02752	3	0.044	AD03721	0.5	0.094
AD02753	3	0.071	AD03722	0.5	0.19
AD02819	1	0.022	AD03723	0.5	0.10
AD02820	1	0.042	AD03765	1	0.080
AD02821	1	0.038	AD03771	1	0.10
AD02825	3	0.050	AD03801	1	0.15
AD02826	3	0.050	AD03802	1	0.18
AD02827	3	0.050	AD03844	1	0.17
AD02828	3	0.050	AD03845	1	0.25
AD02829	3	0.040	AD03848	1	0.10
AD02830	3	0.040	AD03850	1	0.052
AD02831	3	0.030	AD03851	1	0.076
AD02832	3	0.030	AD03852	1	0.13
AD02841	3	0.061	AD03853	1	0.081
AD02842	3	0.16	AD03854	1	0.21
AD02843	3	0.10	AD03856	1	0.32
AD02844	3	0.11	AD03859	1	0.15
AD02845	3	0.22	AD03862	1	0.12
AD02846	3	0.16	AD03863	1	0.12
AD02847	3	0.066	AD03921	1	0.17
AD02848	3	0.055	AD03922	1	0.057
AD02849	3	0.083	AD03923	1	0.066
AD02850	3	0.042	AD03924	1	0.14
AD02851	3	0.063	AD03931	1	0.34
AD02852	3	0.11	AD03932	1	0.15
AD02907	10	0.10	AD03933	1	0.34
AD02908	10	0.11	AD03424	1	0.15

AD02909	10	0.049	AD03425	1	0.21
AD02910	10	0.23	AD03426	1	0.21
AD02911	10	0.20	AD03427	1	0.19
AD02912	10	0.10	AD03428	1	0.18
AD02913	10	0.070	AD03760	0.5	0.21
AD02914	10	0.050	AD03762	0.5	0.17
AD02915	10	0.10	AD03763	0.5	0.21
AD02916	10	0.090	AD03764	0.5	0.28
AD02917	10	0.060	AD03766	0.5	0.065
AD02918	10	0.020	AD03847	1	0.15
AD02919	10	0.030	AD04110	1	0.070

Example 6. *In vivo Screening of LPA RNAi agents and time course of SEAP knockdown.* Cholesterol-conjugated LPA RNAi agents were administered to transiently transgenic mice as described above. Each mouse received a single intravenous (IV) dose of 8 mg/kg of LPA RNAi agent with 8 mg/kg of MLP delivery polymer. SEAP protein levels in serum were monitored for up to 36 days. Knockdown levels and duration of response are shown in Table 9. A decrease in SEAP serum protein level of greater than 85% was obtained following administration of all LPA RNAi agents tested; with all but two LPA RNAi agents tested showing greater than 99.4% knockdown. AD01196 and AD01199 showed >95% knockdown at day 36.

Example 7. *In vivo screening LPA RNAi agents and time course of LPA knockdown at lower LPA RNAi agent doses*. Cholesterol-conjugated LPA RNAi agents were administered to transiently transgenic mice as described above. Each mouse received a single intravenous (IV) dose of 2 mg/kg of LPA RNAi agent with 2 mg/kg of MLP delivery polymer. SEAP protein levels in serum were monitored for up to 43 days (Table 10).

Example 8. *In vivo testing of LPA RNAi agents in apo(a) Transgenic (Tg) mice.* AD01196 was administered to mice as described above. Each mouse received a single intravenous (IV) dose of either 2 mg/kg of LPA RNAi agent with 2 mg/kg of MLP delivery polymer or saline. Human apo(a) (apo(a)) levels in serum were monitored for up to 64 days (Table 11). At day 15, animals in the saline group received a single IV dose of 2 mg/kg of a control mouse Factor VII (F7) RNAi agent with 2 mg/kg of MLP delivery polymer. At day 22, F7 levels were measured in all animals. F7 activity was knocked down by 99% 7 days post dosing, with no effect on serum apo(a) levels. AD01196 showed >3 log10 knockdown of apo(a) levels at nadir, with >80% knockdown observed after 3 weeks (Table 11).

Table 9. Serum SEAP protein levels in SEAP-LPA HTV mice following administration of 8 mg/kg chol-RNAi agents with 8 mg/kg MLP delivery peptide. SEAP levels were normalized to day −1 and saline control.

Treatment	Day −1		Day 4		Day 8		Day 15		Day 22		Day 29		Day 36	
	Ave	SD	Ave	SD	Ave	SD	Ave	SD	Ave	SD	Ave	SD	Ave	SD
Saline	1.00	0.24	1.00	0.34	1.00	0.13	1.00	0.33	1.00	0.09	1.00	0.18	1.00	0.44
AD01184	1.00	0.39	0.27	0.10	0.15	0.06	0.01	0.00	0.07	0.04	0.43	0.39	0.98	0.73
AD01187	1.00	0.53	0.24	0.15	0.13	0.10	0.00	0.00	0.01	0.01	0.08	0.06	0.56	0.47
AD01190	1.00	0.77	0.26	0.20	0.14	0.11	0.00	0.00	0.00	0.00	0.00	0.00	0.02	0.01
AD01193	1.00	0.99	0.25	0.26	0.15	0.17	0.01	0.01	0.00	0.00	0.01	0.01	0.02	0.01
AD01196	1.00	0.59	0.24	0.13	0.14	0.08	0.00	0.00	0.00	0.00	0.01	0.01	0.04	0.03
AD01199	1.00	0.52	0.23	0.15	0.13	0.10	0.00	0.00	0.00	0.00	0.01	0.00	0.04	0.02
AD01202	1.00	0.93	0.25	0.24	0.17	0.16	0.14	0.12	0.56	0.55	0.78	0.66	2.09	2.00

Table 10. Serum SEAP protein levels in SEAP-LPA HTV mice following administration of 2 mg/kg chol-RNAi agents with 2 mg/kg MLP delivery peptide. SEAP levels were normalized to day −1 and saline control.

Treatment	Day -4		Day 4		Day 9		Day 15		Day 22		Day 29		Day 36		Day 43	
	Ave.	SD	Ave.	SD	Ave.	SD	Ave.	SD	Ave.	SD	Ave.	SD	Ave.	SD	Ave.	SD
Saline	1.00	0.00	1.00	0.72	1.00	0.72	1.00	0.71	1.00	0.43	1.00	0.79	1.00	0.48	1.00	0.54
AD01196	1.00	0.00	0.22	0.08	0.05	0.05	0.02	0.01	0.13	0.04	0.36	0.12	0.69	0.08	1.39	0.91
AD01199	1.00	0.00	0.27	0.28	0.07	0.06	0.17	0.17	0.59	0.51	0.74	0.74	0.83	0.82	1.01	0.58
AD01205	1.00	0.00	0.21	0.13	0.31	0.23	0.45	0.21	1.33	0.68	1.11	0.82	1.55	1.30	1.79	1.09
AD01208	1.00	0.00	0.43	0.20	0.35	0.15	0.68	0.19	1.45	0.44	1.32	0.26	1.39	0.52	0.99	0.12
AD01211	1.00	0.00	0.38	0.14	0.53	0.20	0.94	0.38	1.96	0.93	1.05	0.27	1.44	0.38	0.93	0.28
AD01184	1.00	0.00	0.26	0.07	0.20	0.05	0.61	0.17	1.28	0.14	1.21	0.51	1.39	0.80	ND	ND
AD01187	1.00	0.00	0.37	0.18	0.09	0.07	0.18	0.17	0.86	0.84	0.77	0.33	1.80	0.36	ND	ND
AD01190	1.00	0.00	0.26	0.08	0.17	0.07	0.36	0.13	1.16	0.37	1.39	0.69	1.96	1.64	ND	ND
AD01193	1.00	0.00	0.39	0.27	0.22	0.33	0.32	0.37	0.67	0.58	0.84	0.46	1.27	0.23	ND	ND

Table 11. Serum apo(a) protein levels in apo(a) Tg mice following administration of 2 mg/kg cholesterol-conjugated LPA RNAi agent with 2 mg/kg MLP delivery polymer. Apo(a) levels were normalized to day −1 and saline control.

Treatment	Day −1		Day 4		Day 8		Day 15		Day 22	
	Ave	SD	Ave	SD	Ave	SD	Ave	SD	Ave	SD
Saline	1.00	0.00	1.00	0.06	1.00	0.27	1.00	0.06	1.00	0.17
AD01196	1.00	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.15	0.08
	Day 29		Day 36		Day 43		Day 50			
	Ave	SD	Ave	SD	Ave	SD	Ave	SD		
Saline	1.00	0.12	1.00	0.04	1.00	0.26	1.00	0.24		
AD01196	0.40	0.23	0.74	0.61	0.75	0.67	0.77	0.52		

Example 9. *Apolipoprotein (a) (apo(a)) knockdown in non-human primates following LPA RNAi agent delivery by MLP delivery polymer.* MLP delivery polymer and LPA RNAi agent were made and combined in a pharmaceutically acceptable buffer as described above. On day 1, two cynomolgus macaque (Macaca fascicularis) primates (both male, 5.0kg and 8.15 kg, respectively) were injected with 2 mg/kg AD01196 + 2 mg/kg MLP delivery polymer. For each injection, the LPA RNAi agent + MLP delivery polymer (2 ml/kg) was injected into the saphenous vein using a 22 to 25 gauge intravenous catheter. At the indicated time points (indicated in Table 12), blood samples were drawn and analyzed for apo(a) levels, lipid levels and toxicity markers. Blood was collected from the femoral vein and primates were fasted overnight before all blood collections. Blood tests for blood urea nitrogen (BUN), alanine transaminase (ALT), aspartate aminotransferase (AST), creatinine, total cholesterol (TC) and triglycerides (TG) were performed on an automated chemistry analyzer at Meriter laboratories. Blood tests for Lipoprotein (a) (Lp(a)) and Low density lipoprotein (LDL) were measured on an automated chemistry analyzer. Serum apo(a) levels were measured by ELISA. Significant knockdown of apo(a) was observed with an average maximum knockdown of 94.5% observed at day 22. Average maximum knockdown of Lp(a) was 91.5% observed at day 15 (FIG. 3). No dose-related toxicity was observed in treated animals.

Table 12. Serum apo(a) protein, Lipoprotein(a) (mg/dL), Low density Lipoprotein (LDL), Total cholesterol, and triglyceride levels in cynomolgus macaque (Macaca fascicularis) primates following administration of 2 mg/kg AD01196 with 2 mg/kg MLP delivery polymer. Apo(a) levels were normalized to predose.

day	Serum apo(a) protein levels		Lipoprotein(a) levels (mg/dL)		Low Density Lipoprotein calculated (mg/dL)		Total Cholesterol (mg/dL)		Triglycerides (mg/dL)	
	animal 1	animal 2	animal 1	animal 2	animal 1	animal 2	animal 1	animal 2	animal 1	animal 2
pre	1.00	1.00	77.1	126.7	48.4	84.7	95	149	41	36
3	0.47	0.55	46.0	65.0	53.6	83.5	93	143	33	28
8	0.12	0.15	9.3	16.5	53.4	75.9	101	147	36	30
15	0.10	0.10	5.0	7.3	49.8	60.9	106	136	79	34
22	0.05	0.06	7.9	10.3	47.5	63.9	97	136	34	36
29	0.08	0.11	13.4	27.0	55.7	47.5	101	116	20	36
36	0.15	0.25	22.2	50.6	56.8	73.1	-	-	-	-
43	0.19	0.23	31.4	45.5	53.8	55.7	103	138	29	39
50	0.27	0.29	46.1	67.3	52.3	70.9	-	-	-	-
57	0.27	0.3	52.7	69.7	52.1	78.6	104	157	34	39
64	0.33	0.31	68.4	73.7	52.4	75.8	-	-	-	-
71	0.50	0.4	76.8	78.6	62.4	75.0	104	149	43	47
85	0.31	0.34	63.1	75.4	50.3	68.8	102	145	41	49
99	0.27	0.29	67.9	78.8	58.7	72.5	102	150	42	52
120	0.36	0.37	91.7	119.4	53.4	79.8	100	154	43	51

5

Table 13. Urea Nitrogen, Creatinine, Alanine transaminase, and Aspartate aminotransferase levels in cynomolgus macaque (Macaca fascicularis) primates following administration of 2 mg/kg AD01196 with 2 mg/kg MLP delivery polymer.

	Blood Urea Nitrogen (mg/dL)		Creatinine (mg/dL)		Alanine transaminase (U/L)		Aspartate aminotransferase (U/L)	
day	animal 1	animal 2	animal 1	animal 2	animal 1	animal 2	animal 1	animal 2
predose	16	16	0.79	0.70	37	32	32	33
3	11	14	0.70	0.61	40	42	33	35
8	14	13	0.78	0.58	33	38	25	31
15	15	15	0.67	0.59	51	35	47	32
22	15	15	0.8	0.55	47	35	29	30
29	12	12	0.61	0.59	30	31	23	36
36	-	-	-	-	-	-	-	-
43	12	15	0.64	0.58	29	29	25	30
50	-	-	-	-	-	-	-	-
57	14	15	0.72	0.64	32	35	28	31
64	-	-	-	-	-	-	-	-

71	14	15	0.73	0.69	36	35	29	33
85	14	15	0.60	0.70	126	41	51	40
99	15	18	0.66	0.68	151	40	44	37
120	14	19	0.72	0.60	37	51	28	47

Example 10. *In vivo Screening of NAG-conjugated LPA RNAi agents and time course of knockdown.* NAG-conjugated LPA RNAi agents were administered to transiently transgenic mice as described above. Each mouse received either single intravenous (IV) dose of 2 mg/kg of LPA RNAi agent with 1 mg/kg of MLP delivery polymer, or a single subcutaneous (SC) dose of 10 mg/kg of the NAG-conjugated LPA RNAi agent. SEAP protein levels in serum were monitored for up to 22 days. Knockdown levels and duration of response are shown in Tables 14-15. AD01529, AD01532 and AD01533 showed ≥85% knockdown of SEAP levels following IV administration with MLP deliver polymer, and ≥60% maximum knockdown of SEAP levels following SC administration of the NAG-conjugated LPA RNAi agent alone.

Table 14. Serum SEAP protein levels in SEAP-LPA HTV mice following SC administration of 10 mg/kg NAG-conjugated LPA RNAi agents. SEAP levels were normalized to day −1 and saline control.

Treatment	Day −1		Day 4		Day 8		Day 15		Day 22	
	Ave	SD	Ave	SD	Ave	SD	Ave	SD	Ave	SD
Saline	1.00	0.00	1.00	0.14	1.00	0.14	1.00	0.66	1.00	0.27
AD01529	1.00	0.00	0.45	0.07	0.36	0.03	0.60	0.08	0.90	0.37
AD01530	1.00	0.00	0.46	0.15	0.43	0.10	0.79	0.26	0.79	0.32
AD01531	1.00	0.00	0.64	0.13	0.62	0.06	0.99	0.28	1.17	0.29
AD01532	1.00	0.00	0.41	0.12	0.37	0.11	0.99	0.34	1.33	0.11
AD01533	1.00	0.00	0.40	0.03	0.22	0.08	0.37	0.15	0.63	0.13
AD01534	1.00	0.00	0.65	0.19	0.44	0.19	0.74	0.30	1.17	0.55

Table 15. Serum SEAP protein levels in SEAP-LPA HTV mice following IV administration of 1 mg/kg NAG-conjugated LPA RNAi agents + 2 mg/kg MLP delivery polymer. SEAP levels were normalized to day −1 and saline control.

Treatment	Day −1		Day 4		Day 8		Day 15		Day 22	
	Ave	SD	Ave	SD	Ave	SD	Ave	SD	Ave	SD
Saline	1.00	0.00	1.00	0.33	1.00	0.46	1.00	0.21	1.00	0.39
F7 Control	1.00	0.00	0.61	0.05	0.71	0.45	1.25	0.44	1.05	0.49
AD01529	1.00	0.00	0.25	0.04	0.15	0.08	0.47	0.24	0.81	0.40
AD01530	1.00	0.00	0.26	0.06	0.28	0.19	0.78	0.60	1.06	0.63
AD01531	1.00	0.00	0.22	0.07	0.26	0.06	0.72	0.21	1.04	0.12

AD01532	1.00	0.00	0.18	0.05	0.06	0.03	0.13	0.08	0.29	0.18
AD01533	1.00	0.00	0.21	0.04	0.13	0.06	0.32	0.15	0.67	0.28
AD01534	1.00	0.00	0.17	0.04	0.22	0.06	0.66	0.24	0.94	0.24

Example 11. *In vivo Screening of modified NAG-conjugated LPA RNAi agents and time course of knockdown.* The indicated NAG-conjugated LPA RNAi agents were administered to SEAP-LPA HTV mice as described above. Each mouse received a single subcutaneous (SC) dose of 10 mg/kg of the NAG-conjugated LPA RNAi agent. SEAP protein levels in serum were monitored for up to 22 days. Knockdown levels and duration of response are shown in Tables 16-17. AD01765 and AD01768 showed 89% knockdown activity.

Table 16. Serum SEAP protein levels in SEAP-LPA HTV mice following SC administration of 10 mg/kg NAG-conjugated LPA RNAi agent. SEAP levels were normalized to day −1 and saline control.

Treatment	Day −1		Day 3		Day 8		Day 15		Day 22	
	Ave	SD	Ave	SD	Ave	SD	Ave	SD	Ave	SD
Saline	1.00	0.00	1.00	0.16	1.00	0.16	1.00	0.28	1.00	0.24
AD01533	1.00	0.00	0.41	0.08	0.22	0.02	0.47	0.20	0.66	0.29
AD01772	1.00	0.00	0.46	0.13	0.18	0.00	0.34	0.09	0.61	0.14
AD01773	1.00	0.00	0.47	0.08	0.20	0.08	0.45	0.15	0.83	0.12
AD01774	1.00	0.00	0.49	0.09	0.18	0.03	0.44	0.13	0.68	0.08
AD01780	1.00	0.00	0.52	0.13	0.25	0.09	0.44	0.26	0.65	0.37

Table 17. Serum SEAP protein levels in SEAP-LPA HTV mice following SC administration of 10 mg/kg NAG-conjugated LPA RNAi agent. SEAP levels were normalized to day −1 and saline control.

Treatment	Day −1		Day 3		Day 8		Day 15		Day 22	
	Ave	SD	Ave	SD	Ave	SD	Ave	SD	Ave	SD
Saline	1.00	0.00	1.00	0.27	1.00	0.73	1.00	0.87	1.00	0.80
AD01532	1.00	0.00	0.42	0.19	0.35	0.21	0.85	0.25	1.27	0.57
AD01765	1.00	0.00	0.35	0.02	0.11	0.08	0.25	0.14	0.47	0.19
AD01766	1.00	0.00	0.52	0.10	0.36	0.09	1.05	0.13	1.15	0.08
AD01767	1.00	0.00	0.49	0.03	0.44	0.05	1.43	0.23	1.33	0.71
AD01768	1.00	0.00	0.34	0.15	0.11	0.07	0.39	0.13	0.76	0.19
AD01769	1.00	0.00	0.54	0.17	0.46	0.14	1.32	0.12	1.38	0.37
AD01770	1.00	0.00	0.41	0.07	0.20	0.10	0.80	0.52	1.04	0.67

Example 12. *In vivo testing of NAG-conjugated LPA RNAi agents in apo(a) Tg mice.* NAG-conjugated LPA RNAi agents were administered to apo(a) Tg mice as described above. Each mouse received a single subcutaneous (SC) dose of either 10 mg/kg of LPA RNAi agent or saline. Human apo(a) (apo(a)) levels in serum were monitored for up to 22 days (Table 18). AD01765 showed the largest knockdown of apo(a) levels at day 8 with 96% knockdown, and >74% knockdown observed 3 weeks after dosing.

Table 18. Serum apo(a) protein levels in apo(a) Tg mice following SC administration of 10 mg/kg NAG-conjugated LPA RNAi agent. Apo(a) levels were normalized to day −1 and saline control.

Treatment	Day −1		Day 4		Day 8		Day 15		Day 22	
	Ave	SD	Ave	SD	Ave	SD	Ave	SD	Ave	SD
Saline	1.00	0.00	1.00	0.10	1.00	0.16	1.00	0.42	1.00	0.21
AD01532	1.00	0.00	0.12	0.05	0.22	0.08	0.76	0.30	0.56	0.28
AD01765	1.00	0.00	0.09	0.03	0.04	0.02	0.14	0.02	0.26	0.04
AD01768	1.00	0.00	0.11	0.05	0.09	0.05	0.26	0.12	0.38	0.08

Example 13. *In vivo testing of NAG-conjugates LPA RNAi agents in LPA mc HTV mice.* Indicated NAG-conjugated LPA RNAi agents were administered to LPA mc HTV mice as described above. Each mouse received a single subcutaneous (SC) dose of either 10 mg/kg of LPA RNAi agent or saline. Human apo(a) (apo(a)) levels in serum were analyzed at day 4 (Table 19). AD02001, AD01765 and AD01768 showed >90% knockdown at day 4.

Table 19. Serum apo(a) protein levels in LPA mc HTV mice following SC administration of 10 mg/kg NAG-conjugated LPA RNAi agent. Apo(a) levels were normalized to day −1 and saline control.

Treatment	Prebleed		Day 4	
	Ave	SD	Ave	SD
saline	1.00	0.00	1.00	0.12
AD01765	1.00	0.00	0.05	0.02
AD01768	1.00	0.00	0.07	0.01
AD01804	1.00	0.00	0.68	0.16
AD02001	1.00	0.00	0.06	0.03

Example 14. *Apolipoprotein (a) (apo(a)) knockdown in non-human primates following LPA RNAi agent delivery by MLP delivery polymer.* MLP delivery polymer and LPA RNAi agent were made and combined in a pharmaceutically acceptable buffer. On day 1 and day 71, two

cynomolgus macaque (Macaca fascicularis) primates were injected with either 4 mg/kg AD01196 + 4 mg/kg MLP delivery polymer or 6 mg/kg AD01196 + 6 mg/kg MLP delivery polymer. For each injection, the LPA RNAi agent + MLP delivery polymer was injected into the saphenous vein using a 22 to 25 gauge intravenous catheter. At the indicated time points (FIG. 4), blood samples were drawn and analyzed for apo(a) levels, lipid levels and toxicity markers as previously described. Significant knockdown of apo(a) was observed after the first dose with an average maximum knockdown of 96% for 4 mg/kg dose on day 15, and 96% for 6 mg/kg dose observed at day 15. Average maximum knockdown of Lp(a) after the first dose was 98.5% for 4 mg/kg dose on day 29, and 98.5% for 6 mg/kg dose on day 22. No dose-related toxicity was observed in treated animals.

Example 15. *In vivo testing of NAG-conjugated LPA RNAi agents in Lp(a) Tg mice-Dose Response.* NAG-conjugated LPA RNAi agents were administered to Lp(a) Tg mice as described above. Each mouse received a single subcutaneous (SC) dose of either LPA RNAi agent at 0.5 mg/kg or 2 mg/kg dose levels or saline. Lp(a) levels in serum were monitored up to day 43 (FIG. 1, FIG. 2). All LPA RNAi agents showed dose-response with the higher doses showing greater knockdown with nadir between days 15 and 22.

Example 16. *Apolipoprotein (a) (apo(a)) knockdown in non-human primates following apo(a) specific LPA RNAi agent molecule delivery.* LPA RNAi agent was prepared in a pharmaceutically acceptable buffer as described herein for subcutaneous (SC) injection. On days 1, 7, and 15, two cynomolgus macaque (Macaca fascicularis) primates were injected subcutaneously with 3 mg/kg of AD02713, AD02819, AD02820, or AD02821. In addition, AD02819-treated monkeys were dosed again with 3 mg/kg of AD02819 on day 57 and day 85. Blood samples were drawn and analyzed for apo(a) levels, lipid levels and toxicity markers as previously described. Significant knockdown of Lp(a) was observed with an average maximum knockdown of 89% observed at day 43 for AD02713, 87% observed on day 36 for AD02819, 79% observed on day 36 for AD02820, and 95% observed on day 29 for AD02821 (FIG. 5). No dose-related toxicity was observed in treated animals over the time of the experiment.

Example 17. *Apolipoprotein (a) (apo(a)) knockdown in non-human primates following LPA RNAi agent delivery.* LPA RNAi agent was prepared in a pharmaceutically acceptable buffer as described herein for subcutaneous (SC) injection. On day 1, two cynomolgus macaque (Macaca fascicularis) primates were injected subcutaneously with 3 mg/kg of AD03272,

AD03462, AD03549, AD03547, AD03668, AD03460, or AD03536. In addition, AD03460 and AD03536-treated monkeys were dosed again with 1 mg/kg of the respective LPA RNAi agent on day 48. Blood samples were drawn and analyzed for apo(a) levels, lipid levels and toxicity markers as previously described. Significant knockdown of Lp(a) was observed with an average maximum knockdown of 62% for AD03272 on day 15, 28% for AD03462 on day 15, 47% for AD03549 on day 29, 44% for AD03547 on day 15, 53% for AD03668 on day 22, 79% for AD03460 on day 29, and 71% for AD03536 on day 22 (FIG. 6). No dose-related toxicity was observed in treated animals over the time of the experiment.

Example 18. *Apolipoprotein (a) (apo(a)) knockdown in primate following apo(a) specific LPA RNAi agent molecule delivery.* LPA RNAi agent was made and combined in a pharmaceutically acceptable buffer as described above for subcutaneous (SQ) injection. On day 1, cynomolgus macaque (Macaca fascicularis) primates were injected with subcutaneously with saline or 2 mg/kg of AD03460, AD03536, AD03851, AD03853, or AD04110. Blood samples were drawn and analyzed for apo(a) levels, lipid levels and toxicity markers on days 8 and 15 as previously described. Lp(a) levels were normalized to average of three predose values.

Table 20. Lipoprotein(a) levels in cynomolgus macaque primates following administration of either saline or 2 mg/kg AD03460, AD03536, AD03851, AD03853 or AD04110.

	Normalized Lp(a) Day 8	Normalized Lp(a) Day 15
Saline	1.01 ±0.06	1.15 ±0.07
AD03460	0.68 ±0.12	0.40 ±0.13
AD03536	0.54 ±0.07	0.21 ±0.06
AD03851	0.41 ±0.08	0.18 ±0.08
AD03853	0.50 ±0.23	0.27 ±0.17
AD04110	0.59 ±0.13	0.43 ±0.10

Claims:

1. An apo(a) gene (LPA) RNA interference (RNAi) agent comprising a sense strand and an antisense strand, wherein the antisense strand comprises the sequence of any one of SEQ ID NO:1280, SEQ ID NO:1282, SEQ ID NO:1246, SEQ ID NO:1242, SEQ ID NO:1244, or SEQ ID NO:1254, and wherein the sense strand comprises a sequence that is complementary to the sequence of the antisense strand.

2. The LPA RNAi agent of claim 1, wherein the sense strand and antisense strand are each 19 to 26 nucleotides in length.

3. The LPA RNAi agent of claim 2, wherein the sense strand and antisense strand are each 26 nucleotides in length.

4. The LPA RNAi agent of claim 2, wherein the sense strand and antisense strand are each 21 nucleotides in length.

5. The LPA RNAi agent of any one of claims 1 to 4, wherein the LPA RNAi agent comprises at least one overhang.

6. The LPA RNAi agent of claim 5, wherein the LPA RNAi agent comprises an overhang at the 3' end of the antisense strand.

7. The LPA RNAi agent of claim 5, wherein the LPA RNAi agent comprises an overhang at the 3' end of the antisense strand and an overhang at the 3' end of the sense strand.

8. The LPA RNAi agent of any one of claims 1 to 4, wherein the LPA RNAi agent comprises at least one blunt end.

9. The LPA RNAi agent of claim 8, wherein the LPA RNAi agent comprises one blunt end and one frayed end.

10. The LPA RNAi agent of claim 8, wherein the LPA RNAi agent comprises two blunt ends.

11. The LPA RNAi agent of any one of claims 1 to 10, wherein the sense strand, the antisense strand, or both the sense and antisense strand comprise one or more modified nucleotides.

12. The LPA RNAi agent of claim 11, wherein the one or more modified nucleotides are independently selected from a 2'-modified nucleotide, a locked nucleotide, an abasic nucleotide, an inverted deoxynucleotide, a morpholino nucleotide, a 2',3'-seco nucleotide mimic, or a nucleotide containing a non-natural base.

13. The LPA RNAi agent of claim 12, wherein the 2'-modified nucleotide is a 2'-O-methyl nucleotide, a 2'-deoxy-2'-fluoro nucleotide, a 2'-deoxynucleotide, a 2'-methoxyethyl nucleotide, a 2'-amino nucleotide, or a 2'-alkyl nucleotide.

14. The LPA RNAi agent of any one of claims 1 to 13, wherein the LPA RNAi agent comprises one or more phosphorothioate internucleoside linkages.

15. The LPA RNAi agent of claim 14, wherein both the sense and antisense strand independently comprise 1, 2, 3, or 4 phosphorothioate internucleoside linkages.

16. The LPA RNAi agent of any one of claims 1 to 15, wherein the LPA RNAi agent further comprises a targeting group.

17. The LPA RNAi agent of claim 16, wherein the targeting group comprises an asialoglycoprotein receptor ligand.

18. The LPA RNAi agent of claim 17, wherein the asialoglycoprotein receptor ligand comprises galactose, galactosamine, N-acetyl-galactosamine (NAG), or a galactose derivative.

19. The LPA RNAi agent of claim 16, wherein the targeting group is (Chol-TEG), (TEG-Chol), (C11-PEG3-NAG3), (C6-PEG4-NAG3), (NAG3), (NAG4), (NAG3-AA2), (NAG3-Palm), (NAG13), (NAG18), (NAG24), (NAG25), (NAG25)s, (NAG26), (NAG27), (NAG28), (NAG29), (NAG30), (NAG30)s, (NAG31), (NAG13), (NAG31s), (NAG32), (NAG33),

(NAG34), (NAG35), (NAG36), or (NAG37).

20. The LPA RNAi agent of any one of claims 16 to 19, wherein the targeting group is conjugated to the 3' end of the sense strand.

21. The LPA RNAi agent of any one of claims 16 to 19, wherein the targeting group is conjugated to the 5' end of the sense strand.

22. The LPA RNAi agent of any one of claims 1 to 21, wherein:

a) the antisense strand comprises the sequence of SEQ ID NO:1246 and the sense strand comprises the sequence of SEQ ID NO:1247;

b) the antisense strand comprises the sequence of SEQ ID NO:1242 and the sense strand comprises the sequence of SEQ ID NO:1243;

c) the antisense strand comprises the sequence of SEQ ID NO:1244 and the sense strand comprises the sequence of SEQ ID NO:1245;

d) the antisense strand comprises the sequence of SEQ ID NO:1254 and the sense strand comprises the sequence of SEQ ID NO:1255;

e) the antisense strand comprises the sequence of SEQ ID NO:1280 and the sense strand comprises the sequence of SEQ ID NO:1260;

f) the antisense strand comprises the sequence of SEQ ID NO:1280 and the sense strand comprises the sequence of SEQ ID NO:1284; or

g) the antisense strand comprises the sequence of SEQ ID NO:1282 and the sense strand comprises the sequence of SEQ ID NO:1259.

23. The LPA RNAi agent of any one of claims 1 to 21, wherein:

a) the antisense strand comprises the sequence of SEQ ID NO:156 and the sense strand comprises the sequence of SEQ ID NO:310;

b) the antisense strand comprises the sequence of SEQ ID NO:164 and the sense strand comprises the sequence of SEQ ID NO:357;

c) the antisense strand comprises the sequence of SEQ ID NO:188 and the sense strand comprises the sequence of SEQ ID NO:384;

d) the antisense strand comprises the sequence of SEQ ID NO:164 and the sense strand comprises the sequence of SEQ ID NO:376; or

e) the antisense strand comprises the sequence of SEQ ID NO:164 and the sense strand comprises the sequence of SEQ ID NO:384.

24. The LPA RNAi agent of any one of claims 1 to 23, wherein:

a) the antisense strand comprises the sequence of modified nucleotides according to SEQ ID NO: 790 and the sense strand comprises the sequence of modified nucleotides according to SEQ ID NO: 1189;

b) the antisense strand comprises the sequence of modified nucleotides according to SEQ ID NO: 637 and the sense strand comprises the sequence of modified nucleotides according to SEQ ID NO: 1132;

c) the antisense strand comprises the sequence of modified nucleotides according to SEQ ID NO: 709 and the sense strand comprises the sequence of modified nucleotides according to SEQ ID NO: 1135;

d) the antisense strand comprises the sequence of modified nucleotides according to SEQ ID NO: 787 and the sense strand comprises the sequence of modified nucleotides according to SEQ ID NO: 1191; or

e) the antisense strand comprises the sequence of modified nucleotides according to SEQ ID NO: 788 and the sense strand comprises the sequence of modified nucleotides according to SEQ ID NO: 1189.

25. The LPA RNAi agent of claim 24, wherein the LPA RNAi agent further comprises a targeting group of (NAG25) or (NAG25)s conjugated to the 5' end of the sense strand.

26. A pharmaceutical composition comprising the LPA RNAi agent of any one of claims 1 to 25 and a pharmaceutically acceptable excipient.

27. Use of the LPA RNAi agent of any one of claims 1 to 25 in the preparation of a medicament for treating cardiovascular disease or aortic valve stenosis in a subject in need thereof.

28. Use of the LPA RNAi agent of any one of claims 1 to 25 in the preparation of a medicament for treating peripheral artery disease or coronary artery disease in a subject in need thereof.